The Pennington Biomedical Research Center is a campus of the Louisiana State University System and conducts basic, clinical and population research. More than 500 employees occupy several buildings on the 234-acre campus.

Our Donors – Honoring Lifetime Giving

Louis D. Curet
Daniel T. Calongne and Associates
*George A. Daniels
deGravelles & Associates
Mr. Michael T. Delahaye
*Mrs. Eleanor J. Eldredge
Juliet S. Dougherty
Ethicon Endo-Surgery, Inc.
Evans-Graves Engineers, Inc.
Ms. Stephanie Ferry
Sharon and Jack H. Field, Jr.
Mary Barrett Fruehan
General Mills
Grady Crawford Construction Co., Inc.
Bob Greens Family
Gupta/Mittal Family: Alok and Sunita Gupta
Anonymous
Dr. Richard C. Rogers and Dr. Gerlinda Hermann
Dr. and Mrs. Steven B. Heymsfield
Dr. and Mrs. Richard M. Hill
William R. and Marilyn S. Holman
IBERIABANK
Donald and Kitty Ingram
Invitrogen Corporation
Dr. Anne Rossi Jarrett
Jenny Craig Management, Inc.
Dr. and Mrs. William D. Johnsson
Gretchen and Lee Kantrow
Jane and Kris Kirkpatrick
Mr. and Mrs. Luther Kissim IV
Kraft Foods, Inc.
Land O’Lakes Purina Feed
Isabel and Clifton C. Lasseigne, Jr.
Gordon and Terri LeBlanc
Mrs. Jane R. LeBlanc
Lee Michaels Fine Jewelry
LEMIC Insurance Company
CC and Alex Lewis
Louisiana Public Health Institute
Anonymous
*Mrs. Paula Garvey Manship
Mary Beth and Michael H. Martin
Matheme’s Supermarkets
Mc Cormick & Company, Inc.
McDonald’s of Baton Rouge
Jim and Terri Mcllwain
Priss and Robert H. McNeece, Sr.
Henry K. and Penny S. Miller
Morgan Keegan and Company, Inc.
Morgan Stanley
*Hermann Moyse, Jr.
Julie and Leonard R. Nachman II
Nestle’ S.A.
Orexigen Therapeutics, Inc.
*Mrs. Ann Harrison Parnell
Dr. Ruth M. Patrick
The Peanut Institute
PepsiCo, Inc.
Bill and Cherie Peters
Petrin Corporation
Pfizer, Inc.
PepsiCo, Inc.
PepsiCo
PepsiCo
Proctor & Gamble Company
Real Estate Management Services Group, LLC
Renal Associates of Baton Rouge, LLC
Ragan and Virginia Richard
Dr. Jennifer C. Rood and Dr. Michael Rood
Beverly and Rory Russell
Mr. and Mrs. Chris Sammons
Schwab Charitable Fund
Frank and Marcy Simoneaux
Christel C. and William S. Slaughter III
Mr. and Mrs. Lee Solomon, Solomon Family Foundation
Southeastern Cardiovascular Consultants, LLC
Stuart & Company General Contractors, LLC
Ralph and Margi Underwood
Unilever Corporate Research
WAFB-TV Channel 9
Nancy and Gerald L. Walter, Jr.
Weight Watchers International, Inc.
Wills-Knighton Health System
David and Anne Winkler
Bobby and Marsha Yarborough
Janet and John A. Young

* Deceased
During the two-year span of time covered by this issue of the Scientific Report, we have achieved several significant milestones. Noteworthy accomplishments include the opening of our new clinical research building, construction of the biomedical imaging center, and development of our new strategic plan – Vision 2015.

We are grateful to the Louisiana State University System Board of Supervisors, the Louisiana Board of Regents, and the Commissioner of Higher Education, most recently Dr. Jim Purcell, for the support they have given to our efforts. We are especially grateful for the support given by LSU Board of Supervisors Chairmen, James W. Moore, Jr., Ben W. Mount, and Garret “Hank” Danos, and System President Dr. John V. Lombardi.

In recent times, we have benefitted from the support of our city’s business and political leaders. I would like to thank Louisiana Governor Bobby Jindal, Louisiana Department of Economic Development Secretary Stephen Moret, and Baton Rouge Area Chamber President and CEO Adam Knapp. Baton Rouge Mayor Melvin “Kip” Holden has also taken a keen personal and professional interest in the Center, and we are grateful for his commitment. We also want to express our thanks to John Davies and John Spain of the Baton Rouge Area Foundation for their support over the years.

Our deepest gratitude goes to the men and women who serve on the boards of our two supporting foundations: the Pennington Medical Foundation and the Pennington Biomedical Research Foundation. Mrs. Paula Pennington de la Bretonne, Chair of the Pennington Medical Foundation, and Mr. William Silvia, CEO of the Pennington Medical Foundation, lead a group of dedicated individuals who have made it possible for the Pennington Biomedical Research Center to break ground on new facilities and to acquire sophisticated equipment and technologies on a regular basis. Mr. Tim Barfield, Chairman of the Board, and Mrs. Jennifer Winstead, President and CEO of the Pennington Biomedical Research Foundation, and their fellow board members are fully engaged in the task of raising unrestricted funds and creating endowed chairs and professorships. We are all extremely grateful for their dedication and hard work on our behalf. To all the donors who are so generous in their response to the requests from the Pennington Biomedical Research Foundation, we give our heartfelt gratitude and thanks.

The progress we have made during these past two years would not have been possible without the dedication of our faculty, staff and management team. Their devotion to our research and education efforts makes the Pennington Biomedical Research Center an inspiring place to work.

Our vision is to lead the world in eliminating chronic disease, and our new mission is to discover the triggers of chronic diseases through innovative research that improves human health across the lifespan. We are helping people live Well Beyond the Expected. We have continued to develop the breadth and depth of our science and our ability to achieve our mission. In this report, you will discover a wide spectrum of research programs and projects. You will also receive a brief introduction to the process leading to new discoveries.

To learn more about our science and our Center, as well as about supporting our mission, please visit us online at www.pbrc.edu.

Steven B. Heymsfield, MD
Executive Director
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreward</td>
<td>1</td>
</tr>
<tr>
<td>A Message from the Executive Director</td>
<td>4</td>
</tr>
<tr>
<td>Centers and Institutes</td>
<td>8</td>
</tr>
<tr>
<td>What Are Centers of Excellence?</td>
<td>9</td>
</tr>
<tr>
<td>Center for Research on Botanicals and Metabolic Syndrome</td>
<td>10</td>
</tr>
<tr>
<td>Nutrition and Obesity Research Center</td>
<td>11</td>
</tr>
<tr>
<td>Center of Biomedical Research Excellence (COBRE)</td>
<td>12</td>
</tr>
<tr>
<td>Institute for Dementia Research and Prevention</td>
<td>13</td>
</tr>
<tr>
<td>Basic Research</td>
<td>14</td>
</tr>
<tr>
<td>Overview</td>
<td>15</td>
</tr>
<tr>
<td>Adipocyte Biology Laboratory</td>
<td>16</td>
</tr>
<tr>
<td>Aging and Neurodegeneration Laboratory</td>
<td>17</td>
</tr>
<tr>
<td>Antioxidant and Gene Regulation Laboratory</td>
<td>18</td>
</tr>
<tr>
<td>Autonomic Neuroscience Laboratory</td>
<td>19</td>
</tr>
<tr>
<td>The Blood-Brain Barrier (BBB) Group</td>
<td>20</td>
</tr>
<tr>
<td>Developmental Biology Laboratory</td>
<td>21</td>
</tr>
<tr>
<td>Epigenetics and Nuclear Reprogramming Laboratory</td>
<td>22</td>
</tr>
<tr>
<td>Epigenetics and Obesity Laboratory</td>
<td>23</td>
</tr>
<tr>
<td>Gene-Nutrient Interactions Laboratory</td>
<td>24</td>
</tr>
<tr>
<td>Human Genomics Laboratory</td>
<td>25</td>
</tr>
<tr>
<td>Immunobiology Laboratory</td>
<td>26</td>
</tr>
<tr>
<td>Infection and Obesity Laboratory</td>
<td>27</td>
</tr>
<tr>
<td>Inflammation and Neurodegeneration Laboratory</td>
<td>28</td>
</tr>
<tr>
<td>John S. McIlhenny Botanical Research Laboratory</td>
<td>29</td>
</tr>
<tr>
<td>Leptin Signaling in the Brain Laboratory</td>
<td>30</td>
</tr>
<tr>
<td>Mechanisms of Diabetes Complications</td>
<td>31</td>
</tr>
<tr>
<td>Neurobiology and Nutrition Laboratory</td>
<td>32</td>
</tr>
<tr>
<td>Neurosignaling Laboratory</td>
<td>33</td>
</tr>
<tr>
<td>Nutrient Sensing and Adipocyte Signaling Laboratory</td>
<td>34</td>
</tr>
<tr>
<td>Nutrition and Neural Signaling Laboratory</td>
<td>35</td>
</tr>
<tr>
<td>Nutritional Neuroscience and Aging Laboratory</td>
<td>36</td>
</tr>
<tr>
<td>Oxidative Stress and Disease Laboratory</td>
<td>37</td>
</tr>
<tr>
<td>Protein Deficiency and Developmental Biology</td>
<td>38</td>
</tr>
<tr>
<td>Protein Structural Biology Laboratory</td>
<td>39</td>
</tr>
<tr>
<td>Regulation of Gene Expression Laboratory</td>
<td>40</td>
</tr>
<tr>
<td>Stem Cell Biology Laboratory</td>
<td>41</td>
</tr>
<tr>
<td>Taste Genetics Laboratory</td>
<td>42</td>
</tr>
<tr>
<td>The William Hansel Cancer Prevention Laboratory</td>
<td>43</td>
</tr>
<tr>
<td>Ubiquitin Biology Laboratory</td>
<td>44</td>
</tr>
<tr>
<td>Clinical Research</td>
<td>46</td>
</tr>
<tr>
<td>Overview</td>
<td>47</td>
</tr>
<tr>
<td>Behavior Technology: Eating Disorders and Obesity</td>
<td>48</td>
</tr>
<tr>
<td>Behavioral Medicine Laboratory</td>
<td>49</td>
</tr>
<tr>
<td>Behavior Modification Clinical Trials</td>
<td>50</td>
</tr>
<tr>
<td>Exercise Biology Laboratory</td>
<td>51</td>
</tr>
<tr>
<td>Human Physiology Laboratory</td>
<td>52</td>
</tr>
<tr>
<td>Inactivity Physiology Laboratory</td>
<td>53</td>
</tr>
<tr>
<td>Ingestive Behavior Laboratory</td>
<td>54</td>
</tr>
<tr>
<td>John S. McIlhenny Skeletal Muscle Physiology Laboratory I</td>
<td>55</td>
</tr>
<tr>
<td>John S. McIlhenny Skeletal Muscle Physiology Laboratory II</td>
<td>56</td>
</tr>
<tr>
<td>Joint Program on Diabetes, Endocrinology, and Metabolism</td>
<td>57</td>
</tr>
<tr>
<td>Pharmacology-Based Clinical Trials</td>
<td>58</td>
</tr>
<tr>
<td>Physical Activity and Ethnic Minority Health Laboratory</td>
<td>59</td>
</tr>
<tr>
<td>Preventive Medicine Laboratory</td>
<td>60</td>
</tr>
</tbody>
</table>
A MESSAGE FROM THE
EXECUTIVE DIRECTOR

Steven B. Heymsfield, M.D.

IT HAS BEEN ALMOST TWO YEARS since I assumed the role of Executive Director at the Pennington Biomedical Research Center. Since then we have worked collectively on developing Vision 2015 – a plan to advance Pennington Biomedical through three transforming strategies, all aimed at discovering the triggers of chronic disease and improving human health at every stage of life. We have introduced a new vision: to lead the world in eliminating chronic diseases and a new mission - to discover the triggers of chronic diseases through innovative research that improves human health across the lifespan. Part of our branding effort also includes the slogan or tagline “We are helping people live Well Beyond the Expected.”

In this Scientific Report, you will find a description of the basic, clinical and population research activities as well as the various other programs of the Center. You will also read about the core facilities that provide cutting-edge technologies and high quality support to our research enterprise. This report will provide information on the challenges and opportunities and the economic impact potential of the Center as we continue to experience growth in all three program areas.

Organization of the Center

As of this writing, the Pennington Biomedical Research Center has about 525 full-time and part-time employees, including 80 faculty members and 25 postdoctoral researchers. In addition, the Center benefits from the contributions of more than 80 adjunct faculty members. These scientists are grouped among more than 50 laboratories covering basic, clinical, and population science research areas. The research enterprise of the Center is also supported by the resources of 19 core facilities. The administrative organizational structure of the Center has been reorganized to operate more effectively but due to budgetary constraints, not all positions are currently filled.

The Pennington Biomedical Research Center is home to three Centers of Excellence funded by the National Institutes of Health: the Botanical Research Center (BRC), The Nutrition and Obesity Research Center (NORC) and the Center of Biological Research Excellence (COBRE). In addition, we are pleased to house the Institute for Dementia Research and Prevention (IDRP). You will read more about these entities later in this report.

Economic Impact

In 2010, the Pennington Biomedical Research Center completed construction of a new clinical research building. The 90,000 square foot building devoted to clinical research stands as a testament to our vision of growing our science along three large components: basic research, clinical research and population science research. The new clinical research facility was the first building on the campus constructed with capital outlay funds from the State of Louisiana. The state’s investment has helped to fulfill the need for additional clinical research space, as our clinical laboratories, staff, and number of participants had outgrown the original clinical building. Construction of the Biomedical Imaging Center, the second building funded by the State of Louisiana, began in 2010. This 30,000 square foot building, which is expected to open in the Spring of 2012, will house advanced imaging systems along with space for support staff and other imaging equipment. Pennington Biomedical investigators will use the new Biomedical Imaging Center resources to understand evolution of Alzheimer’s disease, the metabolic basis of adult-onset diabetes, the CNS mechanisms leading to obesity, and a host of other conditions. These advanced imaging resources will integrate with the Center’s state-of-the-art physiological and metabolic measurement capabilities.

It is well worth noting that new start-up companies based on findings of Center researchers stand to create significant future returns to Pennington Biomedical, the LSU System and the state. Among these and perhaps most notably is Esperance Pharmaceuticals, Inc. Investors created this company to take a potent cancer treatment compound from the laboratory bench to the first human clinical trials. It is significant that when the FDA reviewed this drug, it was not just examining a new drug...
in an existing category. This compound represents an entirely new category of drug which seeks out and destroys cancer cells. Created here by Dr. William Hansel and collaborators, particularly Drs. Carola Leuschner and Fred Enright, this new category of drug, if it works as well in humans as in animal models, could well save thousands of lives.

Dr. Ken Eilertsen, scientific leader of one of our stem cell research laboratories, created NuPotential, LLC, in an effort to capitalize on a new technology for somatic cell reprogramming. This technology may one day allow a physician to treat a patient suffering from damage to an organ (as in type 1 diabetes, Parkinson and the like) by harvesting the patient’s healthy cells from another tissue and “re-programming them” to generate new, healthy cells and tweaking them to assist the dysfunctional organ.

In addition, Dr. Tiffany Stewart received funding from Themelios for the establishment of Body Evolution Technologies, Inc. Body Evolution develops interactive health media based on peer-reviewed research. Treating body image issues can help a wide range of people from obese to thin, including those suffering with eating disorders.

These are just a few examples of scientific advances that may have considerable impact on medical practice and health care in the future but may also generate substantial economic benefits for the state in general and the Center in particular.

Challenges and Opportunities

The most important challenge we face is that of adequate funding from the Louisiana Legislature as we continue to feel the impact of budget cuts. The Center’s state general fund budget has been reduced by 19.9% from FY08-09 to FY11-12. During this time, new buildings have and are coming online without any increase in operating funds to offset basic operating costs. This has resulted in the need to cut funds used to support certain existing programs and we are unable to increase funding for worthy on-going research. We are working at several levels to secure additional resources for our institution. Obviously, the foundations are continuing their efforts to develop new funding avenues. In addition, we are exploring ways to self-generate new support lines, particularly through opportunities that may develop in the clinical area. Our team is working with governmental leaders to garner additional institutional support and spare the Center of further cuts.

Another challenge is that of being able to generate endowed research chairs in the range of $3 to $5 million so that we can compete in the national and international market place for the best and brightest scientists. The availability of chairs endowed at these levels will play a key role in the future of the Center.

Competition for the best minds has always been very keen. In the case of Pennington Biomedical, there are now several institutions in the United States that are attempting to emulate its success, and a number of these institutions have a much larger endowment. We have lost several key faculty members during the past several years to other institutions with superior funding. It is therefore imperative that we be in a position to offer high quality employment opportunities and generous start-up funds to star faculty candidates, as well as adequate retention measures to highly successful scientists who have made Pennington Biomedical their scientific home.

As the governor and legislature scrutinize higher education,
it is imperative they reflect on the high value return to the citizens generated by cutting edge biomedical research. Adequate state funding is a critical investment, particularly in an environment where the level of federal funding for biomedical scientific research has not increased to any significant extent over the last several years.

We are in a very strong position as a result of the high quality of our faculty and a portfolio of research grants and private research contracts that is equally as strong. Many of our full time scientists at the level of assistant-professor and above each bring in more than $500,000 of external research funds every year. For example, Drs. Leanne Redman and Corby Martin were awarded a National Institutes of Health U01 grant to study weight gain during pregnancy in collaboration with Woman’s Hospital. And a few months ago US Senator Mary Landrieu announced a new competitively awarded $6 million, three-year grant, from the US Department of Defense to discover novel ways to increase warfighter resilience, combat readiness, and optimal performance of soldiers.

Pennington Biomedical researchers continue to publish their findings in prestigious scientific journals such as JAMA and Nature Medicine. Current faculty members have excellent scientific productivity as shown by the fact that they have collectively published approximately 10,000 scientific papers throughout their careers. Moreover, they are influential in the world of science as evidenced by the more than 297,000 lifetime citations that their research has received to-date in the world scientific literature.

Our researchers also continue to be recognized in the scientific community for their accomplishments. For example, Dr. Eric Ravussin received the George A. Bray Founders Award at The Obesity Society’s annual meeting held this past fall; Dr. Kenneth Eilertson was named the “2011 University Technology Leader of the Year” by the Governor’s Louisiana Technology Council; the American Diabetes Association named Dr. William Cefalu the Editor-in-Chief of Diabetes Care; and Dr. Vishwa Deep Dixit was chosen by The Gerontological Society of America to receive the 2011 Nathan Shock New Investigator Award.

Pennington Biomedical is in an excellent position to maintain its leading position and make many contributions because it enjoys a strong and stable infrastructure combined with strong leadership in each of its major research components. The quality of the Center’s administrative units and the level of competency and dedication of the employees is another major asset. Moreover, being able to rely on strong leaders for the BRC, NORC and COBRE center grants as well as for the IDRP initiative bode well for the future. The quality of the existing facilities and the ongoing expansion of the physical plant of the Pennington Biomedical campus constitute
extraordinary assets that will continue to play a major role in the success of the research enterprise of the Center.

In addition, the global field of disease prevention research presents a great future filled with exciting opportunities. To take advantage of these opportunities, our strategy has continued to be one of investing in cutting-edge basic science areas that will allow us to contribute to the definition of the next generation of best practices in public health and preventive medicine.

Vision 2015

As the population ages, preserving personal autonomy and a high quality of life has moved into the forefront of the health agenda. It is in preserving a full, healthy life that presents the most meaningful opportunity for the Center to make unique contributions. It is evident that one’s genes play a critical role, but nutrition and physical activity are also two important determinants of the rate of decline in overall physical and cognitive independence and in well-being associated with aging. In this regard, preventing morbidities and remaining free from disability for a lifetime are of the utmost importance. Prevention can and should begin early in life and, as a result, the Center continues to make important investments in developmental biology, maternal biology and pediatrics. We have a splendid faculty now probing the mysteries of the body from pre-natal to early post-natal through adulthood and to the advanced ages of 80 and 90 plus years. Pennington Biomedical is now uniquely qualified to study prevention issues across the lifespan, with its broad base in basic, clinical, and population science research and its rapidly expanding efforts in aging and dementia research.

Pennington Biomedical will focus its efforts on three transformative strategies, all aimed at discovering the triggers of chronic diseases through innovative research that improves human health across the lifespan. Pennington Biomedical will:

STRATEGY I: Leverage our Expertise in Nutrition, Physical Activity and Genetics to Enhance Research Programs Aimed at Optimal Aging and Health throughout the Lifespan

- Expand Pennington Biomedical’s strong basic science research program in obesity and other chronic diseases to identify and drive novel approaches from theory to practice
- Create a personalized health research program that seeks to determine, on an individual basis, a nutrition and exercise prescription to optimize health
- Develop a multi-faceted effort to combat the diseases of aging by offering new approaches to advance healthier aging

STRATEGY II: Expand Clinical and Public Health Research Efforts to Advance Discoveries that Benefit People in Real World Healthcare Settings

- Develop partnerships that translate research discoveries to improve patient outcomes
- Expand Pennington Biomedical’s capacity for conducting and coordinating clinical trials and longitudinal studies focused on chronic diseases
- Develop an internationally significant pediatric obesity research and treatment program

STRATEGY III: Develop and Harness the Most Progressive, Emerging Technology to Facilitate Innovation in Research

- Create one of the country’s first research-focused biomedical imaging facilities to illuminate the underlying biological processes related to health and disease
- Translate novel ideas into commercial products and services that enhance the health and well-being of people and the scientific and economic vitality of Pennington Biomedical

Despite the challenges we face, Pennington Biomedical will continue to grow and make scientific discoveries, recruit outstanding faculty, expand our research portfolio, and contribute to the economy of the State of Louisiana.

We will help people live Well Beyond the Expected.
CENTERS & INSTITUTES
What Are Centers of Excellence?

Center grants are awarded to institutions with groups of established investigators working in areas of scientific emphasis defined by the National Institutes of Health. The goal of all NIH Centers is to power the discovery process at the heart of all scientific advances by facilitating and enhancing the collaborative efforts of the investigators within each center.

The establishment and support of centers is part of a broader strategy of the NIH whose overall goal is to more effectively translate scientific discoveries into improvements in people’s health. The elements of this strategy include:

1. placing a greater emphasis on mentoring and developing our young faculty who will power the discovery process now and in the future;

2. building our collective understanding of the precise molecular events that lead to disease states;

3. developing a better understanding of the networks of molecules that function in an integrated manner in our cells and tissues; and

4. enhancing multidisciplinary approaches involving research teams with complementary expertise to better tackle the complexity of the research questions we are asking and the disease problems we are addressing.

The Center for Research on Botanicals and Metabolic Syndrome (BRC), the Center of Biomedical Research Excellence (COBRE), and the Nutrition and Obesity Research Center (NORC) are the three NIH Centers of Excellence at Pennington Biomedical. They are organized around the common scientific theme of metabolic disease, and all three address complementary components of NIH’s overall strategy. The Pennington Centers of Excellence are devoted to expanding the research base and infrastructure that will provide scientific discoveries that will in due course lessen the burden of chronic disease and improve the quality of life.
Mission: The mission of the Center for Research on Botanicals and Metabolic Syndrome is to pursue an integrated understanding of the molecular, cellular, and physiological mechanisms by which select botanicals may prevent or reverse the development of insulin resistance, the key pathophyslogic feature of the metabolic syndrome.

The Botanical Research Center was successfully funded for a second 5-year cycle in 2010 by a grant from the National Institutes of Health. Our center is a collaborative effort between the Pennington Biomedical Research Center and the Biotechnology Center for Agriculture and the Environment at Rutgers University.

The theme of our center is “Botanicals and Metabolic Syndrome.” The metabolic syndrome has traditionally defined a condition whose major features consisted of obesity, insulin resistance, development of type 2 diabetes, and accelerated cardiovascular disease. The development and appearance of other traditional risk factors, e.g., hypertension, dyslipidemia, and nontraditional risk factors, e.g., inflammation, coagulopathy, are also associated with the condition. Because of the staggering increase in the prevalence of obesity that has now reached epidemic proportions and the fact that the components of the metabolic syndrome have become increasingly prevalent in children, this syndrome continues to represent one of the most important public health problems facing society today. As such, the study of botanicals and their effects to modulate pathologic processes as part of the metabolic syndrome has become even more important since the inception of our center.

Goals

The scientific goal of our center is to provide a comprehensive evaluation of specific, compelling hypotheses about the molecular, cellular, and physiological mechanisms by which botanicals can modulate the development of the underlying pathophysiologic mechanisms of, and attenuate the development to, metabolic syndrome. To accomplish our goal, our center has encompassed the disciplines of nutrition, plant chemistry/characterization, metabolism, physiology, endocrinology, molecular and cellular biology, and genetics and has spanned both the basic and clinical sciences. Thus, our interdisciplinary approach has allowed for a comprehensive evaluation of botanicals on pathogenic processes by evaluating multiple cellular mechanisms of action.

Our center consists of three specific research projects, each of which evaluates a specific botanical and assesses the effect on pathogenic mechanisms leading to the development of insulin resistance. Project 1 investigators are conducting studies to evaluate mechanisms of action by which selected extracts of Artemisia sp. modulate insulin receptor signaling and insulin sensitivity in both animal and early-phase human studies. Project 2 investigators are focusing on mechanisms by which selected Artemisia sp. extracts and Hypericum perforatum L. (St. John’s wort) affect adipocyte development, adipokines, and insulin action. Project 3 investigators are evaluating how Asclepias incarnata modulates central mechanisms controlling appetite and energy expenditure as a means to improve overall energy balance and weight. Our projects are supported by a Botanical Core and an Administrative Core. A unique aspect of our center is the formation of the Integrative Biology Core, which includes an Animal Research Subcore and the Analytical Chemistry Subcore, comprising a clinical chemistry/stable isotope component and a proteomic/metabolomic component. This combines state-of-the-art in vivo metabolic phenotyping with detailed ex vivo proteomic and metabolomic profiling of serum and tissue samples to provide highly integrated metabolic signatures of the pathophysiology of insulin resistance and its resolution by botanical extracts. As such, each project is supported by cutting-edge technologies that include metabolomic profiling, proteomic assessments, and bioaccessibility determinations.

Collaborative institutions and faculty within the Center for Research on Botanicals and Metabolic Syndrome include:


**Biotech Center, Rutgers University, New Brunswick, NJ:** Ilya Raskin, Ph.D.; David Ribnicky, Ph.D.

**North Carolina State University Plants for Human Health Institute:** Slavko Komarnytsky, Ph.D.
**Mission:** The mission of the Nutrition and Obesity Research Center (NORC) is 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 application.

The NORC has chosen “**Nutritional Programming: Environmental and Molecular Interactions**” as a central focus to develop. This focus is based upon convincing basic science and clinical data indicating that an interaction between genes and early life environmental conditions is important in the development of obesity and the different facets of the metabolic syndrome. Our aim is to focus the NORC’s efforts around this emerging and important theme. By keeping this tight focus and avoiding too broad an approach, the NORC is more likely to produce meaningful synergies and expansion of research efforts including basic, clinical, and population science.

The National Institutes of Health (NIH)-funded research base on which the NORC has been established includes basic and clinical research addressing the most prominent causes of morbidity and mortality in the United States related to nutritionally induced chronic diseases, many of them linked to obesity. The NORC’s platform includes three scientific cores: a Molecular Mechanisms Core (genomics and cellular imaging), very closely related to a Human Phenotyping Core (characterization of phenotypes predisposing to obesity and the metabolic syndrome and behavioral interventions to counteract those), and an Animal Models and Phenotyping Core (generation of genetically engineered animal models and a battery of instruments to phenotype them).

Furthermore, the NORC supports clinical investigation addressing the etiology of nutritionally induced chronic diseases across the entire age span, from gestational and perinatal development through childhood and adolescence, to young and middle-aged adults up to elderly individuals.

The resources of the NORC assist investigators at the center and Louisiana State University (LSU) in Baton Rouge and at the LSU Health Sciences Center in New Orleans to address the pathophysiology and molecular mechanisms leading to different facets of the metabolic syndrome. These research programs are conducted to instigate the effects of gender, racial, and ethnic background within a context of cultural factors.

The NORC is bringing to the established research base at Pennington Biomedical a structured system to provide core services to:

(a) support the research base, and

(b) promote novel investigation around our chosen theme of molecular mechanisms of nutritional programming induced by environmental factors.

The NORC provides a mechanism to enable both Pennington Biomedical and the NIH to maximize the effect of research funding. As of November 2011, there were more than 120 members of the NORC, including people outside of Pennington Biomedical. One of the most successful programs provided by this Center Grant is the yearly funding of Pilot and Feasibility grants to implement new innovative research around our theme of nutritional programming. Such studies allow young investigators to collect adequate preliminary data as the basis for larger NIH research grants. Since the start of the NORC in 2005, a total of 34 Pilot and Feasibility grants have been awarded from our funding (approximately $20,000-30,000/each award). From these projects, 15 grants have been submitted and 7 have been funded (5 NIH, 2 American Diabetes Association).

For more information on the NORC, visit [http://norc.pbr.edu/](http://norc.pbr.edu/)

---

The mouse T-maze was developed at the Pennington NORC from the Stone T-maze for detection of learning and memory impairments in mouse models. It is unique in requiring the mice to wade through water to "escape" to a dry, dark goal box, which minimizes noncompliance since the mice are motivated to get out of the water. At the same time, since mice are wading rather than swimming, it can be successfully completed by old or motor-impaired mice. It also measures learning without use of food rewards, providing a clear measure of learning independent of differences in food-based motivation that may be characteristic of certain mouse models of obesity.
Mission: The mission of the Pennington Center of Biomedical Research Excellence (COBRE) is to expand the critical mass of scientists in Louisiana focused on advancing our understanding of the cellular and molecular mechanisms of metabolic disease.

The Pennington Biomedical COBRE is accomplishing its goal by (1) fostering a collaborative and interactive research environment that places strong emphasis on mentoring and developing the young scientists who will power the discovery process, and (2) providing our young scientists with the cutting-edge technology that is needed to make fundamental discoveries of the underlying mechanisms of metabolic disease.

Nearly two-thirds of the U.S. population is either clinically overweight or obese, and 8% of the population has adult-onset diabetes. Obesity and diabetes are central elements of a cluster of pathologies collectively referred to as “metabolic syndrome.” The Pennington Biomedical COBRE is leading an effort to enhance research on metabolic disease by recruiting accomplished senior investigators and promising young scientists who will be mentored to independence by Pennington Biomedical investigators. The COBRE supports five projects from outstanding junior faculty who are employing a combination of cellular, molecular, and translational approaches to address questions ranging from neural mechanisms of glucose sensing and energy homeostasis, to inflammatory mechanisms linked to adipogenesis, to epigenetic programming in obesity, to regulation of mitochondrial biogenesis in adipocytes. Using in vivo, ex vivo and in vitro techniques, each project is pursuing fundamental questions critical to regulation of energy homeostasis and the associated pathologies of metabolic disease linked to the expansion of adipose tissue mass during the development of obesity.

The specific aims of the Pennington Biomedical COBRE in its second five years are to further expand the critical mass of productive investigators engaged in obesity/diabetes research by (a) developing and retaining outstanding junior faculty from within the institution and mentoring them to sustainable independent funding, (b) recruiting outstanding junior and senior faculty engaged in metabolic disease research that complements existing strengths of Center investigators, (c) developing and fostering new opportunities for collaborative interactions with institutional colleagues engaged in clinical/translational research, and (d) enhancing utilization of the outstanding research infrastructure that we have developed during the first five years of the COBRE. Our goal during the next five years is to build upon our many ongoing successes as we continue to support the discovery of solutions to the expanding national health problem of metabolic disease.

http://cobre.pbrc.edu/

The Pennington Biomedical COBRE is supported by a grant from the National Center of Research Resources at the National Institutes of Health.
A central focus of the Institute for Dementia Research and Prevention (IDRP) is obtaining information from our growing registry of over 1,600 individuals from Louisiana, aged 60 and over, who receive annual neurocognitive exams and a host of other evaluations focused on understanding the basis of brain aging and dementia. Studies use cutting-edge analysis in laboratory and free-living settings and will soon be incorporating neuroimaging. An increasing number of Pennington Biomedical faculty and faculty from institutions around the country are working with the IDRP to increase the impact of its efforts. This is accomplished by using our registry and existing data to secure more grants and publications in multiple areas of geriatric research. In addition to these efforts, the IDRP conducts a variety of clinical trials focused on dementia treatment, participating in major pharmaceutical industry-sponsored trials as well as lifestyle interventions. Those interested in learning more about any of these research efforts or who would like to participate are encouraged to contact the IDRP at 1-877-276-8306 or to e-mail dementia@pbrc.edu for more details.

The IDRP is supported by private philanthropy as well as a combination of National Institutes of Health, private foundation grants, and pharmaceutical industry sponsored studies.

**Focus:** This Institute is currently involved in a wide range of studies aimed at understanding the causes of brain aging and identifying the basis by which aging promotes the development of dementia, focusing on lifestyle choices as modulators of cognition. Secondary emphasis is understanding the basis for frailty and falls in elderly with and without dementia.
At Pennington Biomedical Research Center, Basic Science continues to be a thriving and world-class research program. At the heart of the Basic Science research efforts is a focus on understanding how metabolic dysfunction contributes to the genesis and progression of the chronic diseases that affect us today. It is now clear that the metabolic dysfunction associated with conditions such as obesity and diabetes is intimately involved in many of the worst diseases of the 21st century including cardiovascular disease, immune disorders, cancer, and dementia. Given the long-standing history of the Center as a leader in metabolism research, we are perfectly suited to increase the understanding of the interconnected nature of chronic diseases. The theme of metabolic dysfunction is the thread that unites the diverse expertise and scientific interests in the Basic Science program, and it is one of the major factors distinguishing the work at Pennington Biomedical.

The Basic Science program at Pennington Biomedical has added several key faculty to strengthen our repertoire in the areas of oxidative stress, neuroscience, cell signaling, and physiology. The addition of these faculty not only brings new state-of-the-art and cutting-edge research programs to the Center, but also allows us to leverage this expertise with our existing scientists to increase the impact of ongoing research. Coupled with continued investment by Pennington Biomedical into the Basic Science core facilities, the Pennington Biomedical Basic Science program is well poised to continue to build off of our successes. And we have had multiple successes, including the fact that since the last reporting period we have renewed our National Institutes of Health (NIH) grants for the Center of Biomedical Research Excellence (COBRE) and the Center for Research on Botanicals and Metabolic Syndrome, providing another 5 years of vital support. The ability to renew these center grants during a period of intense competition for NIH dollars is a tremendous testament to the Basic Science researchers involved in each of these large programs. Our scientists continue to be prolific in their publications (over 200 peer-reviewed publications since the last report), with the highest tier of journals represented. This includes a publication by multiple Pennington Biomedical scientists in *Nature* (led by Dr. Vishwa Deep Dixit’s research team). Our Basic Science faculty have demonstrated their innovation by generating multiple patent applications and successful business grants, with Dr. Kenneth J. Eilertsen receiving the University Technology Leader of the Year Award from the Louisiana Technology Council.

Our faculty in Basic Science have made important findings in multiple areas of research, and these findings will have a significant impact on the future of medicine and health. Work in Basic Science at Pennington Biomedical has identified the triggers responsible for regulating hunger, increased our understanding of the mechanisms by which dietary fat and obesity mediate disease, and helped to uncover the process by which communication between the brain and peripheral tissues occurs. Importantly, efforts in Basic Science have also identified the basis for complications of metabolic disorders such as diabetes, providing insight as to the origins of diabetic neuropathy and diabetic nephropathy. Studies in these areas are of the highest impact because of the Basic Science core laboratories, which provide our faculty with the most cutting-edge genomics, proteomics, transgenic animal, animal behavior and phenotyping, and cell bi imaging technologies available. These findings are vital in moving from “bench to bedside,” taking our findings from the laboratory to the clinic in order to develop new and important treatments for chronic diseases.

The landscape of Basic Science research continues to change and evolve. With the tightening of NIH budgets and constant improvements in science and technology, our researchers must continue to be the best, brightest, and most equipped in order to succeed. Our scientists continue to secure competitive funding at every level, ranging from independent investigator grants to large center grants. And while the environment will remain challenging, we believe that we will continue to be successful. This assurance comes from our long track record of success, the commitment of Pennington Biomedical to continuing to grow a strong Basic Science program, the collaborative spirit of our faculty, and the unique resources and expertise that allow us to delineate the role of metabolic dysfunction as a trigger for the diseases of today.
FOCUS: The goal of this laboratory is to use biochemical approaches to understand cellular pathways involved in the molecular pathogenesis of type 2 diabetes.

Adipocytes are highly specialized cells that play a major role in energy homeostasis in vertebrate organisms. These insulin-sensitive cells make hormones that contribute to the regulation of energy homeostasis in the whole body. Obesity is the primary disease of fat cells and a major risk factor for the development of type 2 diabetes (T2DM), cardiovascular disease, and hypertension. Obesity and its related disorders result in dysregulation of the mechanisms that control lipid storage, insulin action, and hormone secretion from adipocytes. The Adipocyte Biology Laboratory studies basic functions of fat cells at the molecular level and determines how these cells contribute to the pathogenesis of metabolic diseases including obesity, T2DM, and metabolic syndrome.

The understanding of how adipocytes contribute to disease has been significantly advanced by the identification of transcription factors that regulate the differentiation of fat cells and are involved in the induction and maintenance of adipocyte gene expression. Hence, our research has focused on transcription factors that are master regulators of development and several other important cellular processes. In particular, we have studied the STAT family of latent transcription factors, which are activated by a variety of hormones and growth factors. When activated, STATs move into the nucleus. STATs are both signaling molecules and proteins that can bind to DNA to regulate gene expression. We have recently shown that one of these proteins, STAT5A, contributes to adipocyte development in mammals. In mature fat cells, we have shown how STAT5 regulates genes associated with lipid synthesis and insulin action. Our most recent experiments have revealed that STAT5 can also control the expression of proteins secreted from fat cells and modulate overall insulin sensitivity in the whole animal. Our studies will hopefully lead to insights into the molecular mechanisms regulating energy homeostasis and may contribute to understanding the defects underlying obesity and T2DM. This project started in 1996 and is funded by the National Institutes of Health (NIH).

We are also working with the Center for Research on Botanicals and Metabolic Syndrome at Pennington Biomedical to identify botanicals that can regulate adipocyte function. These studies have largely been conducted by LSU undergraduates. We hope to identify botanicals that could have beneficial effects in individuals affected by metabolic diseases.

Research in this laboratory is supported by grants from the NIH and by funds from the NIH-supported Center for Research on Botanicals and Metabolic Syndrome.
FOCUS: This laboratory is currently involved in a wide range of studies aimed at understanding the causes of brain aging and identifying the basis by which aging promotes the development of brain pathology and brain diseases such as Alzheimer’s disease.

The studies in our laboratory look at the molecular basis of brain aging, focusing on the effects of diet-induced obesity (DIO) and the mechanisms by which adipose tissue promotes brain aging and pathology. Studies are designed to understand what metabolic disorders or factors from adipose tissue are responsible for mediating neuropathology and dementia. Our studies build upon previously published work showing that fat associated with organs of the abdomen (visceral adipose) is more involved in mediating brain dysfunction than subcutaneous adipose (tissue under the skin). Our current National Institutes of Health (NIH)-funded studies focus on the role of oxidative stress in mediating neuropathology and dementia, as well as directly looking at the role of visceral adipose tissue in mediating specific aspects of brain pathogenesis and cognitive decline.

Our studies look at a variety of pathologies including oxidative stress, inflammation, vascular pathology, and Alzheimer’s pathology. In addition, our studies use classic and innovative analysis of animal behavior (learning, memory, motor function) to understand how cognitive function is altered across a spectrum of aging and disease. We use a variety of experimental models, molecular studies, and neuroimaging to study this important area of research. These efforts will not only be important in understanding the role of diet and obesity in regulating brain pathogenesis, but also may lead to novel interventions for the treatment of age-related dementias such as Alzheimer’s disease.

These basic science efforts are complemented by the Institute for Dementia Research and Prevention (IDRP), founded and directed by Dr. Jeffrey Keller. The IDRP conducts a longitudinal aging study in more than 1,800 individuals over 60 in Louisiana, examining the causes of dementia and increased falls in the elderly, as well as developing new tests for the identification of early dementia. This study of longitudinal aging is complemented by a longitudinal study in individuals with active dementia, the Jo Lamar Dementia Study. Dr Keller also conducts a variety of clinical trials for dementia including exercise based clinical trials, as well as directing clinical trials for Alzheimer’s disease with major pharmaceutical companies.

Research in this laboratory is supported by grants from the NIH by the NIA and NIDDK, and philanthropy from the Lamar Family, Coypu Foundation, and other benefactors.
FOCUS: Our research is conducted to address two questions: (1) Why does inflammation occur in obesity? (2) How does inflammation regulate insulin resistance? Obesity-associated inflammation has been well documented for its detrimental activities in the pathogenesis of insulin sensitivity. However, anti-inflammation approaches have not been able to provide solid evidence in clinical trials to support the concept. We believe that this is due to the beneficial activities of inflammation in the body, which have been uncovered by studies in several laboratories including ours.

Obesity-associated inflammation contributes to the pathogenesis of many chronic diseases including type 2 diabetes, metabolic syndrome, fatty liver, and atherosclerosis. Adipose tissue is a primary site of chronic inflammation in obesity. The inflammation is associated with metabolic disorders in glucose and fatty acids. The cellular mechanism is related to inhibition of adipogenesis, induction of adipocyte degeneration, stimulation of lipolysis, and suppression of adiponectin expression. The molecular mechanism involves suppression of transcription factors such as C/EBPs, and PPARγ. Although these negative effects of inflammation have been well documented in the literature, the beneficial activities of inflammation remain largely unknown in obesity. It is not clear whether inflammation plays a role in adipose tissue remodeling and maintenance of energy homeostasis in the body. Our studies suggest that: (a) inflammation stimulates angiogenesis in adipose tissue during quick tissue expansion; and (b) inflammation enhances energy expenditure in the maintenance of energy homeostasis. These two activities represent the body’s feedback responses to the energy surplus in obesity.

In the first effect, inflammation is derived from a hypoxia response in adipose tissue to amplify the angiogenic signals in the process of compensatory tissue remodeling. We reported that obesity leads to a reduction in oxygen pressure in adipose tissue. The inflammation is induced in adipose tissue after activation of transcription factors such as HIF-1α and NF-kB in response to the hypoxia. Additionally, hypoxia contributes to chronic inflammation by induction of lipolysis and apoptosis in adipocytes. Macrophage infiltration is elevated, and expression of angiogenic factors is enhanced. The concept of adipose tissue hypoxia has been accepted by an increasing number of investigators in the obesity field.

In the second activity, inflammation contributes to the maintenance of energy homeostasis by stimulation of energy expenditure. Different from the local effect in tissue remodeling, this inflammatory activity has a broad impact and is mediated by inflammatory cytokines produced by adipose tissue. This conclusion is derived from phenotype studies of two mouse models of dietary obesity. Chronic inflammation in these models protects both lines of transgenic mice from obesity and insulin resistance when fed a high-fat diet. The mechanism is related to an increase in energy expenditure that prevents fat accumulation in the body. These results have led us to propose that obesity-associated inflammation plays an important role in the regulation of energy metabolism. If the body loses the response to this activity of inflammation, the inflammation will not be able to promote energy expenditure, leading to an increased risk of obesity. We call this condition “inflammation resistance,” and we believe that it is required for the development of obesity.

Research in this laboratory is supported by grants from the National Institutes of Health and the American Diabetes Association.
FOCUS: This laboratory is generally interested in determining how the brainstem controls autonomic functions related to metabolic and behavioral homeostasis.

Present activities include investigations of:

- the basic neural circuitry involved in the control of digestive processes,
- the mechanism by which immune cells activated during infection, cancer, radiation, or autoimmune disease cause autonomic regulation of the stomach to fail,
- the mechanisms by which glial cells in the brainstem detect chemical signals and in turn regulate neurons responsible for autonomic control,
- the mechanism responsible for the regulation of metabolic heat production by the brainstem, and
- chemosensory functions of cranial nerve afferents.

This work has been supported by five grants from the National Institutes of Health (NIH). Some of our more recent publications deal with a phenomenon that is new to neuroscience: communication between glia and neurons resulting in changes in autonomic control as a function of disease.

Eighty years ago, the famous physician and endocrinologist Harvey Cushing observed that bleeding closed head injuries often produced severe gastric ulcers caused primarily by a complete suppression of gastrointestinal motility. His original theory was that increases in intracranial pressure caused by head trauma directly activated parts of the brainstem involved in the regulation of digestion. It was later shown that while intracranial pressure does not correlate well with failed autonomic control of the stomach, trauma in general does. That is, severe bleeding caused by transplant surgery, accident trauma, and severe burns are all highly correlated with failed autonomic control of the stomach.

We suspected that a critical component of the blood-clotting cascade, thrombin, might be responsible for the connection between trauma and autonomic failure. The portion of the brainstem responsible for autonomic control of the gut has a high concentration of sites through which thrombin can act to evoke changes in cellular activity. These areas of the brainstem are outside the blood-brain barrier and therefore can be affected by thrombin generated either within the brain or in the periphery in response to injury. We found that thrombin and thrombin-like peptides applied to the brainstem produce gastric stasis. Surprisingly, this effect was mediated within the brainstem by a novel interaction between glial cells and neurons. Gial cells have long been thought of as passive supporters of neurons, the cells responsible for long-distance electrical communications. By using live-cell imaging methods developed in this laboratory, we found that thrombin first activates glial cells in the brainstem by causing the release of stored calcium. This, in turn, causes glial cells to release glutamate, normally a neuronal transmitter substance, onto adjacent neurons involved in the reflex regulation of the stomach. These gastric-control neurons are then activated, eventually causing a shutdown of gastric motility.

The discovery of a glial cell-mediated autonomic reflex is a completely new phenomenon, one that may be very important in the general understanding of how the brain detects and reacts to chemical agents released by other cells following injury or the onset of disease.

In addition, we have determined that vagal afferent fibers that direct changes in autonomic control based on changes in physiological parameters also regulate the sensitivity of glial cells to chemical stimulation. This discovery supports the idea that glial cells and neurons form a complex functional network that regulates bodily functions.

Research in this laboratory is supported by grants from the NIH.
FOCUS: This laboratory investigates how cytokines modulate central nervous system functions by way of the BBB, as well as the regulation of cerebral blood flow and metabolism by neuroinflammation. It also investigates the role of the BBB endothelia and astrocytes in neuroendocrine control, particularly related to peptides/polypeptides involved in feeding behavior.

Several decades ago, we pioneered the concept that peptides in the periphery have central nervous system (CNS) effects, and we are still leading the way in describing the mechanisms involved. In recent years, we showed that these small proteins not only cross the BBB, but also elicit signaling transduction in the cerebral endothelial cells composing the BBB. The significance of these studies lies in the concept that the BBB is a dynamic interface between the body and brain that is actively engaged in regulatory functions while protecting the brain from harmful substances. Lately, we have been focusing on the role of astrocytes, another component of the BBB, in obesity, neuroinflammation, and autoimmune diseases.

1. Role of leptin signaling on astrocyte functions. We have shown that the leptin receptor is upregulated in mice with diet-induced obesity and experimental autoimmune encephalomyelitis. To elucidate the functions of the astrocytic leptin receptor, our cell culture approaches test the expression of inflammatory markers and determine the production of gliotransmitters. In addition, hypoxic and excitotoxic challenges have shown that leptin signaling modulates astrocytic activities. Our in vivo studies use behavioral, electrophysiological, immunohistological, and biochemical methods to characterize the phenotype of astrocyte-specific leptin receptor knockout mice generated in our lab.

2. How do obesity and other challenges to the CNS upregulate astrocytic leptin receptors? Are the changes in the astrocytic leptin system selective or nonspecific as a result of reactive astrogliosis? We are conducting BBB transport studies and cellular assays to determine the metabolic factors and intracellular signaling mechanisms responsible for the translational regulation in astrocytes.

3. Effects of astrocytic activity or the astrocytic leptin receptor on neuronal leptin signaling and behavioral outcome, including feeding, metabolism, and cognition. This will be achieved by the use of selective astrocyte activity inhibitors and the astrocyte-specific leptin receptor knockout mice.

4. What is the role of endothelial leptin signaling in the development of obesity and the autoimmune response? We will determine the outcome of a high-fat diet or experimental autoimmune encephalomyelitis in endothelial-specific leptin receptor knockout mice generated in our lab.

5. How does TNF modulate endogenous IL15 trafficking in cerebral endothelia? We have shown that TNF is a strong positive regulator of IL15 production in endothelia and a facilitator of cerebral IL15 signaling. Cellular trafficking studies will further determine the compartmentalization and fate of IL15 in response to a TNF challenge. This illustrates an important principle of signaling modification by the BBB in the event of neuroinflammatory signals from the periphery.

Research in the BBB Group is supported by the National Institutes of Health.
The goal of this laboratory is to understand how maternal factors, such as nutrition or diseases during pregnancy, shape how information encoded in the genome is realized into a three-dimensional living organism during development.

It is generally believed that developmental programs encompass both gene-gene and gene-environment interactions, but few of the genes involved in these latter interactions have been identified to date. Our model system uses diabetic pregnancies in the mouse since diabetes is a well-known teratogen, causing primarily heart and neural tube defects. In humans, pregnancies complicated by maternal diabetes are accompanied by a higher risk for congenital defects, with heart defects and neural tube defects particularly common in infants exposed to maternal diabetes. Therefore, our mouse models reflect processes in human development and are well-suited to identify critical dietary factors as well as interacting genes.

Our efforts in the past 2 years have demonstrated that genes belonging to Wnt signaling pathways are misregulated in embryos exposed to diabetes. Wnt signaling is known to be critical for normal development, but its role in embryogenesis under conditions of maternal diabetes is unknown. There is emerging evidence that links Wnt signaling to nutrition and metabolism, both under normal and pathological conditions such as obesity. Therefore, we also established a mouse model for obesity during pregnancy, which is also known to be a strong risk factor for neural tube defects.

Neural tube defects can be prevented by a diet that is rich in folic acid, an essential vitamin. Folic acid is present in leafy green vegetables and folate-fortified grain and cereal products; many multivitamin supplements also contain folic acid. Despite its wide use, the mechanisms underlying the beneficial effect of folate supplementation are poorly understood. In fact, it has recently been shown in mice that folate is not a panacea, but that it can even promote neural tube defects, highlighting the need for more research. We are using mouse models to investigate the effects of folate supplementation on key morphogenetic processes, such as neural tube closure and development of the skeleton. In the past 2 years, we have identified the visceral endoderm as the major site of expression for folate receptor 1, the primary transporter of folate to the developing embryo prior to neural tube closure. This work was awarded the James G. Wilson Publication Award of the Teratology Society for the Best Paper published in the scientific journal Birth Defects Research in 2009. We also recently identified genes that respond to folate; intriguingly, they provide a link to energy metabolism.

Genes in the placenta that respond to dietary factors such as fat and protein content were also recently identified in our lab. These genes suggest that there is inflammation in the placenta in diabetic pregnancies, and that this may be aggravated by an adverse diet. The composition of maternal diet also influences the risk for neural tube defects at earlier stages in development, indicating a complex interplay between gene expression, nutritional environment, and disease. Emerging evidence shows that intrauterine development has long-lasting consequences for the health of the individual, such that adverse exposures raise the risk for disease later in life, including metabolic syndrome and obesity. The knowledge gained from our studies will help to optimize maternal diet during pregnancy to prevent birth defects and promote long-term health.
The goal of this laboratory is to develop and validate novel laboratory models of chronic diseases such as type 2 diabetes (T2D) that give researchers a look at a patient in a Petri dish. Our aim is to put patients into the process of drug and therapeutic discovery at an earlier time than has been done historically. This appears to be possible with recent advances in a technology referred to as “reprogramming.” Reprogramming allows adult cells to be converted to an embryo-like state called induced pluripotent stem (iPS) cells, which have the potential to become any cell in the body. These cells avoid the numerous ethical issues associated with embryonic stem cells but also make it possible for researchers to develop an ample supply of pluripotent cells directly from patients whose disease they are studying. Thus, a researcher can make iPS cells from a patient and then coax the cells to become the tissues that are affected by a given disease. For example, skin cells can be obtained from a patient with amyotrophic lateral sclerosis (ALS) and can be reprogrammed into iPS cells. The iPS cells can then be redifferentiated into neural cells. By comparing the behavior of ALS cells with non-diseased cells, it may be possible to understand what is killing a patient’s neurons. Companies are using iPS cells to screen drugs for possible side effects, to identify new drug entities, and to develop “virtual clinical trials” to test thousands of drugs.

Recent key developments in our lab include:

1. Demonstration that cells obtained from mouse ears express the Gtl2 imprinted locus and are efficiently reprogrammed to iPS cells (see figure)
2. Demonstration that epigenetic priming using histone deacetylase inhibitors improves the efficiency of iPS cell colony formation
3. Development of methods to reprogram human muscle progenitor cells from a variety of patient types, including obese and T2D
4. Identification of a mechanism contributing to persistent epigenetic memory (PEM), which limits reprogramming efficiency and is associated with redundancies previously thought not to exist in the epigenome

Research in this laboratory is funded by grants from the Louisiana Board of Regents Industrial Ties Program.
**FOCUS:** The goal of this laboratory is to identify epigenetic determinants of obesity and related metabolic disorders.

Obesity is a complex metabolic syndrome caused by interactions between an individual’s genetic predisposition to developing the disease and the nutritional and physical environment. Although studies have shown that nutritional status during development can “permanently” alter an individual’s susceptibility to obesity and related metabolic disorders in later life, very little is known about the biological mechanisms that cause these changes. To identify these potential epigenetic contributions to obesity, we have characterized an inbred mouse strain that gives rise to large variations in obesity among individuals when reared in controlled environmental conditions. Global analyses of gene expression in the adipose tissue of mice with low and high weight gain after being fed an energy-rich, high-fat diet allowed for the identification of several genes associated with variations in obesity among individual mice. These include imprinted genes, developmental genes, and genes involved in Wnt signaling, angiogenesis, vascularization, and cytoskeletal organization. Because individual mice within our inbred mouse population are essentially genetically identical, we hypothesize that epigenetic mechanisms must underlie the regulation of some of the genes or gene pathways associated with the development of obesity in this model.

Mesoderm specific transcript (Mest), an imprinted gene known to be regulated by epigenetic mechanisms, showed the largest variation in gene expression (~80-fold) among adipose tissue depots in the mice. Mest belongs to the \( \alpha/\beta \) hydrolase family of proteins and is expressed only from the paternal allele. Many studies have established a role for Mest in growth and development, and we have shown that Mest is strongly associated with fat mass expansion under conditions of positive energy balance. Our goal is to identify the epigenetic mechanism(s) that either directly or indirectly regulate Mest in the adipose tissue of adult mice and to determine the catalytic function of MEST and how it regulates fat mass expansion in mice fed excess dietary fat. To aid in these studies, we have recently developed a mouse model that can be used to selectively knock out the Mest gene in adipose tissue.

Other genes that show significant associations with weight gain in mice are co-regulated with Mest in adipose tissue after feeding mice a high-fat diet. These genes include the Wnt signaling antagonist secreted frizzled-related sequence protein 5 (Sfrp5) and the osteogenic antagonist bone morphogenetic protein 3 (Bmp3). Studies are under way to determine the mechanisms involved in the coordinated regulation of these genes and to demonstrate their role in adipose tissue expansion in an obesogenic environment. These studies will unravel biological mechanisms associated with variations of adiposity, and identify pathways that can be evaluated as therapeutic targets for the treatment of obesity.

Research in this laboratory is supported by grants from the National Institutes of Health.

Schematic represents potential roles for mesoderm-specific transcript protein (MEST) in modulating fat mass expansion in the adipocyte. MEST resides within the endoplasmic reticulum (ER)/Golgi complex where it may enhance lipid storage by accelerating the synthesis of nascent lipid droplets (NLDs) and mature lipid bodies (MLBs). Alternatively, the putative catalytic function of MEST as an epoxide hydrolase may lead to conversion of epoxyoctadecanoic and epoxyeicosatrienoic acids (EpOEMs and EETs) to their respective diol derivatives. Fatty acid epoxide derivatives have been shown to effect cellular signaling, possibly through interaction with peroxisome proliferator-activated receptors (PPARs).
FOCUS: This laboratory utilizes an integrative approach combining genetic engineering techniques in mice, clinical studies, cellular physiology, and nutrition studies to understand the basis of obesity and type 2 diabetes.

It is well established that type 2 diabetes (T2D) is a progressive disease, and the hallmark of prediabetes is insulin resistance, which is strongly associated with obesity and the ectopic accumulation of lipids in skeletal muscle and liver. The use of dietary supplements, such as L-carnitine, that ameliorate lipid accumulation in skeletal muscle and liver represents a very attractive approach for adjunctive therapy of diabetes. L-carnitine plays a critical role in the shuttling of acyl moieties across mitochondrial membranes, and it has been speculated that carnitine supplementation would improve glucose disposal by reducing the cellular concentrations of long-chain acyl-CoAs (LC-CoA) and acetyl-CoA, which are potent inhibitors of glucose utilization.

L-carnitine is a conditionally essential nutrient that is synthesized endogenously or obtained from dietary sources. There are at least two major functions of L-carnitine. Fatty acids require L-carnitine for transport across the inner membrane of the mitochondria for β-oxidation. Another important function of L-carnitine is to transport acetyl-CoA and possibly partially oxidized fatty acids from the mitochondria. The carnitine hypothesis posits that carnitine would reduce lipid metabolites within skeletal muscle via increased oxidation and increased mitochondrial export and that this reduction in lipotoxic metabolites would lead to an increase in insulin signaling and improve mitochondrial capacity.

Our investigations have found that dietary carnitine supplementation improved insulin sensitivity in three mouse models of impaired insulin action: aging, genetic diabetes, and high-fat feeding. Concomitant with the benefits of supplemental carnitine on insulin sensitivity were increases in the cellular export and excretion of lipotoxic metabolites. These data suggest that abnormalities in fuel metabolism may arise from the mitochondrial accumulation of lipotoxic metabolites. Additionally, carnitine insufficiency is suspected as causative to mitochondrial dysfunction and insulin resistance. Low carnitine levels in severely obese rats were associated with aberrant mitochondrial fuel metabolism, whereas oral carnitine supplementation reversed these perturbations in concert with improved glucose tolerance and increased acylcarnitine efflux. These results provide the initial “proof of concept” that dietary carnitine is effective at improving insulin-stimulated glucose utilization and in reversing the abnormalities of fuel metabolism associated with T2D.

Key to understanding the extent of the contribution of mitochondrial efflux fatty acids to the overall benefit of supplemental carnitine is the manipulation of carnitine acetyltransferase (CRAT) in mice. The reduction of CRAT activity in muscle led to a moderate increase in fat mass when mice were fed a high-fat diet. However, the Crat knockout mice had higher blood glucose values and were less responsive to insulin irrespective of diet, indicating that insulin resistance in these mice is not secondary to obesity and suggesting a direct role of CRAT in muscle for glucose homeostasis. These data support the role of CRAT as a key enzyme in mitochondrial energy homeostasis.

Research in this laboratory is supported by grants from the American Diabetes Association and the National Institutes of Health.
FOCUS: This laboratory investigates the genetic and molecular basis of the response to a physically active lifestyle, emphasizing cardiorespiratory endurance, cardiovascular disease, and type 2 diabetes risk factors, as well as the genetic and molecular background of obesity and its comorbidities.

The Human Genomics Laboratory relies on several cohorts to pursue its goal of defining the genetic and molecular basis of complex traits. Recent results from four of these resources are described here.

HERITAGE Family Study: The HERITAGE Family Study began in 1992 and has been continuously funded by the National Institutes of Health (NIH). One of the most recent interesting findings of HERITAGE relates to the genomic predictors of the ability to increase cardiorespiratory fitness in response to regular exercise. A genome-wide association study (GWAS) performed on the sample of families of European descent in HERITAGE used a panel of more than 320,000 genomic markers and revealed that 21 of these markers accounted for the genetic component of the ability to increase maximal oxygen uptake in response to regular exercise. This is illustrated in the figure.

CARDIA Fitness Study: We examined the associations of single nucleotide polymorphisms (SNPs) from candidate genes with changes in cardiorespiratory fitness over 20 years, as well as the associations of gene-by-fitness and gene-by-BMI interactions with incident hypertension over 20 years in the CARDIA Fitness Study. We found that alleles at genes related to skeletal muscle Na⁺/K⁺ transport, hypoxia, and mitochondrial metabolism are associated with symptom-limited exercise test duration over 20 years in adults. Conversely, we found that SNPs in seven blood pressure and/or fitness candidate genes did not modify the associations between baseline fitness or BMI and risk of hypertension over 20 years in CARDIA participants.

The Pennington Center Longitudinal Study (PCLS): The PCLS cohort consists of all subjects who have been screened at the Pennington Biomedical clinic since 1994. The central database includes approximately 14,000 subjects who have participated in clinical studies. The Human Genomics Laboratory has established a DNA bank for the PCLS cohort, which currently consists of over 8,500 extracted and diluted DNA samples. Genetics studies on obesity and metabolic comorbidities using state-of-the-art techniques (e.g., GWAS, genome-wide exome sequencing, deep resequencing) will be performed on PCLS subjects.

Swedish Obese Subjects (SOS) Study: We examined the associations of SNPs from candidate genes or identified through GWAS with changes in weight and HDL-cholesterol after bariatric surgery in SOS patients. We found two SNPs in the FTO gene to be associated with maximum weight loss after banding surgery. We also found that SNPs in the CETP, LIPC, and LPL gene loci contribute significantly to plasma HDL-cholesterol levels in morbidly obese individuals; however, these genes were not associated with surgery-induced changes.

The Human Genomics Laboratory continues to contribute to the Quebec Family Study and participates in specific GWAS projects pursued by the GIANT, INSHAPE, and MAGIC consortia.

In 2010 and 2011, the laboratory published 44 peer-reviewed original papers and 7 book chapters.

Research in this laboratory is supported by grants from the NIH and the American Heart Association.
**FOCUS:** This laboratory focuses on immune cell dysfunction in aging and obesity.

The Immunobiology Laboratory studies the interactions between metabolic and immune systems that contribute to inflammation and immune dysfunction related to aging and obesity.

The two major areas of interest of Dr. Dixit’s laboratory are:

1. **Immune senescence:** To discover mechanisms that cause the decline of naïve T cell production from thymus and to develop approaches to enhance protective immunity in the elderly.

2. **Inflammation:** To identify the origin of metabolically driven inflammation that leads to obesity- and aging-associated chronic diseases like diabetes, cardiovascular disease, cancer, and dementia.

**Immune Senescence:** The diminished ability of the thymus to produce naïve T cells with advancing age remains a fundamental and puzzling phenomenon for biology and, to date, an intractable clinical condition that contributes to reduced immune surveillance in elderly persons. An important goal of aging research is to compress morbidity and extend the healthy life span by keeping all organ systems equally strong as we age. Intriguingly, aging of the thymus even in good health precedes aging of several other organs. The recent data from Dr. Dixit’s lab demonstrates that by 45 years of age in metabolically healthy individuals, greater than 75% of thymus is dysfunctional and is transformed into adipose tissue, which results in very low production of protective naïve T cells. This process manifests itself later in life with increased risk of cancers, infections, and vaccination failures in the elderly because the body is unable to cope with the prolonged lack of naïve T cells. Therefore, Dr. Dixit and his collaborators are aggressively pursuing research to address the causes of excessive lipogenesis in thymus in an effort to enhance the production of naïve T cells in the elderly and extend the healthy life span. The emerging evidence suggests that the disruption of specific mechanisms may prevent the decline of immune function.

**Inflammation:** It has been established that the circulating and tissue levels of pro-inflammatory cytokines are elevated in obesity and aging. This chronic inflammation is known to trigger several diseases like diabetes, heart disease, dementia, and cancers. Therefore, the overall goal of Dr. Dixit’s research in this area is to discover the endogenous “danger signals” or “inducers” recognized by specific immune “sensors” that regulate the production of inflammation mediators. This laboratory is among the first to discover that the NLRP3 inflammasome is an important molecular sensor and regulator of inflammation in obesity. Dr. Dixit’s research team has shown that blocking the NLRP3 inflammasome can prevent insulin resistance and type 2 diabetes in experimental animals. These findings were recently published in a leading biomedical journal, *Nature Medicine*. In addition, these findings were highlighted in editorial commentaries in several high-impact journals including *Nature Medicine, Nature Immunology, Cell Research, and Circulation Research*, which suggested that additional research in humans related to the Dixit lab’s discovery may lead to the development of drugs against obesity-related diseases.

Research in this laboratory is supported by grants from the National Institutes of Health and the Coypu Foundation.

**Histology of pancreas showing that in advanced obesity, pancreatic islets that produce insulin undergo inflammation-induced fibrosis (sky blue color as indicator of fibrosis, left-hand panels). Right-hand panels show that blocking the NLRP3 inflammasome can prevent obesity-induced damage to pancreas and protect against diabetes.**
FOCUS: The goal of this laboratory is to understand the metabolic pathways altered in obesity by certain infections.

The primary interest of the Infection and Obesity Laboratory is to discover effective strategies to prevent or treat obesity and its related comorbidities. A more complete understanding of the varied etiological factors contributing to the human obesity epidemic may lead to specific treatments and better management of this important disease. In this regard, if a subset of obesity is caused by certain infections, the strategies required for its cause-specific prevention and treatment may differ considerably from the currently available conventional approaches.

In the past two decades, 10 obesity-promoting pathogens have been described, including our reports of the first human virus, adenovirus type 36 (Ad36). The following is a description of past discoveries, as well as current objectives and research directions.

Ad36 increases adiposity: We showed that Ad36 causes obesity in experimentally infected chickens, mice, rats, and nonhuman primates and reduces serum cholesterol and triglycerides. In humans, natural Ad36 infection is associated with obesity and relative hypolipidemia.

Ad36 improves glycemic control: In addition to increasing adiposity, Ad36 robustly improves glycemic control in experimentally infected nonobese as well as diabetic animals and reduces lipid accumulation in their livers. Humans who are naturally infected with Ad36 have significantly better glycemic control compared to uninfected individuals.

E4orf1 protein of Ad36 identified as the candidate: Extensive studies conducted using animal models, as well as animal or human cells and tissues, indicate that the E4orf1 protein of Ad36 is necessary and sufficient to increase adiposity and to improve glucose disposal.

Objectives: Ad36 and adiposity

i. To determine whether Ad36 contributes to obesity in human adults and children

ii. To develop a vaccine to prevent Ad36-induced obesity

Rationale: Although Ad36 is associated with an improved lipid and glycemic profile in humans, increased adiposity can have several adverse health effects. Hence, determining the causative role of Ad36 in human obesity and developing preventive measures are important.

Objectives: Ad36 & glycemic control

To develop new therapies based on the action of E4orf1 protein:

i. To treat diabetes (U.S. patent obtained)

ii. To reduce accumulation of liver fat in conditions such as nonalcoholic fatty liver disease (patent pending)

Rationale: The beneficial properties of Ad36 may be harnessed to improve glycemic control. However, infection with Ad36 is impractical as a treatment. Instead, we are developing the use of its E4orf1 protein as a therapeutic agent.

Additional implications: (a) Investigation of the mechanism of action of E4orf1 is revealing new modulators of cell signaling with broader interest in the obesity and diabetes field. (b) Studies with Ad36 are providing a template to determine the role of other candidate microbes in human obesity and metabolism.

Research in this laboratory is funded by grants from the Federal Emergency Management Agency, Vital Health Initiatives, LLC, the Mathile Institute for the Advancement of Human Nutrition, and the American Egg Board.
**FOCUS:** This laboratory seeks to understand how brain inflammation is caused by disease and metabolic dysfunction and how such inflammation disrupts brain function.

Dr. Bruce-Keller has over 20 years of experience in the study of inflammation in brain injury, neurodegeneration, and cognitive impairment. In that time, she has developed numerous techniques to manipulate and measure redox signaling in cultured cells, as well as expertise in the analysis of animal behavior and in the design and implementation of novel cell type-specific and inducible transgenic animal models. These tools are all put to use to understand how inflammation initiates neurodegeneration and cognitive impairment in diseases such as Alzheimer’s disease (AD) and neuroAIDS, as well as in models of metabolic syndrome, diabetes, and diet-induced obesity.

A large grant from the National Institutes of Health (NIH) is funding AD research at Pennington Biomedical in collaboration with investigators at the University of Kentucky. The objectives of this grant are to understand the mechanisms of amyloid pathology in cultured cells, in transgenic AD mice, and in human AD patients. PROJ 4 (“Aβ and NOX in MCI and AD”) is focused on delineating the role of an enzyme called NADPH oxidase (NOX), which produces both oxidative stress and inflammation, in mediating brain injury and dysfunction in AD. The figure shows NOX-positive neurons (black) in close proximity to amyloid plaques (red).

Dr. Bruce-Keller has recently moved this research into the clinical arena. She is working with the Institute for Dementia Research and Prevention (IDRP) at Pennington Biomedical, which was established in 2008 to spearhead cutting-edge brain aging and dementia research on the roles of lifestyle risk factors such as metabolism and nutrition. The IDRP now has a longitudinal registry of >1,600 individuals, with more than 97% returning for annual screenings. Several research projects designed to test novel interventions for dementia have been developed recently based on information gained from this patient registry. Indeed, these clinical studies have fostered extensive collaboration between IDRP faculty and clinical departments at the LSU Health Sciences Center. This includes the development of a research project on the role of insulin resistance in age-related frailty in HIV patients, currently under review at the National Institutes of Health (NIH).

Research in this laboratory is supported by funds from the NIH.

**Inflammation and Neurodegeneration Laboratory**

Annadora Bruce-Keller, Ph.D.
Associate Professor

**Faculty:**
Annadora Bruce-Keller, Ph.D.

**Research Team:**
Sunita Gupta, M.S.; Alecia G. Knight, M.S.; Jennifer Pepping

NADPH oxidase (NOX) in Alzheimer’s disease (AD). Histological sections were prepared from formalin-fixed tissues derived from human AD brain, then processed to identify NOX and senile plaques (dense amyloid deposits). Images suggest that NOX-positive neurons (black) are in close proximity to amyloid plaques (red) and that NOX may be important in mediating neuronal and cognitive dysfunction in AD.
FOCUS: The primary mission of our laboratory is to study the cellular mechanisms operative in insulin-sensitive tissues that contribute to the development of insulin resistance on a whole-body level in humans. In addition, our goal is to evaluate phytochemicals that may prove valuable in addressing the underlying pathophysiological parameters contributing to obesity, metabolic syndrome, and type 2 diabetes.

One of the most desirable treatment goals for patients with type 2 diabetes is to increase insulin sensitivity in vivo. Caloric restriction and exercise greatly improve insulin resistance, but it is difficult to maintain these long-term lifestyle changes. Therefore, designing strategies to improve insulin resistance by pharmacologic or nutritional supplementation represents a very attractive approach to the treatment of type 2 diabetes.

Our lab has been evaluating dietary interventions that include altering the intake of trace minerals, in addition to evaluating the effect on specific phytochemicals. Our collective work to date with the trace mineral chromium (Cr) has demonstrated that this mineral may enhance insulin action in vivo and has identified a specific phenotype in humans that is responsive to Cr supplementation. Specifically, we have demonstrated that subject phenotype, not Cr status, determines clinical response. We have provided evidence that Cr may enhance insulin receptor signaling in skeletal muscle and that Cr’s effect on insulin action at the whole-body level is related to enhanced insulin sensitivity in muscle, and not secondary to enhanced hepatic glucose production. In pursuit of mechanisms for this effect, we have demonstrated that Cr reduces intracellular lipid content in human skeletal muscle and liver and that Cr modulates negative regulators of insulin receptor signaling (protein tyrosine phosphatases, i.e., PTPases) in skeletal muscle in preclinical studies.

Thus, the combined observations that myocellular lipids and PTPases are modulated by Cr provide a strong rationale for exploring the cellular mechanisms linking Cr’s actions on lipid metabolism and signaling molecules to Cr’s overall beneficial effect on carbohydrate metabolism in humans as proposed. Thus, the lab’s current focus is to precisely define the mechanism by which Cr modulates lipid metabolism and insulin receptor signaling in muscle as the precise mechanism of action for Cr.

Our lab, as part of Pennington Biomedical’s National Institutes of Health (NIH)-funded Center for Research on Botanicals and Metabolic Syndrome, is also active in the investigation of botanical supplements on insulin resistance and other aspects of metabolic syndrome. In the initial funding cycle, we evaluated an extract of Artemisia dracunculus L. (Russian tarragon) for its ability to enhance insulin action. This botanical was originally identified from a screening of extracts for hypoglycemic activity in mice as the most promising candidate for the development of a nutritional supplement to improve insulin resistance in human subjects. We demonstrated that a well-characterized extract of A. dracunculus L. (called PMI 5011) regulates insulin receptor signaling at the cellular level and increases insulin sensitivity in vivo, and we have identified novel proteins and several intracellular pathways modulated by the extract. Specifically, our studies have demonstrated that the mechanism by which A. dracunculus L. regulates insulin action at the cellular level may be secondary to modulating negative regulators of insulin receptor signaling, i.e., PTPases, and reducing lipid intermediates in target tissues. In addition, we provided evidence that dietary supplementation with A. dracunculus L. increases whole-body insulin action in early-phase human studies.

Our investigations have expanded in two major areas. First, based on the success of our center’s botanical screening efforts to identify other promising botanical leads, we are including other selected members of the Artemisia genus representing both closely and distantly related species since it remains unclear how their diverse biochemical and taxonomical characteristics are related. Second, with use of state-of-the-art metabolomic profiling and proteomic techniques, we have expanded investigations to provide in-depth and comprehensive analysis of the cellular mechanisms of action operative in vivo by which extracts of Artemisia sp. improve insulin sensitivity. Thus, the primary objective of our current projects is to evaluate the combined effects of selected Artemisia sp. extracts to enhance and modify cellular lipid metabolism while simultaneously modulating negative regulators of insulin receptor signaling, i.e., PTPases, in skeletal muscle and liver as complementary components of the mechanism by which these botanicals enhance insulin sensitivity and attenuate the progression to metabolic syndrome.

Research in this laboratory is supported by grants from the NIH and the Coypu Foundation.
FOCUS: The goal of this laboratory is to investigate novel leptin target neurons and their impact on the regulation of food intake, energy expenditure, and body weight.

Leptin, a hormone produced from white adipose tissue, is a key regulator of energy balance, as demonstrated by severe hyperphagia and morbid obesity in humans or rodents null for leptin or its receptor (LepRb).

However, most obese patients have already high leptin levels and are insensitive to leptin therapy. Conversely, body weight loss obtained from dieting evokes energy-saving mechanisms and increased hunger sensation because of falling leptin levels.

In order to enable pharmacological interventions for these inappropriate leptin actions, it is important to explore the function of distinct LepRb-expressing neuronal populations and dissect their specific role in overall leptin action.

The majority of LepRb-expressing neurons have not been studied, and their relative contribution to overall leptin action is unknown. For example, the dorsomedial and lateral hypothalamus are known to regulate feeding circuits and energy expenditure and contain large populations of LepRb-expressing neurons, thus suggesting an important contribution of these LepRb populations to regulation of energy homeostasis.

We recently discovered a subpopulation of LepRb-expressing neurons in the dorsomedial hypothalamus that mediates thermoregulatory leptin action via the brown adipose tissue (Figure 1). Brown adipose tissue is able to generate heat and increase energy expenditure, features that should promote weight loss. Indeed, we found that leptin action in the dorsomedial hypothalamus is sufficient to reduce body weight without affecting food intake.

We are currently exploring the neuronal circuits and involved mechanisms that mediate thermoregulatory leptin action and associated body weight regulation.

We further characterized another population of LepRb neurons by their co-expression of the neuropeptide galanin (Gal) (Figure 2). Gal-LepRb neurons are found in the dorsomedial and lateral hypothalamus and the brainstem. We generated mice with genetic LepRb deletion in galanin neurons to demonstrate that Gal-LepRb neurons regulate energy expenditure and feeding behavior.

We use several molecular genetics tools and behavioral tests to investigate the specific subsets of LepRb-expressing neurons. These include: (a) neuron-specific perturbation of LepRb neurons (e.g., neuronal stimulation, neuronal inhibition, LepRb deletion) to determine the contribution of these LepRb populations to regulation of energy homeostasis and feeding behavior,(b) visualization of specific LepRb subpopulations in reporter mouse models to identify regulatory mechanisms of LepRb-expressing neurons, and (c) virus-driven neuron-specific tracing to identify the connecting neuron circuits of these specific LepRb populations.

Research in this laboratory is supported by the National Institutes of Health, the Center of Biomedical Research Excellence (COBRE), and the Nutrition and Obesity Research Center, as well as the National Science Foundation and Louisiana Board of Reagents (Louisiana Experimental Program to Stimulate Competitive Research [EPSCoR], Supervised Undergraduate Research Experience [SURE]).
FOCUS: The goal of this laboratory is to understand the pathogenesis of and identify new therapeutic targets for the complications of diabetes, especially neuropathy.

We previously demonstrated an important role for the 12/15-lipoxygenase (12/15-LO) in nerve conduction deficit, small sensory nerve fiber dysfunction, and axonal atrophy of large myelinated fibers in diabetic peripheral neuropathy (DPN). Our new studies in streptozotocin-diabetic C57B16/J mice suggest that activation of the 12/15-LO pathway in DPN results from increased sorbitol pathway activity and is inhibited by the aldose reductase inhibitor fidarestat. We also found that increased phosphorylation of p38 MAPK, ERK, and SAPK/JNK is clearly manifest in ciatic nerve of diabetic mice. 12/15-LO inhibition with CDC or 12/15-LO gene deficiency counteracted diabetes-associated p38 MAPK and ERK, but not SAPK/JNK, phosphorylation. Similar findings were obtained in high glucose-exposed cultured human Schwann cells, which suggests clinical relevance of our work.

In another project, we found that overexpression and activation of Na+/H+ -exchanger-1 (NHE-1), which plays a key role in control of intracellular pH, contribute to DPN in both type 1 and type 2 diabetes. Our experiments were performed in streptozotocin-diabetic rats, ZDF rats, and leptin-deficient (ob/ob) mice, in which we used the specific inhibitor of NHE-1 cariporide, as well as in NHE-1+/− mice. We found that this mechanism leads to nerve conduction slowing, neurovascular dysfunction, small sensory fiber neuropathy, and diabetic neuropathic pain. We also found that upregulation of the NHE-1 plays an important role in the intraepidermal nerve fiber loss, a marker of small sensory nerve fiber degeneration, and that NHE-1 inhibition with cariporide at least partially restored this variable (i.e., caused small sensory nerve fiber regeneration). Our futher studies revealed that NHE-1 upregulation contributes to DPN through advanced glycation end-product (AGE) formation and oxidative-nitrosative stress. Cariporide treatment reduced concentrations of methylglyoxal-derived AGE, 4-hydroxynonenal adducts, and nitrotyrosine in sciatic nerve and spinal cord, as well as 4-hydroxynonenal adduct and nitrotyrosine immunoreactivities in dorsal root ganglion neurons. In in vitro experiments, high glucose-exposed cultured human Schwann cells transfected with NHE-1 si-RNA displayed reduced oxidative stress, compared with non-transfected or non-silencing si-RNA-transfected cells (see figure).

The Mechanisms of Diabetes Complications Laboratory is also involved in evaluating the roles of peroxynitrite and protein nitration, as well as endoplasmic reticulum stress, in diabetic neuropathy and other diabetic complications.

Research in this laboratory is supported by grants from the American Diabetes Association and the National Institutes of Health.
FOCUS: Our laboratory has a general interest in the neural mechanisms of nutrient detection, control of appetite, regulation of energy balance, and their involvement in the development of obesity, type 2 diabetes, and the metabolic syndrome. We are particularly interested in how metabolic signals and the hypothalamic regulatory circuits interact with the cognitive, rewarding, and emotional brain, representing the main interface with the increasingly obesogenic environment.

In one project, we are looking at the role of the brain in the overpowering of homeostatic control systems by increased food availability, palatability, and energy density associated with the modern environment and lifestyle. We are testing the competing hypotheses that (1) predisposing differences in the brain reward system, (2) repeated exposure to palatable, high-energy-dense foods, (3) secondary effects of the obese state, or (4) combinations of these mechanisms cause alterations in food reward behavior, increased food intake, and obesity. We are interested in the neural pathways and behavioral manifestation of potential food addiction. Using chemical manipulation of the nucleus accumbens in rats and mice, a brain area recognized for its crucial role in reward-driven behavior, we have demonstrated that anatomical projections from parts of this nucleus to hypothalamic peptidergic neurons known to be involved in the regulation of appetite and energy balance may play an important role in the reward-driven overriding of metabolic controls of food intake. Specifically, orexin neurons located in the lateral hypothalamus and their projections to the ventral tegmental area, a midbrain nucleus harboring dopamine neurons that give rise to the mesolimbic dopamine system, seem to be necessary for feeding effects induced in the nucleus accumbens. The results of these studies are expected to generate new behavioral and pharmaceutical strategies to lessen the impact of the obesogenic environment on appetitive behavior.

In another project, we have started identifying the powerful hormonal and neural mechanisms responsible for reversing obesity and type 2 diabetes after bariatric surgeries, in particular Roux-en-Y gastric bypass and vertical sleeve gastrectomy surgeries. We are testing the hypothesis that the sustained weight loss after surgery is due to the action of altered circulating gut hormones on various brain areas involved in the homeostatic regulatory and hedonic aspects of food intake and energy balance controls. We are also testing the role of neural, particularly vagal sensory, input to the brain in bringing about the beneficial effects. We are testing the possible role of vagal and spinal mechano- and chemosensors in the gastrointestinal tract, hepatic portal vein, and liver in changing neural functions involved in energy intake, meal patterns, and food choice, and we are assessing structural and functional changes in the gut. Knowing “how bariatric surgeries work” should lead to “knife-less” pharmacological and behavioral approaches that are more effective than currently available drugs.

Research in this laboratory is supported by grants from the National Institutes of Health and by private funding from the pharmaceutical industry.
The goal of this laboratory is to investigate neural mechanisms that control food intake in response to changes in nutritional status.

The regulation of food intake is one of the most essential regulatory phenomena in biology. Free-feeding organisms must balance their need for multiple macro- and micronutrients against the uncertainties of food availability and quality. How is this complicated task accomplished? The Neurosignaling Laboratory focuses on the mechanisms whereby the brain detects changes in nutritional status and uses this information to regulate food intake and selection. One area of focus is the neuronal circuits and signaling molecules utilized by hormones such as leptin and insulin. Our data demonstrate that lean animals voluntarily reduce their food intake and rapidly lose weight following a period of forced weight gain. In other words, lean animals seem to resist excess weight gain. Our data indicate that this adaptive reduction in food intake is impaired in animals that lack leptin signaling, suggesting that intact leptin signaling is required for an effective defense against weight gain. Considering that obesity is associated with a loss of brain leptin signaling, these observations suggest that the loss of leptin action may contribute to weight gain and obesity.

In addition to the regulation of energy intake, a large body of literature supports a specific regulation of protein intake. High-protein diets suppress food intake while low-protein diets increase food intake, and animals will voluntarily self-select between multiple diets to ensure they consume an adequate amount of protein. How they balance protein intake to meet protein need is currently unclear. Our recent data indicate that the amino acid leucine acts in the brain to suppress food intake and that it does so in part by influencing the same populations of brain neurons that mediate the effects of leptin and other nutritional signals (see figure). These data indicate that leucine may be a key signal of protein, and in our current work, we are specifically testing whether leucine represents a physiological regulator of protein intake and selection. We are also interested in the relationship between protein intake and energy intake and whether alterations in dietary protein or the neural mechanisms that detect protein can be used to protect against obesity.

Research in this laboratory is supported by grants from the National Institutes of Health and by the Pennington Medical Foundation.
**FOCUS:** The goal of this laboratory is to investigate the underlying signaling mechanisms that link dietary methionine restriction to enhancement of insulin sensitivity.

**Current Investigations**

*Dietary Methionine Restriction Enhances Insulin Sensitivity.* Obesity is the product of a chronic positive energy balance, and accumulation of excess adipose tissue is strongly linked to disordered lipid metabolism, development of insulin resistance, and a cluster of comorbidities called metabolic syndrome. Dietary methionine restriction produces a highly integrated series of physiological responses that reduce adiposity, improve biomarkers of metabolic health, and enhance insulin sensitivity. We recently showed that dietary methionine restriction increased fat oxidation and reduced hepatic lipid content in humans with metabolic syndrome. Our recent studies make a compelling case that dietary methionine restriction reduces adiposity through centrally mediated effects on energy balance and enhances insulin sensitivity through direct effects in peripheral tissues to reduce circulating lipids and amplify tissue-specific responses to insulin. The net result of these coordinated responses is a profound enhancement of insulin sensitivity.

The most significant unanswered questions being addressed in the laboratory are: (a) How and where is the reduction in methionine sensed? (b) Are the beneficial effects of methionine restriction specific to methionine or would restriction of other essential amino acids be equally beneficial? (c) Will dietary methionine restriction reverse preexisting insulin resistance of different etiologies?

*Research in this lab is supported by grants from the National Institutes of Health and American Diabetes Association.*
FOCUS: The goal of this laboratory is to identify and characterize the changes within the central nervous system that contribute to the development of diet-induced obesity.

Feeding behavior and energy homeostasis are organized in a complex, hierarchical fashion in the central nervous system (CNS). Information about metabolic status is sensed via a variety of hormonal and neural signals. The hypothalamus is an important integrator of these signals. The arcuate nucleus of the hypothalamus is of particular interest. Neural circuits within the arcuate nucleus contain both orexigenic and anorexic peptides that have been shown to play an important role in energy homeostasis.

Data from our laboratory have demonstrated that within the arcuate nucleus there is a population of mu opioid receptors (MOR). Activation of this receptor population makes animals increase their food intake and selectively change their dietary preference to a diet high in fat, independent of their original dietary preference. Our laboratory is interested in this receptor population because: (1) when we make animals obese, the density of MOR is significantly increased in the arcuate nucleus; and (2) MOR are colocalized on neurons within the arcuate nucleus that contain the orexigenic (neuropeptide Y, agouti-related protein) and anorexic (pro-opiomelanocortin) peptides that play a role in maintaining energy homeostasis. The possibility exists that changes in this receptor population are contributing to the overeating and increased fat preference observed in obese animals.

The studies in our laboratory are designed to determine: (1) what causes mu opioid receptors to increase in obese animals; (2) potential mechanisms by which mu opioid receptors make animals hyperphagic and increase fat preference; and (3) whether increased mu opioid receptors potentiate the development of obesity. The results obtained from these studies can provide a potential target to attenuate the overeating and increased fat preference observed in humans who are obese.

Research in this laboratory is supported by a grant from the National Institute of Diabetes, Digestive and Kidney Diseases.
BASIC RESEARCH

FOCUS: The goal of this laboratory is to discover and develop nutraceutical and pharmacological interventions that retard aging and age-related disease and promote late-life brain and behavioral function.

Aging is regulated through multiple interacting genetic and environmental factors, with nutrition playing a major role. As our primary focus, we have been investigating the beneficial effects of low-calorie diets on aging, longevity, and function. In various rodent models, nutritious diets with calories reduced 30% to 50% below normal levels markedly increase lifespan, reduce age-related disease and pathology, enhance stress responses, and improve function.

Although studies conducted in humans have indicated that this calorie restriction (CR) might provide health benefits paralleling those observed in animals, such stringent diets may be difficult to maintain. To address this challenge, we have initiated research to evaluate pharmaceuticals and nutraceuticals that can stimulate cellular signaling pathways to invoke protective mechanisms activated by CR. In principle, these “CR mimetics” would provide the benefits of CR without requiring dieting. We have been exploring several compounds designed to inhibit glucose metabolism in order to induce cellular responses observed in CR. As our current focus, we are examining inhibitors of hexokinase, the first step in glucose metabolism. The lead compound is an avocado extract containing high concentrations of the sugar mannoheptulose (MH). Addition of MH to diets improves insulin function and protection against unhealthy consequences of high-fat diets, similar to the effects of CR, including improved motor and cognitive function. We are currently extending our findings of MH to several other rodent models, including transgenic models of Alzheimer’s disease, in which we have shown that CR can attenuate pathogenesis.

In other nutritional studies conducted in collaboration with Dr. Joseph Francis, Associate Professor at the LSU School of Veterinary Medicine, we are examining the beneficial effects of a diet supplemented with blueberries (BB: 2% by weight) in rodent models of hypertension. When the BB diet was fed for 6 to 12 weeks, we noted greatly attenuated pathophysiology in different models by decreased production of oxygen radicals and upregulated antioxidant systems. Paradoxically, when we examined the responses of animals on the BB diet for only 2 days, we noted increased oxidative stress. “Hormesis” is the term used to describe this short-term response to stress that increases long-term protection, and it is a growing research field proposed to explain the effects of CR and exercise, as well as many botanical products. Currently, we are attempting to map the kinetics of the hormetic response and identify the cellular signaling pathways required to provide long-term protection. In addition to nutritional interventions, we are wrapping up an investigation of the dietary supplement Juvenon, containing acetyl-L-carnitine and alpha-lipoic acid, by exploring its beneficial effects on memory and brain glucose metabolism.

Research in this laboratory is supported by grants from the Glenn Foundation for Medical Research, the Alzheimer’s Association, the Wild Blueberry Association of North America, Juvenon, Inc., the National Center for Complementary and Alternative Medicine, and the National Institutes of Health sponsored Nutrition and Obesity Research Center (NORC).
Diabetes mellitus is a chronic metabolic condition, and oxidative stress has often been implicated in the pathogenesis of the disease. Free radical production has been demonstrated in both type 1 and type 2 diabetes and possibly contributes to the development of complications through diverse mechanisms. However, the detailed mechanisms responsible for the pathogenesis of certain diabetic complications, metabolic imbalance and insulin resistance, are still largely unknown.

The Oxidative Stress and Disease Laboratory focuses on the exact free radical mechanisms that can play a role in the pathogenesis of the above-mentioned conditions, ultimately contributing to insulin resistance or leading to tissue damage, metabolic imbalance, and complications.

Electron spin resonance (ESR) spectroscopy has been the gold standard to characterize these free radical processes, as it detects the radicals or radical adducts directly, not through their fingerprint markers. Through the use of in vivo electron spin resonance (EPR) methodologies and spin trapping, we are able to directly and specifically detect increased free radical production in tissues, body fluids, and cells. In addition, with the combination of EPR and immunological techniques (e.g., confocal microscopy, immunohistochemistry), a detailed search for the sources and the localization of reactive intermediates and their targets (lipids or proteins) can be achieved. The uniqueness of EPR spectroscopy combined with in vivo spin trapping allows us to identify free radical metabolites and the participating primary reactive species unambiguously, while the sensitivity of a novel immuno-spin trapping approach makes the identification of the targets and their localization within the cell possible.

Currently, we are interested in (a) how the accumulation of toxic lipid metabolites interferes with the insulin receptor signaling pathway during hyperglycemia, hypertension, and heart failure and participates in the development of insulin resistance; (b) how renal mitochondrial oxidative stress and lipid overload relate to redox imbalance and pathology in obesity; and (c) how lipotoxicity (albumin-bound fatty acids, ceramides, etc.) affects bioenergetics and redox balance in various kidney cells such as podocytes or proximal tubular cells.

Research in this laboratory is funded by the Pennington Foundation, by a grant from the National Institutes of Health, by a pilot grant from a National Institute of Diabetes and Digestive and Kidney Diseases-supported Nutrition and Obesity Research Center program project, and by a Louisiana Board of Regents Supervised Undergraduate Research Experiences (SURE) Award.
Focus: Circadian rhythm plays a significant role in numerous biological processes, and the goal of my laboratory is to understand how aberrant circadian rhythm contributes to the development of metabolic syndrome in fetuses exposed to protein deficiency in utero.

Type 2 diabetes (T2D) is one of the most widely acknowledged disease states known in the Western World. Maternal Nutrition is an important part of a healthy lifespan, with malnutrition in utero resulting in offspring that have increased risk for developing cardiovascular disease and T2D later in life. Work in my laboratory seeks to identify the molecular targets that influence circadian rhythm in utero, and identify the role of aberrant circadian rhythm in modulating the risk for T2D in offspring from malnourished mothers.

Data from our laboratory using a rodent model of maternal malnutrition suggest that protein deficiency in utero results in offspring that have an altered circadian rhythm profile and increased risk for metabolic disease. Additionally, one specific circadian rhythm gene (Rev-erba), has been identified by our laboratory as the most likely candidate for increased T2D risk following maternal malnutrition. Rev-erba is linked to metabolism through the regulation of a number of downstream genes involved in inflammation, lipogenesis and mitochondrial function. By targeting Rev-erba with standard drugs we hope to prevent the T2D observed in the offspring of malnourished mothers.

Research in this laboratory is funded by grants from the American Diabetes Association, and NIH/NIDDK Nutrition Obesity Research Center.
**FOCUS:** The goal of this laboratory is the development and application of analytical and biophysical techniques to study disease biology.

**Amyloid disease biology.** Protein aggregation and abnormal tissue deposition of normally soluble proteins are associated with >25 amyloid-associated diseases (e.g., Alzheimer’s disease, Parkinson’s disease, diabetes). Oligomeric aggregates that develop during the course of amyloid formation have been implicated in disease pathogenesis and are considered to be cytotoxic. Amyloid aggregates are heterogenous mixtures of oligomers *in vitro*, but the specific structures of cytotoxic species, their relationship to amyloid formation, and the mechanism of toxicity are unknown. Each of the different aggregate species formed during amyloid formation can have unique chemical and physical properties providing a basis for differential toxicity. A single technique cannot resolve each of the different aggregate species; thus, we are utilizing an array of technologies to achieve complete understanding of the aggregation reaction.

We have developed mass spectrometry-based approaches to characterize the structure of amyloid fibrils, oligomers, and monomers. These methods are excellent tools to follow aggregation kinetics and provide insight into the extent of secondary structure; however, these methods do not allow concentration or manipulation of various aggregate structures within the amyloid mixture. Therefore, we are now developing and applying capillary electrophoresis (CE) and microfluidics-based separation methods (in collaboration with researchers at LSU and Arizona State University) that allow rapid and gentle interrogation of populations of aggregate species within the mixture (see figure). CE separates aggregates of various sizes and shapes, and online detection with absorbance, laser-induced fluorescence, laser-light scattering, and laser-induced fluorescence anisotropy provides further structural information. These techniques are broadly applicable to various diseases associated with protein misfolding and aggregation.

**Proteomic and metabolomic assessment for botanicals and metabolic syndrome.**

Insulin resistance is the major pathophysiologic parameter that defines metabolic syndrome and type 2 diabetes. Insulin resistance is a pre-diabetic condition, as it typically presents 5 to 10 years prior to the onset and diagnosis of type 2 diabetes and is a contributing factor in the development of cardiovascular diseases. A variety of botanical treatments are postulated to modulate insulin action; however, the exact mechanism by which these extracts modify glucose and insulin levels is unclear. In collaboration with the Center for Research on Botanicals and Metabolic Syndrome at Pennington Biomedical, funded by the National Institutes of Health (NIH), we are evaluating mechanisms by which a well-characterized ethanolic extract of *Artemisia dracunculus* L., termed PMI-5011, improves insulin action. Using global proteomics technologies, we have demonstrated that modulation of inflammatory pathways and GLUT4 transport are the central factors defining the cellular mechanism by which PMI-5011 enhances insulin sensitivity in states of metabolic dysregulation. We are now utilizing mass spectrometry-based targeted proteomics and metabolomics approaches to test these pathways *in vitro* using primary human skeletal muscle culture and *in vivo* using a mouse model of insulin resistance. These studies are providing essential data to understand the mechanism of action of botanical extracts in improving insulin sensitivity at the molecular level.

*Research in this laboratory is supported by grants from the LSU Board of Regents, the NIH, and the Pennington Medical Foundation.*
FOCUS: The goal of this laboratory is to understand the relationship between diabetes, nutrition, birth defects, and gene expression in the embryo.

Diabetes is a major health concern in the United States and worldwide. Both type 1 and type 2 diabetes not only severely compromise the health of the afflicted individual, but diabetes also affects embryonic development: maternal diabetes during pregnancy can cause severe birth defects. Our goal is to understand how maternal diabetes affects the embryo, with a focus on the early developing nervous system and the pathogenesis of neural tube defects.

The hypothesis for this research project is that maternal diabetes during pregnancy alters gene expression in the embryo. We have now identified more than 2000 genes that are altered in their expression in maternal diabetes-exposed embryos. At present, there are approximately 400 genes that are known to play a role in neural tube defects; one-third of these neural tube defect genes are deregulated by maternal diabetes. This demonstrates that maternal diabetes does not affect all neural tube defect genes across the board and implies that the pathology of diabetes-induced neural tube defects may include more than one molecular etiology.

Birth defects such as neural tube defects do not arise in every individual offspring of a diabetic mother. This fact is most obvious in the mouse model: despite sharing the exposure to the diabetic milieu of the dam, only a fraction of the litter is afflicted with the birth defect. Such a pattern matches the classical definition of phenotypes of incomplete penetrance, and explanations for these phenotypes require an element of biological variation.

Our studies now suggest that we have identified a molecular correlate for this variable element: we found that maternal diabetes not only causes changes in the expression levels of specific genes but also leads to a general increase in the variability of gene expression levels. We posit that maternal diabetes leads to a loss of “regulatory precision” in the embryo and suggest that system properties of gene regulation, such as the embryonic epigenome, are the principal target of maternal diabetes.

We have observed this increase in variability of gene expression in models with both chemical and genetic induction of diabetes. In fact, increased variability could be used as a diagnostic tool to distinguish embryos from diabetic pregnancies with or without a neural tube defect: while indistinguishable based on expression levels, embryos with neural tube defects show very different gene variability patterns than embryos without a defect (see figure). We have now begun to characterize these hypervariable genes based on their role in birth defect etiology and to pursue the question of how maternal diabetes leads to the degraded regulatory precision that is so detrimental to the developing embryo.

Research in this laboratory is supported by the National Institutes of Health.

Figure 1: An early embryo with spina bifida.

Figure 2: Graphical representation of a bioinformatics analysis of gene expression variability in embryos from diabetic pregnancies with (NTD) and without (no NTD) a neural tube defect. The color intensity signifies the magnitude of deviation from the mean, with yellow depicting higher and blue representing lower than the mean. Embryos with neural tube defects cluster together, as shown by the brighter colors.
FOCUS: The goal of this laboratory is to further the characterization and understanding of adipose tissue and adult stem cells for circadian, metabolic, and regenerative medical studies.

The Stem Cell Biology Laboratory maintains both a clinical translational and basic science focus in its research efforts. The laboratory’s work on adult stromal/stem cells from adipose tissue and bone marrow has potential tissue-engineering and regenerative medical applications. The laboratory continues to develop new approaches to the isolation, characterization, differentiation, and cryopreservation of stromal/stem cells using both in vitro and in vivo models. This includes collaborations with investigators at the LSU School of Veterinary Medicine and the LSU Department of Mechanical Engineering, as well as national and international centers including the following universities: Columbia, Johns Hopkins, Harvard, MIT, Memorial Sloan-Kettering Cancer Center, Tulane, and Tufts. The laboratory is actively pursuing the role of circadian biological mechanisms in regulating the metabolism of adipose tissue and bone. These studies involve transcriptomics and molecular approaches at the stromal/stem cell and tissue levels. The outcomes have potential implications for the use of chronotherapy for the treatment of obesity, osteoporosis, and related metabolic disorders.

Research in this laboratory is funded by grant(s) from the National Institutes of Health, the Maryland Stem Cell Initiative, and the Pennington Biomedical Research Foundation.
FOCUS: The goal of this laboratory is to identify the genetic factors contributing to macronutrient and total energy intakes.

Similar to people, mice vary widely in the amount of fat and carbohydrate they choose to eat when selecting among various food choices. Finding the influential DNA sequence variation that is responsible for these traits or phenotypes in animals will help us understand how genetic variation contributes to food preferences in humans. Toward this aim, our laboratory identified the first quantitative trait loci (QTL) for fat, carbohydrate, and total calorie intake in mammals, thus providing strong evidence for multiple genetic controls on food intake. A QTL is a region of DNA associated with a physical trait or phenotype, measured on a quantitative scale. Current efforts are focused on a region of mouse chromosome (Chr) 17 that encompasses the QTL for increased carbohydrate and total calorie intake. To isolate this chromosomal region of interest, we developed a congenic strain possessing the genome of one strain (recipient) and a small segment of Chr 17 DNA from a second (donor) strain. This congenic strain retained the phenotypic effects associated with the Chr 17 QTL and surprisingly showed that increased physical activity cosegregates with the food-intake traits.

To resolve the location of the QTL and identify the responsible genes, we carried out fine-structure genetic mapping in a congenic–by–recipient F2 cross using a high-density, custom SNP genotyping panel; data analysis is now under way using composite interval mapping. Positional candidate genes contained within the refined QTL region will be determined based on several criteria including bioinformatics analysis, functional annotation, differential gene expression between parental strains, and biological relevance.

Enzymes within fatty acid metabolic pathways may serve as pharmacological targets to treat the obesity epidemic, yet controversy exists over which aspect of fatty acid availability may alter food intake. Another project is focused on understanding how food preferences are affected by signals from fatty acid oxidation, using a mouse strain with a genetic inactivation of short-chain acyl-CoA dehydrogenase (Acads). Acads encodes the enzyme responsible for mitochondrial beta-oxidation of short-chain fatty acids. When offered a dietary choice, Acads-deficient mice shift food consumption away from fat and toward carbohydrate, demonstrating that the loss of a specific enzyme in the oxidation of fatty acids alters food choice. To better understand the molecular mediators associated with fatty acid oxidation and fat intake, we performed a microarray analysis of global gene expression in the brain of Acads−/− and Acads+/+ mice fed either a high-fat or low-fat diet. We found that the transcriptional responses of Acads-deficient mice to a high-fat diet mirror those of Acads+/+ control mice fed a low-fat diet. Ingenuity Pathway Analysis revealed the three top-scoring pathways most significantly modified by genotype or diet: oxidative phosphorylation, mitochondrial dysfunction, and CREB signaling in neurons. Together these findings suggest that Acads-deficient mice may be protected against the effects of a high-fat diet on gene expression in the brain. Follow-up studies on genes involved in energy-sensing pathways have pointed to cellular energy-sensing mechanisms as the putative link between fatty acid oxidation and eating behavior.

Research in this laboratory is supported by grants from the National Institutes of Health.
The goal of this laboratory is to prolong and improve the quality of life of cancer patients by developing effective treatments and methods to prevent the recurrence of cancer after treatments.

In previous studies, our team developed a new class of drugs (lytic peptide conjugates) that proved effective in targeting and destroying human cancer cells in tumors and in metastases in test mice. These conjugates of a hormone, such as luteinizing hormone-releasing hormone (LHRH), and a lytic peptide, such as Phor21, bind to hormone receptor molecules on the cancer cell membrane. They may be likened to guided missiles (the hormone) bearing warheads (the lytic peptide) that destroy the cell membrane. These drugs effectively target and destroy prostate, breast, ovarian, testicular, and pancreatic cancers in the nude mouse model. One of the LHRH-lytic peptides is now being tested in Phase 2 clinical trials.

**Current Project**

The efficacy of the LHRH-lytic peptide drugs is dependent on the number of LHRH receptors expressed on the cancer cell membrane. In a laboratory experiment, we noticed that adding one of the pituitary hormones that control reproduction in all animals (follicle stimulating hormone, FSH) to the culture medium increased expression of the gene that controls LHRH receptor expression in pancreatic cancer cells.

This observation led us to carry out an experiment to test the idea that FSH pretreatment before administration of the LHRH-lytic peptide (EP-100) in nude mice bearing human pancreatic cancer cell tumors would increase the number of LHRH receptors and result in a more effective treatment. As shown in the figure, this proved to be the case. When administered alone at each of two dose levels (0.02 and 0.2 mg/kg) to mice bearing PANC-1 human pancreatic tumors, the LHRH-lytic peptide (EP-100) caused significant decreases in tumor weights at necropsy. Pretreatment with FSH caused further decreases in tumor weights. In contrast, treatment with saline (vehicle) or FSH alone allowed continued tumor growth. These results are significant because no really effective treatments for pancreatic cancer are currently available.

Research in this laboratory is supported by grants from Esperance Pharmaceuticals, Inc., and the Pennington Family Foundation.
FOCUS: The goal of this laboratory is to understand how adipocyte formation and function is influenced by ubiquitin-proteasome regulation of protein stability and activity.

Obesity is associated with the development of metabolic syndrome, type 2 diabetes, and cardiovascular diseases such as hypertension. Adipocytes (fat cells) play a central role in the physiological consequences of the energy imbalance inherent to obesity. The formation of adipocytes depends on the peroxisome proliferator-activated receptor gamma (PPARγ), a protein that functions as the “master switch” in regulating the production of other proteins needed for lipid and carbohydrate metabolism in adipocytes. PPARγ is the cellular target of a commonly prescribed class of antidiabetic drugs, the thiazolidinediones (TZDs). These drugs alter PPARγ activity and stability, an indication that understanding the link between PPARγ activity and stability may offer new insights into how obesity contributes to type 2 diabetes.

The stability of most intracellular proteins, such as PPARγ, is determined by a complex set of enzymes called the ubiquitin-proteasome system. The ubiquitin-proteasome system is a highly conserved pathway responsible for the carefully timed destruction of proteins, making this pathway central to cellular functions. Our studies show that PPARγ activity is regulated by the ubiquitin-proteasome system in adipocytes. To understand this connection between PPARγ activity and degradation, we have used cellular and molecular approaches to dissect how PPARγ is recognized by components of the ubiquitin-proteasome pathway. Using these approaches, we found that the region of PPARγ responsible for binding TZDs is recognized by the ubiquitin-proteasome system, and that a functioning ubiquitin system is necessary for TZD-dependent regulation of PPARγ activity in adipocytes. To accomplish this task, we developed a novel high-throughput screening method based on RNA interference technology to identify a small set of ubiquitin system enzymes that alter PPARγ stability and activity in adipocytes. In our screen, we focused on the ubiquitin ligases because these enzymes are particularly attractive targets for drug development.

After screening over 225 ubiquitin ligases, we identified 5 ubiquitin ligases that alter PPARγ stability in adipocytes. Our studies are currently centered on one of the enzymes we identified, a protein called Siah2. In the past year, we learned that Siah2 is necessary for activation of PPARγ by TZDs, that Siah2 interacts with PPARγ in adipocytes, and that Siah2 affects insulin sensitivity in adipocytes. We also learned that Siah2 is necessary for forming adipocytes, lending support to the idea that Siah2 determines the activity of PPARγ in adipocytes. Taken together, our findings indicate Siah2 as an important component of adipocyte biology and strengthen the idea that the ubiquitin-proteasome system is a critical factor in understanding the link between obesity and metabolic disorders such as type 2 diabetes.

Research in this laboratory is supported by grants from the American Diabetes Association, the National Institutes of Health, and the Pennington Biomedical Center for Research on Botanicals and Metabolic Syndrome.
Opened in 1988, Pennington Biomedical now houses 52 laboratories that span the Center’s three programs - Basic Research, Clinical Research, and Population Science. The Center has nineteen Core Service laboratories and over $20 million in technologically advanced equipment.
At Pennington Biomedical Research Center, Clinical Research is a vital component of our enterprise. Our strategy to produce excellence in research results begins with support from the inception of the research question and continues through support for the analysis of results and publication. This is not a do-it-yourself model. In the 19 years since our first clinical study, we've developed a systematic approach to Clinical Research support. We provide peer-review services for every study proposal by assigning anonymous reviewers. Our Institutional Review Board provides online templates and processes research protocols in a timely manner. The Scheduling Committee assures that funding is in place for all of the 11 Core service providers and schedules the study so that we can maximize efficiency of our Inpatient and Outpatient Units. Our clinic assigns a study coordinator, and our Clinical Biostatistics and Data Management Core and Recruitment Core are engaged early in the launch of the study. We provide ongoing monitoring via our Record Library services. There are intranet applications to allow investigators to track participants and their data in real-time from investigators’ desktop computers. Our Biostatistics and Data Management Core is available to assist with analyses. There are online applications available to assure that all investigators are up to date for training in privacy and HIPAA compliance issues, in Good Clinical Practices, and in Human Subjects Protections. The overall approach at Pennington Biomedical is one of systematic and uniform processes and a commitment to the highest quality possible in the conduct of Clinical Research.

Since the inception of our first clinical studies in 1992, the strong infrastructure outlined above has resulted in an enviable record of completed research. As shown in the figure, this approach has resulted in more than 18,000 patients being enrolled in more than 400 studies.

Two major shifts in direction are upcoming for our Clinical Research operations. While we are now established in adult research operations in a new Clinical Research Building, renovations are under way for a new outpatient pediatrics wing. We plan to use this new wing to initiate a programmatic approach to childhood obesity. Another new direction will be reflected in closer ties to the Louisiana State University School of Medicine in New Orleans, as we build collaborative relationships and focus ever more on a broader range of disease states on which to focus our research efforts.

<table>
<thead>
<tr>
<th>Year</th>
<th># Telephone Contacts</th>
<th># Screening Visits</th>
<th>% Females</th>
<th>% Minority</th>
<th># Enrolled in Studies</th>
<th>% Females</th>
<th>% Minority</th>
<th>Studies Started</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>1962</td>
<td>771</td>
<td>67%</td>
<td>13%</td>
<td>255</td>
<td>61%</td>
<td>15%</td>
<td>5</td>
</tr>
<tr>
<td>1993</td>
<td>2543</td>
<td>1124</td>
<td>59%</td>
<td>20%</td>
<td>575</td>
<td>58%</td>
<td>20%</td>
<td>14</td>
</tr>
<tr>
<td>1994</td>
<td>3742</td>
<td>1423</td>
<td>49%</td>
<td>37%</td>
<td>451</td>
<td>57%</td>
<td>24%</td>
<td>15</td>
</tr>
<tr>
<td>1995</td>
<td>6020</td>
<td>2005</td>
<td>49%</td>
<td>52%</td>
<td>574</td>
<td>48%</td>
<td>22%</td>
<td>7</td>
</tr>
<tr>
<td>1996</td>
<td>4799</td>
<td>1432</td>
<td>54%</td>
<td>25%</td>
<td>628</td>
<td>44%</td>
<td>19%</td>
<td>13</td>
</tr>
<tr>
<td>1997</td>
<td>4261</td>
<td>1667</td>
<td>63%</td>
<td>32%</td>
<td>612</td>
<td>56%</td>
<td>23%</td>
<td>11</td>
</tr>
<tr>
<td>1998</td>
<td>5282</td>
<td>2218</td>
<td>68%</td>
<td>33%</td>
<td>783</td>
<td>73%</td>
<td>22%</td>
<td>25</td>
</tr>
<tr>
<td>1999</td>
<td>4537</td>
<td>1686</td>
<td>61%</td>
<td>26%</td>
<td>618</td>
<td>58%</td>
<td>22%</td>
<td>13</td>
</tr>
<tr>
<td>2000</td>
<td>5458</td>
<td>1933</td>
<td>76%</td>
<td>32%</td>
<td>731</td>
<td>69%</td>
<td>24%</td>
<td>24</td>
</tr>
<tr>
<td>2001</td>
<td>4432</td>
<td>1707</td>
<td>76%</td>
<td>39%</td>
<td>804</td>
<td>77%</td>
<td>37%</td>
<td>26</td>
</tr>
<tr>
<td>2002</td>
<td>4388</td>
<td>1836</td>
<td>69%</td>
<td>35%</td>
<td>999</td>
<td>69%</td>
<td>36%</td>
<td>24</td>
</tr>
<tr>
<td>2003</td>
<td>6224</td>
<td>2391</td>
<td>71%</td>
<td>41%</td>
<td>1394</td>
<td>72%</td>
<td>37%</td>
<td>29</td>
</tr>
<tr>
<td>2004</td>
<td>6741</td>
<td>2502</td>
<td>67%</td>
<td>44%</td>
<td>1429</td>
<td>66%</td>
<td>38%</td>
<td>36</td>
</tr>
<tr>
<td>2005</td>
<td>8576</td>
<td>3775</td>
<td>57%</td>
<td>39%</td>
<td>1723</td>
<td>64%</td>
<td>35%</td>
<td>16</td>
</tr>
<tr>
<td>2006</td>
<td>6984</td>
<td>2213</td>
<td>67%</td>
<td>39%</td>
<td>1189</td>
<td>68%</td>
<td>36%</td>
<td>35</td>
</tr>
<tr>
<td>2007</td>
<td>7501</td>
<td>1974</td>
<td>67%</td>
<td>42%</td>
<td>1011</td>
<td>67%</td>
<td>35%</td>
<td>32</td>
</tr>
<tr>
<td>2008</td>
<td>16876</td>
<td>2199</td>
<td>68%</td>
<td>43%</td>
<td>1556</td>
<td>66%</td>
<td>38%</td>
<td>30</td>
</tr>
<tr>
<td>2009</td>
<td>16490</td>
<td>1934</td>
<td>64%</td>
<td>28%</td>
<td>1011</td>
<td>59%</td>
<td>23%</td>
<td>25</td>
</tr>
<tr>
<td>2010</td>
<td>13032</td>
<td>2483</td>
<td>58%</td>
<td>27%</td>
<td>1790</td>
<td>58%</td>
<td>22%</td>
<td>39</td>
</tr>
<tr>
<td>TOTAL</td>
<td>129,848</td>
<td>37,273</td>
<td>18,133</td>
<td>419</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FOCUS: To investigate the impact of technologically advanced programs for eating disorders, weight management, and body image disturbance on health behaviors.

The Behavior Technology Laboratory conducts research on behavioral approaches for the assessment, prevention, and treatment of eating disorders, obesity, and body image disturbance. This research involves testing the efficacy of community-based, clinic-based, and internet/technologically advanced mobile-based (e.g., Smartphones) interventions for changes in health behaviors.

Weight Measurements and Standards for Soldiers. As a part of the Weight Measurements and Standards for Soldiers Project, the Healthy Eating, Activity, and Lifestyle Training Headquarters (H.E.A.L.T.H.) program was developed at PBRC and represents an ongoing, ten-year collaborative effort between PBRC and the Department of Defense. The H.E.A.L.T.H. program is designed to aid Soldiers in maintaining healthy weight status, fitness status, combat readiness, and Warfighter performance. H.E.A.L.T.H. also includes programming to aid Soldier’s family members in reaching overall health and fitness goals. H.E.A.L.T.H. incorporates cutting edge interactive technology and is “portable” (e.g., Internet, Smartphone) so Soldiers and their family members can use it wherever they are in the world. H.E.A.L.T.H. is considered a population health program, has been deployed and tested in two pilot projects (Ft. Bragg, NC, and New England Reserves), and is being tested in the Louisiana Army National Guard (LANG). This study is expected to result in dissemination of the H.E.A.L.T.H. program to all branches of the Military and improve combat readiness for our technologically advanced fighting force.

Healthy Weight Intervention in Female Athletes. Given the cost of treating eating disorders (EDs) and the substantial morbidity and mortality associated with these disorders, prevention of EDs has considerable public health significance. Research supports the use of a Healthy Weight (HW) program targeting small lifestyle modifications in the prevention of ED onset and in reducing ED and obesity risk factors. Research suggests that disordered eating among female athletes is prevalent, and is especially dangerous in female athletes because it increases risk for the Female Athlete Triad (i.e., low energy availability/disordered eating, menstrual disorders, and decreased bone mineral density/osteoporosis) and subsequent injury. This study is a cluster randomized controlled trial to test the effectiveness of the HW intervention among 500 collegiate female athletes in four sites.

Body Evolution Technologies (BE). BE is a company formed to commercialize evidence-based health behavior technology and is an entrepreneurial venture (formed as a result of scientific discovery at PBRC) funded by angel and venture capital investors. BE adapts evidence-based offline approaches into online/digital experiences, i.e., learning programs including interactive, digital media applications, and health e-games (e.g., Internet, Smartphone, ipad apps) that address a wide range of health behaviors including body image, eating disorders, and weight management. The programs and assessment tools are integrated within a social network environment to reinforce learning and promote adherence. These programs reside on Emer.ge, an e-health, online platform. BE is currently engaged in a number of partnerships including with Delta Delta Delta Fraternity, to deliver eating disorder prevention to large scale populations, e.g., university students.

Research in this laboratory is funded by the National Institutes of Health, the U.S. Department of Defense, and Themelios Ventures.
FOCUS: The goal of this laboratory is to investigate weight loss techniques that promote long-term weight management and examine their impact on biomarkers and health outcomes.

Weight Loss Maintenance Trial: The Weight Loss Maintenance (WLM) trial was a three-phase, multicenter randomized trial comparing alternative strategies for maintaining long-term weight loss. Our laboratory was one of four clinical sites participating in the study. Persons were eligible if they were overweight/obese and on medications for hypertension and/or dyslipidemia. Phase I was a six-month weight loss program. During Phase II, participants who lost ≥ 4 kg in Phase I were randomized to one of three maintenance conditions: Internet-based (IT) treatment, monthly personal contact (PC), or a self-directed (SD) control condition for 30 months. In Phase III, SD participants continued without further intervention, while PC participants were re-randomized to no further intervention (PC-Control) or continued intervention (PC-Active) for 30 more months (n=489). Results from Phases I and II have been published. During Phase I, mean weight loss was 7.9 kg. During the next 30 months (Phase II), weight regain was less in PC than SD (mean adjusted difference at 30 months of -1.6 kg; 95% CI -2.8 to -0.43). Over the next 30 months (Phase III), mean weight increased by 1.0 kg in PC-Active and by 0.5 kg in PC-Control (mean adjusted difference of 0.6 kg; 95% CI -1.4 to 2.7; p = 0.54). Mean weight change at 66 months was -3.2 kg in those originally assigned to PC and -1.6 kg in SD (mean difference of -1.6 kg; 95% CI -3.0 to -0.1; p = 0.04). Overall, 77% of those originally assigned to PC remained below entry weight compared to 63% in SD (p = 0.002).

These findings suggest that after an initial 30 months, continuation of a behavioral intervention provided no additional benefit on weight over the next 30 months. However, after 5 years, the majority of individuals who successfully lost weight maintained a weight below their initial level.

Weight Management of Severely Obese Adults: Louisiana’s rates of overweight and obesity rank among the highest in the United States. Along with its association with cardiovascular disease and diabetes, obesity’s economic burden to individuals and society is enormous. Members of our laboratory collaborate with the Louisiana Office of Group Benefits (OGB), the state-managed health insurer, to study the feasibility and effectiveness of providing medical and surgical treatments to severely obese adults. In one study, severely obese members volunteered, and 40 were randomly selected for insurance-covered weight loss surgery (WLS). Several outcomes were studied, including the change in total medical and pharmacy expenditures and the subcategories of medical and pharmacy expenditures in obese individuals following WLS. We also compared these costs to expenditures in severely obese members not receiving WLS (n=911). Total non-pharmacy medical costs were lower for WLS patients compared to non-WLS patients beginning four years post-surgery and lasting through six years post-surgery. Total pharmacy costs were lower for WLS participants at two and three years post-surgery, but these lower costs were not maintained (see figure). However, costs remained lower for antidiabetic agents, antihypertensive agents, and dyslipidemic agents through all six post-surgery years under study.

Research in this laboratory is supported by grants from the National Institutes of Health and the State of Louisiana through the Office of Group Benefits.
FOCUS: This unit focuses on behavior, diet, and activity modification to achieve weight loss and the evaluation of the effects of weight loss on multiple end points.

Diabetes Prevention Program Outcomes Study: This double-blind, randomized trial compared an intensive lifestyle program versus metformin or placebo on the rate of conversion to diabetes in a population of over 3,000 men and women with impaired glucose tolerance and a high risk of diabetes. A total of 22 centers across the United States are involved. This study has now completed its 13th year. In the initial 3.2 years during the double-blind, randomized phase, those assigned to the initial intensive lifestyle program lost an average of 7% of their body weight and reduced the incidence of diabetes by 58%; responses were similar among men and women, as well as across several ethnic groups. Metformin slowed the conversion rate to diabetes by 31% and produced a small but significant 2.5% weight loss. After these results were announced, the trial was converted into a mixed outcomes-intervention study with people taking metformin remaining on treatment with metformin and the intensive lifestyle group getting extra behavioral intervention. From the time the trial was converted to an outcomes study, the conversion rates were similar in all groups and corresponded to those of the initial lifestyle group (i.e., everyone benefited). The trial has been refunded to 2014 to follow outcomes of diabetes. An ancillary study involving the Pennington Center was funded to examine the level of activity in the various treatment groups by using accelerometry. This phase of the trial has just gotten under way.

Look AHEAD (Action for Health in Diabetes) Trial: This 16-center randomized clinical trial in overweight and obese patients with type 2 diabetes evaluated the long-term effects of an intensive weight loss intervention on the time to incidence for major cardiovascular events. The weight loss of the intensive lifestyle intervention (ILI) group was 8.6% versus 0.7% in the diabetes support and education (DSE) group (p < 0.001) at year 1. This faded somewhat over the next three years. Mean fitness increased in ILI by 20.9% versus 5.8% in DSE (p < 0.001). A greater proportion of ILI participants had reductions in diabetes, hypertension, and lipid-lowering medicines. Mean HgbA1c dropped from 7.3% to 6.6% in ILI (p < 0.001) versus 7.3% to 7.2% in DSE. The success of the trial has led to its refunding through 2013. An ancillary study involving the Pennington Center was funded in 2009. It is testing the memory and movement abilities of the participants. It is anticipated that people who have lost weight will have improved mobility; whether this is also reflected in the mental acuity remains to be determined.

Research in this laboratory is funded by grants from the National Institutes of Health.
FOCUS: The goal of this laboratory is to understand the effects of exercise and nutrition on metabolism, obesity, and fatigue as they relate to physical performance and health.

The Exercise Biology Laboratory comprises the Exercise Testing Core, Fitness Center, and Wellness Program. The Exercise Testing Core provides reliable assessments of physiologic, cardiorespiratory, and muscular strength parameters related to exercise performance. The Fitness Center provides accurate exercise monitoring for studies requiring specific exercise interventions, and the Wellness Program is in place to help Pennington Biomedical employees adopt healthy lifestyles. The Exercise Biology Laboratory is also tasked with exploring various means of improving exercise performance through exercise training, new technologies, and nutrition supplementation.

Exercise Training: During the past 2 years, we have explored the use of interval training vs. traditional steady-state aerobic training through a National Institutes of Health (NIH)-funded grant. Interval training involves periods of intense exercise lasting 30 seconds to ~2-minutes, followed by an equal period of recovery. The results of this pilot study demonstrated that interval training may improve several parameters related to insulin resistance and metabolic syndrome better than traditional recommendations. Interestingly, the interval training group included no dropouts from the study, while ~20% of the traditional training group dropped out.

New Technologies: A current interest of our lab is the continued exploration of using magnetic resonance spectroscopy (31P-MRS) to explore skeletal muscle energy pathways. The examination of these pathways is important to those individuals involved in sport and pursuing overall health and is tied to various aging- and mortality-related disease processes. One of our goals is to build and validate the necessary equipment to examine various muscle groups by accounting for the amount of work performed in a given muscular work task, along with a more repeatable and valid way to perform these assessments.

Nutrition Supplementation: In a recent study, we discovered that supplementation with a carotenoid compound known as astaxanthin increased cycling performance in local, competitive, amateur cyclists and triathletes (see figure). Astaxanthin, which has high levels of antioxidants and the ability to increase fat metabolism in mice, is a phytochemical best known for its use as a feed additive for farm-raised salmon, giving the fish their pink flesh, but is also abundant in crawfish.

One of our current studies is now focusing on the examination of black and green tea extracts on exercise performance. Black and green tea exhibit antioxidant and anti-inflammatory properties that, in some studies, have been shown independently to improve exercise recovery. Though black and green tea have similar mechanisms of action, they also have unique characteristics that may be complementary. The goal of the TEA Study is to examine how this combination affects exercise performance, recovery, and muscle damage that may accompany intense bouts of exercise.

Data show that cyclists supplementing with astaxanthin improved their cycling performance during a 20 km time trial by an average of two minutes. By comparison, ingesting traditional carbohydrate typically improves 40 km time trial performance by 30 to 40 seconds.

Research in this laboratory is funded by the NIH, Gatorade Sports Science Institute, and Kemin Health.
FOCUS: The goal of this laboratory is to understand the relationships between adipose tissue expansion in obesity and metabolic abnormalities, with emphasis on cellular and molecular mechanisms in skeletal muscles; to investigate the impact of environmental and/or pharmacological interventions on brown adipose mass and activity; and to perform research in aging designed to assess the impact of caloric restriction in nonobese humans on biomarkers of longevity.

Increases in adipocyte size (hypertrophy) and number (hyperplasty) contribute to the accumulation of adipose tissue in obesity. The degree of adipocyte hypertrophy and hyperplasty varies among individuals. Fat gain is associated with metabolic abnormalities. It is hypothesized that the inability of the subcutaneous adipose tissue to accommodate excessive dietary fat leads to increased deposition of fat in visceral depots and ectopic sites, which results in insulin resistance. We hypothesize that hypertrophic obesity is associated with the inability of the subcutaneous adipose tissue to expand. Moreover, we hypothesize that the availability of the adipocyte precursors – preadipocytes – and their capacity to differentiate to adipocytes are important regulators of adipocyte hypertrophy/hyperplasty. The Human Physiology Laboratory just completed an eight-week 40% overfeeding study in 35 lean and overweight participants who had similar total body fat but hypertrophic or hyperplastic adipocytes. We are analyzing the data and writing up the results to look at the impacts of weight gain on the deterioration of insulin sensitivity and its molecular determinants.

Recently, four major manuscripts have suggested that brown adipose tissue may have an important role in the regulation of energy balance in adult humans. We are therefore looking at the impact of cold exposure, overfeeding, and thyroid hormones on mass and activity using either infrared thermography or positron emission tomography (PET)/computed tomography (CT) techniques.

Another endeavor in our lab is the study of the impact of hypoxia on insulin sensitivity in skeletal muscle, adipose tissue, and liver. These studies have combined state-of-the-art techniques to study the physiological and molecular impacts of hypoxia in these tissues.

After completing the first phase of the Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) study designed to assess the feasibility and safety of caloric restriction (CR) in nonobese humans, we are now conducting a new study of CR in collaboration with Washington University, Tufts University, and Duke University. The study is a multicenter, parallel-group, randomized controlled trial (RCT) with a total enrollment of 225 participants assigned to either the CR intervention or an ad libitum control group. A 2:1 allocation ratio in favor of the CR intervention is applied in order to maximize the number of subjects receiving the intervention of greater scientific interest. Participants in both treatment arms are followed over a period of 24 months. Our last participant just finished the intervention in March 2012.

An exciting development of the Human Physiology Lab is the establishment of a new group led by Dr. Tchoukalova who will continue to focus on adipose tissue kinetics in central obesity vs. peripheral obesity. Furthermore, Dr. Tchoukalova was recently awarded a 5-year R01 grant to study the kinetics of preadipocytes and adipocytes by deuterium enrichment in DNA in response to pharmacological intervention.

Research in this laboratory is supported by grants from the National Institutes of Health, an institutional grant, and private contracts from pharmaceutical and nutrition companies.
Inactivity physiology, an emerging new area of medical research, is a novel way of thinking about the medical consequences of and the solutions for a “sedentary lifestyle.” The work often focuses on how “sitting too much” is distinct from “not exercising enough.” This area has promise for reversing the trends for chronic metabolic conditions caused by excessive physical inactivity. In the Inactivity Physiology Laboratory, we are translating our basic research findings in order to most efficiently identify the lifestyle changes that can best prevent the health hazards caused by inactivity in the workplace, schools, and other venues. One of the new concepts is that in contrast to traditional exercise recommendations that require taking time out of the day for exercise, it may be possible to simply replace sedentary time with very light physical activity without interrupting the normal day. This is exciting because health may be improved beyond the expected in the majority of people in our society who do not exercise.

The research in this laboratory involves both basic and clinical science. We have been identifying molecular mechanisms regarding the metabolic processes regulated by sitting and very light contractions in skeletal muscles compared to inactivity. We have focused heavily on the processes in skeletal muscle mediating the metabolism of plasma lipids and glucose during physical inactivity. These studies offer insights for understanding why exercise is not the perfect antidote to physical inactivity, but rather it appears better to spread out low-intensity contractions throughout the day.

Experimental studies in human subjects and laboratory animals are proving to be very efficient for guiding clinical trials in the most effective direction. Research by our team revealed that the physiological effects of sitting too much are largely independent of body weight, and significant effects on clinically relevant metabolic outcomes are evident within just a single day of inactivity intervention. One of the most important concepts from the basic science studies is that physical inactivity is not the biological equivalent of too little exercise. And in two recent human trials, we found that the amount of time spent sitting was hazardous for metabolic processes whether or not people exercised. We have even learned that the effectiveness of a common pharmaceutical used for treating atherogenic dyslipidemia depends on the amount of physical inactivity. These concepts are leading to a paradigm shift for how public health experts recommend physical activity for chronic disease prevention.

Research in this laboratory is supported by grants from the U.S. Department of Agriculture, the National Institutes of Health, the American Heart Association, Coca-Cola, and the Edward G. Schlieder Educational Foundation.
**FOCUS:** The goal of this laboratory is to understand the regulation of food intake and activity and to develop and test the efficacy of interventions to reduce food intake, increase activity levels, and promote weight management.

The Ingestive Behavior Laboratory (IBL) specializes in the measurement of food intake and energy expenditure (activity) in both laboratory and free-living conditions. For example, the IBL developed and validated the smartphone-based Remote Food Photography Method, which remotely measures the food intake of people in near real time while they live at home. The IBL also tests the efficacy of behavioral (lifestyle) and pharmacological interventions on food intake, energy expenditure, and body weight.

Through a collaboration with Diana Thomas, Ph.D., at Montclair State University, the IBL helped develop and validate mathematical models that accurately predict an individual’s weight change during under- and overfeeding. These models are used to create graphs for individual patients that depict the amount of weight they will lose over time if they adhere to a prescribed diet. The graphs are used to quantify dietary adherence, which is then utilized to guide treatment delivery (see figure).

Recently, a mathematical model was developed and validated to help pregnant women meet national gestational weight gain recommendations.

During a study funded by the National Institutes of Health (NIH), the IBL recently developed and tested the efficacy of an e-health weight loss intervention called SmartLoss, which built upon the IBL’s previous work. In this randomized controlled trial, overweight and obese adults were randomized to either the SmartLoss intervention or an attention-matched health information control group. Both groups received treatment advice or health information via smartphone while they lived at home; they did not visit the center for treatment. In the SmartLoss group, objective body weight, exercise, and food intake data were transmitted from participants’ homes to clinicians, who then sent treatment recommendations based on these data to participants via smartphone. The previously described weight graphs were used in the SmartLoss intervention to track adherence.

Over three months, participants in the SmartLoss group lost more weight than participants in the health information control group (~9% and ~1% of initial body weight, respectively). The SmartLoss group also experienced improvements in blood pressure and waist circumference compared to the control group. Further, user-satisfaction ratings showed that the vast majority of participants were very satisfied with the SmartLoss intervention.

Plans are under way to test the ability of the SmartLoss intervention to promote long-term weight loss maintenance and to explore commercialization and large-scale dissemination of the technology. Additionally, the approach was adapted to help pregnant women meet national gestational weight gain guidelines. This approach is called SmartMoms, and it was developed in collaboration with Dr. Thomas and Leanne Redman, Ph.D., of Pennington Biomedical. The efficacy of the SmartMoms intervention will be tested over the next five years as part of an NIH-funded randomized controlled trial, which will be conducted in close collaboration with colleagues from Woman’s Hospital in Baton Rouge.

Research in this laboratory is funded by grants from the NIH and the U.S. Department of Agriculture and through contracts with industry.
FOCUS: The goal of this laboratory is to understand and characterize the molecular mechanism(s) of mitochondrial dysfunction in skeletal muscle and its relationship to obesity, insulin resistance, type 2 diabetes mellitus, and aging.

Over the past few years, our group has conducted cellular, molecular, and functional studies in skeletal muscle samples obtained from the following clinical studies: MITO, EAT, FLEX, PRISM, BARIA, and CALERIE I. We use a wide array of assays to assess the metabolic, mitochondrial, and physiological characteristics of skeletal muscle.

MITO: Effects of aging on skeletal muscle function. Oxidative capacity in skeletal muscle has been shown to decrease with age and may be related to increased accumulation of intramyocellular lipid (IMCL) or fat metabolites (DAG, ceramides), fewer mitochondria, and a preferential loss of oxidative type 1 muscle fibers. The purpose of the MITO study was to further investigate these relationships in elderly and young individuals. Using immunohistochemistry techniques, we found significantly higher IMCL in elderly compared with young individuals but no difference in the number of type 1 or type 2 muscle fibers.

FLEX: Role of muscle mitochondrial density on metabolic flexibility. Metabolic flexibility is the ability to match fuel oxidation to availability. Skeletal muscle metabolic inflexibility has been implicated in the origin of insulin resistance because of a mismatch between lipid availability and oxidation leading to increased muscle lipid accumulation. This metabolic inflexibility to lipid is proposed to be a consequence of impaired muscle mitochondrial density and/or function in insulin-resistant individuals. The influence of mitochondrial density on metabolic flexibility to lipid may be more evident when lipid oxidative demand is increased. We conducted a study to investigate the reliance on fat oxidation in individuals with high and low skeletal muscle mitochondrial capacity. In response to the same energy demand during a moderate-intensity, prolonged exercise session, the reliance on fat oxidation was the same in the two groups, suggesting that muscle lipid accumulation may not be determined by muscle mitochondrial capacity.

EAT: Fat cell size and overfeeding. The purpose of this protocol was to characterize the morphological and metabolic characteristics of both adipose and muscle tissues predisposing to ectopic fat deposition and insulin resistance before and after eight weeks of overfeeding. The overarching hypothesis is that overfeeding will significantly increase ectopic fat deposition and insulin resistance and decrease muscle oxidative capacity in individuals with hypertrophic adipocytes more so than in individuals with hyperplasic adipocytes. This study was completed within the past year, and data analysis for publication is in process. We collaborated with Drs. Saverio Cinti (Ancona, Italy) and Bret Goodpaster (University of Pittsburgh).

ACTIV. Skeletal muscle mitochondrial defects and a high level of IMCL are often associated with insulin resistance in sedentary obese and/or type 2 diabetes mellitus (T2DM) patients. The purpose of the ACTIV study was to compare and contrast mitochondrial capacity (measured by magnetic resonance spectroscopy [MRS]) and IMCL (measured from muscle biopsy) in sedentary healthy controls with (FH+) or without (FH-) a family history of diabetes, in obese subjects, in subjects with T2DM, and in endurance trained athletes. We also investigated the effects of short-term exercise training (~3 weeks) on skeletal muscle oxidative capacity, insulin sensitivity, and IMCL content. In people with T2DM, mitochondrial capacity was low and not correlated with insulin action. Lipid measured in myotubes (in vitro) was not associated with IMCL measured directly from skeletal muscle tissue (in vivo). However, myotubes retained important clinical phenotypes such as mitochondrial function, insulin sensitivity, and physical fitness (see figure).

Dr. Robert Noland will initiate studies on the role of nutrition in the skeletal muscle production of acylcarnitines and its impact on insulin resistance. Metabolomics profiling analyses revealed that models of insulin resistance display diminished free carnitine levels with concomitant elevations in acylcarnitine accumulation. Dietary carnitine supplementation improved whole-body glucose homeostasis and mitochondrial function in animal and human models of impaired glucose tolerance, and these improvements are associated with increased elimination of excess acylcarnitines. Current studies are directed toward establishing the direct mechanisms responsible for these beneficial adaptations.

Research in this lab is supported by grants from the National Institutes of Health, institutional funding, and grants from various pharmaceutical corporations.
**FOCUS:** The goals of this laboratory are: (1) to understand and characterize the molecular mechanism(s) of mitochondrial remodeling and dysfunction and its relationship to muscle wasting, insulin resistance, type 2 diabetes mellitus, and aging, and (2) preclinical development of drug targets.

The newly formed John S. McIlhenny Skeletal Muscle Physiology Laboratory II is currently conducting cellular, molecular, and functional studies in skeletal muscle samples obtained from the P.I.M.A-2 and E3-L-R studies (see below). In collaboration with Exergy BioPharma L.L.C., the laboratory has a vigorous program in the area of peptide drug-mimetics for metabolic disease.

Why mitochondria? Mitochondrial dysfunction is an important component of many pathologies associated with aging, such as type 2 diabetes mellitus (T2DM), Alzheimer’s and Parkinson’s diseases, and some cancers. Both aging and T2DM are associated with skeletal muscle insulin resistance, lower oxidation capacity, reduced mitochondrial content, and elevated reactive oxygen species (ROS) production. As ROS can cause damage to mtDNA, proteins, and membrane lipids, a self-perpetuating and destructive cycle can ensue in which increased ROS production leads to incremental damage and further ROS production. Prolonged ROS production can lead to severe mitochondrial uncoupling and oxidative damage and eventually to loss of skeletal muscle fibers (i.e., sarcopenia) in old age.

**P.I.M.A-2: The effects of PARL on skeletal muscle function.** Recent work shows that mitochondrial remodeling (fusion and fission) are pivotal processes for maintaining the function of the organelle. In mammals, fusion is regulated in part by the rhomboid protease PARL. Our laboratory has shown that PARL protein is correlated to mitochondrial content and downregulated in the muscle of elderly individuals and subjects with T2DM. siRNA-mediated reduction in PARL protein results in a lowering of mitochondrial mass and energetics and elevated oxidative damage to mitochondria. Conversely, expression of PARL in primary myotubes was able to induce mitochondrial biogenesis and upregulate the protein content of SIRT1, one of the principal genes thought to mediate the molecular response(s) to caloric restriction (CR). Knockout (KO) of PARL protein in the muscle of transgenic (Tg) mice lowered mitochondrial content, impaired insulin signaling, increased oxidative damage, and changed the internal structure of mitochondria (see figure). The primary objective of the P.I.M.A study is to phenotype Tg mice with muscle-specific overexpression of PARL and to study the relationships between PARL, biomarkers of aging, body weight regulation, mitochondrial function, and the development of insulin resistance.

**E3-L-R Study.** CR has been shown to suppress the development of age-associated diseases including T2DM, cancer, and cardiovascular disease, as well as overweight and obesity. There is still uncertainty as to the underlying mechanism(s) of CR. The John S. McIlhenny Skeletal Muscle Physiology Laboratories I and II have identified a newly discovered E3 ubiquitin ligase called “R-0” (name is coded) that regulates DNA processing, histone function, and gene regulation. Preliminary data are exciting and provide the first evidence that R-0 is upregulated by CR and downregulated in insulin-resistant states in humans. Furthermore, we have demonstrated that R-0 can improve glucose and redox metabolism, two defects widely observed in aging and T2DM. We are currently generating a rodent KO-model to better understand the function of R-0 in relation to metabolism, CR, and CR-mediated DNA transcription.

**Drug-Mimetics.** We have an active analog program to develop peptide hormone-mimetics with selective agonists in skeletal muscle metabolism. The goal of the preclinical exploration is to identify peptides and proteins for potential utility as therapeutics for metabolic diseases, as either single agents or in a combinatorial space.

---

**Representative transmission electron microscopy of cross-sectional slices of PARL positive (+) (Panel A) and PARL negative (-) (Panel B) mitochondria in transgenic mice muscles at high (x20,000) magnification.**
FOCUS: The Joint Program on Diabetes, Endocrinology, and Metabolism is a single academic program across two distinct campuses of the LSU System. Specifically, the Joint Program represents a collaborative effort between the Pennington Biomedical Research Center in Baton Rouge and the LSU Health Sciences Center (LSUHSC) School of Medicine in New Orleans. The purpose of the Joint Program is to enhance the research, education, and medical care in diabetes, endocrinology, and metabolism by aligning both institutions, so as to promote collaboration, facilitate sharing of resources, and avoid duplication of efforts. The recognized research expertise in endocrinology and clinical research at Pennington Biomedical has been aligned with the medical care provision and endocrinology fellowship education and training efforts at LSUHSC, thus creating a seamless Joint Program. The Joint Program is led by William T. Cefalu, MD, who is jointly appointed to the faculty at both institutions and whose time allocation is divided between the two institutions at approximately 50% effort at each. The faculty of the Joint Program are appointed to either or both institutions.

The Joint Program provides a wide range of services including patient care, resident supervision, student teaching, and both basic and clinical research.

Clinical Care: Our areas of expertise include the diagnosis and treatment of diabetes and endocrine abnormalities. Our clinics offer comprehensive diabetes and obesity evaluation and treatment, osteoporosis screening, and management and treatment of thyroid disorders.

Clinical Research: The program is heavily involved in many clinical trials evaluating type 2 diabetes and its related complications. In this regard, we have trials that evaluate patients who are considered very early in the disease process (i.e., prediabetic) and for whom lifestyle and nutritional intervention is being evaluated. In addition, the program has trials that are evaluating individuals who have had diabetes and are currently on monotherapy with a single agent, combination therapy with several oral agents, or insulin therapy. The program is also conducting studies with the goal of evaluating how diabetes presents in a minority population in the New Orleans area (e.g., Vietnamese).

Basic Research: The basic research interests of the program have been dedicated to interdisciplinary approaches to metabolic research, with particular interest in evaluating mechanisms of action by which nutrients and nutritional interventions enhance insulin sensitivity in muscle and adipose tissue. In this regard, the program’s faculty are involved in basic laboratory investigation and mechanisms operable in both animal models and human subjects. Interventions currently being evaluated include fatty acids, the trace mineral chromium, and specific bioactives as to their effect in modulating cellular insulin action. In addition, experiments are being conducted to determine the mechanisms involved in the oral sensing of dietary fat in animal models and to investigate the important relationship between feeding and reproductive behaviors, particularly investigating neuropeptides that affect the consumption of energy-dense foods.

Training: The program is focused on training at all levels, and students and house officers are trained in a variety of settings: public clinics, private clinics, didactics, and small group discussions. Patient care and outside reading are vital components of the endocrine experience. Research training opportunities are also available. The component of the Joint Program based in New Orleans (i.e., the Division of Endocrinology and Metabolism of the Department of Medicine at the LSUHSC School of Medicine) is pleased to offer two Accreditation Council for Graduate Medical Education (ACGME) accredited fellowships for Endocrinology, Diabetes, and Metabolism (Program # 1432112193).
FOCUS: The outpatient clinical trials program focuses on obesity in the areas of pharmaceutical development, dietary herbal supplements, foods, and medical devices.

Current Projects

Our pharmaceutical trials range from those in which it is the first time a new drug has been used in man (phase I), to early proof-of-concept trials determining whether the drug is effective, to trials determining the proper dose of the drug (phase II), to large drug-approval trials (phase III), to trials of drugs after approval (phase IV).

In a phase I trial, we tested two forms of nitrite, an immediate release and a slow-release formulation. We found that levels of nitrite in the blood were safe and that methemoglobin, which could prevent oxygen release, was not elevated. We next plan a proof-of-concept study to show that nitrite will help to heal foot ulcers in diabetic patients by delivering oxygen to the wounds.

We performed a phase IV trial of orlistat, a drug approved without a prescription for the treatment of obesity. We showed that orlistat treatment resulted in a decrease of fat inside the abdomen, the fat that is most closely associated with diabetes and a risk for heart and blood vessel disease (see figure).

Dietary herbal supplements are regulated as foods, and advertising claims must be supported by studies demonstrating the supplements’ efficacy. The root of the balloon flower is a type of radish that is pickled and used in the Korean diet in a food called kimchi. We demonstrated that the balloon flower inhibits the growth of new blood vessels in the laboratory, and it is known that such blood vessel growth inhibitors have the ability to reverse obesity in rodents. Inhibition of blood vessel growth should be safe, since healthy adults need new blood vessels only for pregnancy and menses. An extract from the balloon flower root was created with a known amount of the active ingredient. This extract was given to volunteers, and their blood was able to inhibit new blood vessel formation in the laboratory. The extract was safe and absorbed into the bloodstream when taken orally, unlike other foods we have identified with inhibitors of blood vessel growth. Further studies are planned to identify the best dose and to test the effect of the balloon flower root extract as a treatment for obesity.

The outpatient clinical trials program focuses on the treatment of obesity and its medical complications such as diabetic foot ulcers. Obesity is a serious problem that is growing in prevalence and has no good medical treatment. Pennington Biomedical’s Outpatient Clinic is addressing this unmet need through research into new pharmaceuticals, dietary herbal supplements, novel foods, and devices. We hope that these efforts will have a positive impact on the obesity epidemic, improve public health, and stimulate economic development in Louisiana.

Research in this unit is supported by multiple public and private grants and contracts.
FOCUS: The goal of this laboratory is to study the impact of physical activity and inactivity on the health of ethnic minority populations.

African-Americans suffer disproportionately from various health conditions, including obesity, hypertension, and diabetes. Decreased physical activity and increased inactivity levels have been shown to be independent risk factors for the development of chronic diseases including cardiovascular disease, diabetes, and obesity. It also has been shown that African-Americans spend less time in activity and more time in inactivity than is recommended. Thus, African-American adults are prime targets for studying the relationship between physical activity/inactivity and chronic disease. The lab’s ultimate goal is to find effective behavioral strategies to increase physical activity and decrease sedentary behavior in ethnic minorities.

Our lab is currently focused on studying several different aspects of inactivity through the Sedentary Behavior in African-Americans (SeBA) study. We are assessing the energy cost of typical sedentary behaviors, including watching TV, reading, and typing, and their relationship to body composition. The goal of SeBA is to provide objective data on the energy cost of activities for African-American adults because metabolic rates differ among ethnic populations. We are also studying the relationship between objectively measured inactivity and risk factors for cardiovascular disease. For this study, we will utilize existing data from the Jackson Heart Study, an epidemiological study of cardiovascular disease risk in African-American participants. A subset of these participants wore accelerometers providing objective measures of activity while they were assessed for cardiovascular disease risk factors. This data will allow us to assess the association between physical activity and physical inactivity with cardiovascular risk factors. In the long run, we will be able to assess the relationship between these measures and actual cardiovascular disease occurrence.

Our lab is also utilizing technology to assist in maintenance of behavior change. Mobile phones are becoming ubiquitous across the country, and technology is increasingly being utilized in health care. We developed an intervention that utilizes technology as well as addresses the lack of physical activity in the nation’s children. The P-Mobile intervention will be delivered to parents, via mobile phone, with the goal of increasing their children’s physical activity to the recommended levels. We will recruit families who have a designated child between the ages of 6 and 10 years old who is either overweight or obese. The intervention will be conducted over the course of three months. The P-Mobile and related technology intervention will be adapted to African-American populations.

Research in this laboratory is supported by grants from the National Institutes of Health, the Clinical Nutrition Research Unit of Pennington Biomedical Research Center, and the Coca-Cola Foundation.
In November 2010, the Preventive Medicine Laboratory published the results of a large National Institutes of Health (NIH)-funded clinical trial titled HART-D in the Journal of the American Medical Association. The goal of the Health Benefits of Aerobic and Resistance Training in individuals with type 2 Diabetes study was to compare the effects of nine months of resistance training alone, resistance training in combination with aerobic training, and aerobic training alone on hemoglobin A1c in sedentary women and men with type 2 diabetes. We found that while resistance and aerobic training alone each had benefit to hemoglobin A1c, the combination of resistance and aerobic training had the greatest benefit. This was also seen for changes in fitness and fat loss. It is important to note that on average each of the exercise prescriptions took approximately 140 minutes per week.

We are currently in year 3 of the NIH-funded Lifestyle Intervention and Independence for Elders (LIFE) study, which is examining the role of physical activity in preventing disability in 70- to 89-year-old individuals with existing function limitations. We are one of eight U.S. study sites and recently completed recruitment six months ahead of schedule as we enrolled our 208th participant. We have partnered with the East Baton Rouge Parish Recreation and Park Commission (BREC) and the Baton Rouge YMCA to create more convenient intervention sites for the participants, and this appears to be working, as demonstrated by our very high compliance and retention rates.

We just started two new NIH-funded multisite trials titled ASPREE and SPRINT. Both studies are focused on preventing cardiovascular disease and dementia. ASPREE is examining the role of aspirin in preventing cardiovascular disease and dementia in individuals without a history of heart disease or stroke. While it is widely accepted that aspirin is of benefit for individuals with a history of heart disease, the benefit of daily aspirin in individuals without a history of heart disease remains a topic of great debate. The ASPREE study will help shine some much needed light on this issue. The SPRINT study is examining the risks and benefits of maintaining systolic blood pressure below 120 mmHg compared to below 140 mmHg in older individuals with hypertension. While the population-based data suggest that lower blood pressure is better, there are remarkably few clinical trials that have directly addressed this very important issue. The findings from both of these studies will provide valuable outcomes data that will shape future clinical guidelines related to the use of aspirin and setting optimal blood pressure ranges.

In addition to the above, we have ongoing pilot studies examining the benefits of exercise in individuals with post-traumatic stress syndrome and in reducing depressive symptoms in individuals with dementia.

Research in this laboratory is supported by grants from the NIH, the Coypu Foundation, the Edward G. Schlieder Educational Foundation, Coca-Cola, and the Pennington Medical Foundation.
The goal of this laboratory is to conduct clinical and translational research studies to better understand the impact of the obesigenic environment, including diet and physical activity, on women’s health across the life span.

Dr. Redman recently founded the Reproductive Endocrinology and Women’s Health Laboratory. She has several years of training in clinical physiology under Dr. Eric Ravussin, and she is an expert in human physiology and metabolism and in studies that use diet and physical activity to regulate energy balance (body weight) and energy metabolism.

In collaboration with Dr. Diana Thomas, Ph.D., at Montclair State University and other colleagues including Steven Heymsfield, M.D., and Corby Martin, Ph.D., of Pennington Biomedical, Dr. Redman participated in the development and validation of mathematical models that accurately predict how under- and overfeeding will alter the body weight of a given individual. Most recently, a mathematical model was developed and validated to characterize healthy weight gain during pregnancy and to define the amount of energy intake required to sustain healthy gestational weight gain. This new model was designed to help pregnant women achieve national gestational weight gain recommendations.

Dr. Redman has a strong interest in women’s health. Her current research is in polycystic ovary syndrome, gestational diabetes, and pregnancy and has received national and local funding to support her research group.

In a newly awarded grant from the National Institutes of Health (NIH), Dr. Redman will conduct a randomized controlled trial in women with polycystic ovary syndrome. The objective of the study called PULSE is to characterize how changes in body weight and/or insulin action restore normal reproductive function in women with polycystic ovary syndrome. This is an important study that will hopefully lead to the development of a specific weight management program that fosters reproductive health for women affected by the syndrome.

The laboratory has strong collaborations with Woman’s Hospital (Baton Rouge, Louisiana). Together with Dr. Karen Elkind-Hirsch, Ph.D., Director of the Woman’s Research Center at Woman’s Hospital, Dr. Redman is conducting an eight-month study in women who had gestational diabetes in a pregnancy within the past four months. Women who develop diabetes during pregnancy have a high susceptibility of developing impaired glucose tolerance and type 2 diabetes. The objective of the study called PRIDE is to implement a structured, behavioral-based weight management program that focuses on diet and physical activity between 4 and 12 months postpartum and on retention of excess weight gain and prevention of type 2 diabetes. Recognizing the challenges many mothers face after birth, we are evaluating the efficacy of a weight management program delivered over the telephone in comparison to a traditional clinic program.

An exciting development for Dr. Redman is the receipt of a prestigious NIH grant to implement a weight management program for overweight and obese pregnant women. In collaboration with Woman’s Hospital, Dr. Redman and Dr. Martin will lead the study called Expecting Success: Personalized Management of Body Weight during Pregnancy. The study will follow 300 mothers and offspring throughout pregnancy and for one year after birth.

Research in this laboratory is funded by grant(s) from the NIH, the C.B. and Irene Pennington Foundation, and the Botanicals Research Center Pilot and Feasibility Program.
FOCUS: The focus of the Sleep Health Center is to phenotype sleep in different diseases and their animal models and to determine how sleep manipulations affect neurobehavior, neurochemistry, autonomic nervous system control of the cardiovascular and immune systems, and metabolic functions. The findings are expected to advance our understanding of the cerebral mechanisms of sleep disorders in an effort to maximize human potential by improving neuroplasticity.

The Pennington Biomedical Sleep Health Center came into existence recently to launch several projects related to obesity, neuroinflammation, and neurodegeneration. Being translational in nature, we tackle a variety of scientific questions in the settings of clinical research, mouse sleep studies, ex vivo electrophysiological recording, and circadian rhythm analyses. We also combine polysomnographic recording with heart rate variability analyses, functional magnetic resonance imaging (fMRI) of the brain, and, hopefully in the future, metabolic profiling. Ongoing studies include: (1) how a cytokine modulates sleep architecture in a cell type- and brain region-specific manner and how the signals are integrated in an organ or whole system; (2) the functional role of sleep in neuroinflammation, such as in experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis, in mice with adult-onset obesity, and in neurodegenerative disorders such as Alzheimer’s disease and Parkinson’s disease; (3) revisiting and challenging the theories of sleep homeostasis regulation by focusing on glial cell signaling rather than neuronal projection pathways to expand our understanding of the regulation of pathophysiological (rather than normal) situations; (4) mechanisms of oculomotor regulation during sleep and their clinical significance in Parkinson’s disease and major depression.

The human sleep lab collaborates with investigators engaged in obesity trials, interactions between endocrine disorders and sleep, and interactions between exercise and sleep. Clinical sleep evaluation is provided by a board-certified sleep neurologist, and overnight polysomnography is performed in a two-bed sleep lab, as well as with full-spectrum portable monitoring by devices that are American Academy of Sleep Medicine (AASM) level II monitors.

The mouse sleep lab contains 10 units and is capable of baseline recording, electrocardiogram spectrum analysis, and chronic sleep restriction procedures with rigidly controlled experimental conditions. As this program was initiated at the Center for which there was no prior program, and despite challenges, the sleep lab has made steady progress from ground zero. In combination with telemetry recordings, metabolic analyses, neurobehavioral quantification, and biochemical, electrophysiological, and histological assays, we hope to bring sleep and circadian rhythm research to a high level with its involvement in pathological conditions.

Research in this unit is supported by a small startup fund from Pennington Biomedical Research Center, until National Institutes of Health and other extramural funding is available.
FOCUS: The objective of this laboratory is to study the role of fat and other macronutrient intakes and fat preferences in the control of food intake and body weight.

Women rated their cravings for sweet, high-carbohydrate, and high-fat foods. Using the modified Geiselman Food Preference Questionnaire (FPQ), subjects also rated their cravings for specific foods in which fat content varies significantly and systematically with sugar, complex carbohydrates, and protein content. In all assessments, women rated the cravings that they were experiencing at the present moment. A second test visit was conducted four weeks later to determine test-retest reliability. To reduce error variance, we controlled for the effects of female sex hormones and nutritional status (following a 10-hour overnight fast) across the two study visits.

Stepwise, multiple regression analyses revealed that the females’ cravings for specific foods high in both sugar and fat content provided the best predictor for their cravings for sweet foods ($p < .001$), as well as the best predictor for their cravings for high-carbohydrate foods ($p < .001$). No other predictor variables were entered into these regression equations. Cravings for specific foods high in both sugar and fat content also provided the best predictor for the women’s cravings for high-fat foods ($p < .001$), and cravings for foods high in both complex carbohydrate and fat content ($p < .001$) were the second predictor variable entered into the regression equation.

Hence, these results have validated craving scales for sweet, high-carbohydrate, and high-fat foods with respect to the macronutrient content of the craved foods in females. In addition, test-retest reliability for each of the three craving scales was strong ($p < .001$ for each).

The FPQ is being used in numerous studies at Pennington Biomedical. In addition, the FPQ is being used at the National Institutes of Health (NIH) and at other institutions and universities in this country and around the world (United States, Canada, United Kingdom, South Africa, and Australia).

The development of the FPQ was funded by the U.S. Department of Agriculture. The above-reported research in this laboratory is supported by grants from the Wrigley Science Institute.
POPULATION SCIENCE

[Image: Children running on a grass field]

[Image: Older woman exercising with dumbbells]
Background

The establishment of Population Science as a research focus was a priority in Pennington Biomedical’s five-year strategic plan, Vision 2010. This goal was realized in August 2007 when the position of Associate Executive Director for Population Science was created. In the past four years, we have added five new Population Science laboratories at the Center, in addition to two existing ones, to complement our research strengths in Basic and Clinical Science. In addition, we have expanded our program evaluation efforts, and we currently are the external evaluator for the Louisiana Department of Health and Hospitals Tobacco Control Program and the Blue Cross and Blue Shield of Louisiana Foundation’s Challenge for a Healthier Louisiana grant program.

Current Status

Population scientists at Pennington Biomedical are involved in research, evaluation, education, and scientific advocacy activities. Our population scientists are studying health issues at the level of the community and population rather than in a laboratory, with the overarching mission of improving the health of the population. Our research efforts in Population Science initially focused on nutritional epidemiology and health care delivery. We have recently expanded our focus by adding laboratories in contextual risk factors, walking behavior, physical activity and obesity epidemiology, comparative effectiveness research, and chronic disease epidemiology. All of the Population Science laboratories contribute to the mission of the Center and expand upon the research strengths in Basic and Clinical Science.

In addition to our research and evaluation efforts, the Population Science unit has developed two initiatives in education and scientific advocacy. First, for the past four years, Pennington Biomedical has organized an annual public health conference on the topic of childhood obesity, which is quickly becoming the greatest public health challenge facing America. During the past three decades, the number of overweight and obese children has skyrocketed, resulting in a growing number of children facing health consequences that were traditionally experienced only by adults. This public health conference brings together approximately 500 local, national, and international experts on the topic of childhood obesity, with a focus on prevention. The major goal is to develop public health strategies that can be employed to tackle the growing problem of childhood obesity.

The second major public outreach effort initiated by the Population Science faculty is Louisiana’s Report Card on Physical Activity & Health for Children and Youth. The primary goal of the Report Card is to assess the level of physical activity and sedentary behaviors in Louisiana’s children and youth, the facilitators and barriers of physical activity behavior, and related health outcomes. The Report Card, which is currently in its fifth year, is an advocacy tool designed to increase awareness of the health concerns of Louisiana’s children. The main target audience of the Report Card is adult decision makers, and through this effort, we hope to provide a level of accountability on behalf of the children and youth of Louisiana.

The Future

According to the World Health Organization, about 80% of all deaths worldwide are the result of non-communicable diseases (NCDs), or chronic diseases. On September 19-20, 2011, the United Nations held an historic high-level meeting in New York City to address the growing global burden of NCDs and to challenge the world’s nations to focus on the prevention of NCDs. The situation is even more acute in North America. An aging population, coupled with an increasing prevalence of obesity, does not portend well for the health of the population. In addition to individual-level behavior changes, large-scale population shifts in normative behavior are required to see real reductions in NCDs and improvements in population health. The population scientists at Pennington Biomedical Research Center are well positioned to make major contributions to seeing these much-needed health improvements through to fruition.
FOCUS: The goal of this laboratory is to assess the role of lifestyle and other risk factors and their interactions on the risk of chronic diseases including coronary heart disease, stroke, heart failure, diabetes, cancer, and Parkinson’s disease.

The Chronic Disease Epidemiology Laboratory is collaborating with several large-scale epidemiological studies and clinical trials, including the Louisiana State University Hospital-based Longitudinal Study (LSUHLS), the FINRISK Study, Tianjin Gestational Diabetes Prevention Project (TGDPP), and Tianjin Children Obesity Study.

LSUHLS: Louisiana State University Health Care Services Division (LSUHCSD) operates seven public hospitals and affiliated clinics in different areas in Louisiana. Since 1990, the LSUHSC facilities have served about 1.6 million unique patients, representing approximately 35% of the Louisiana population. The LSUHCSD Disease Management Evaluation Database contains administrative data, anthropometric and blood pressure measurement data, laboratory data, treatment data, and clinical diagnosis data. All these data have been available in electronic form since 1990 for both inpatients and outpatients. Most patients in LSUHLS have now been followed for more than 10 years.

The FINRISK Study: The FINRISK Study is one of the largest prospective epidemiological studies of chronic disease risk factors in the world. The total sample consists of 62,013 individuals from Finland (30,031 men and 31,982 women) aged 25 to 74 years. The follow-up is virtually complete through the nationwide register linkages including the Causes of Death Registry, the National Hospital Discharge Registry, the National Social Insurance Institution’s drug register, and the National Cancer Registry. Follow-up databases have been recently updated, and outcome data as of the end of 2008 are available. Approximately 13,000 deaths, 6,000 coronary heart disease cases, 4,000 stroke cases, 3,500 heart failure cases, 800 Parkinson’s disease cases, and 6,500 cancer cases have been ascertained during the mean 20 years of follow-up.

TGDPP: This project is an ongoing three-year lifestyle intervention program among 1,180 Chinese women with gestational diabetes mellitus (GDM) at least one year after delivery. The specific aims of the TGDPP are: (1) to test the hypothesis that lifestyle intervention can reduce incident type 2 diabetes in women with prior GDM; (2) to evaluate the interactions between lifestyle intervention and variations in established genes for glucose, insulin resistance, lipids, obesity, and type 2 diabetes in relation to metabolic traits for diabetes in women with prior GDM; and (3) to assess the effects of a lifestyle intervention program in mothers with GDM on their offspring’s health status, including childhood obesity and metabolic abnormalities.

Tianjin Children Obesity Study: This retrospective longitudinal study includes 15,928 children aged 3 to 6 years in Tianjin, China.

Research in this laboratory is supported by the Louisiana Department of Health and Hospitals, the American Heart Association, Merck, EFSD/Chinese Diabetes Society Programme for Collaborative Research between China and Europe, and International Diabetes Federation (IDF) Bringing Research in Diabetes to Global Environments and Systems (BRIDGES).
**FOCUS:** The goal of this laboratory is to understand how the different contexts in which we live—e.g., neighborhoods, schools, work, parks, social networks—shape our disease risks and health outcomes.

In recent years, a new epidemiological research paradigm has emerged that recognizes that traditional risk factors like smoking, poor diet, physical inactivity, and obesity are themselves shaped by the social and physical environments in which we live. The goal of the Contextual Risk Factors Laboratory is to identify modifiable aspects of the social, physical, and policy environments that are linked with individual health risk factors or behaviors. Currently, we are focusing on risk factors and behaviors in the broad areas of cardiovascular disease (CVD) and obesity.

One project involves studying the biological pathways through which a child’s neighborhood contributes to development of early markers of CVD, including obesity and diabetes. The framework for this research is shown in the accompanying figure. We are currently studying the neighborhood environments of 400 children who took part in a recently completed Pennington Biomedical study. This project involves linking neighborhood characteristics like food retail outlets, opportunities for physical activity, and neighborhood safety and disorder to behavioral data and cutting-edge biological measures that indicate early CVD risk. Results from this research will shed light on specific pathways linking the neighborhood environment to development of CVD risk during a critical time period, thus providing tools for improved disease screening, an impetus for targeted environmental and policy change, and a basis for future preventive efforts.

Our lab is also participating in a large international study of obesity and physical activity in 10-year-old children. Through this study, we will be able to look at the contributions of a child’s home, neighborhood, and school environments to diet and physical activity behaviors across the world.

In research conducted with colleagues at the Louisiana State University Health Sciences Center (LSUHSC) School of Public Health in New Orleans, we are studying the role that neighborhood parks play in fostering “social capital” among park users. We have shown that parks with higher social capital are used by more people and support higher amounts of physical activity than parks with lower social capital. We hope to extend this research by developing programs within parks and their surrounding neighborhoods to cultivate social capital and to increase neighborhood park use and physical activity within the parks.

Research in this laboratory is supported by the American Heart Association, the National Institutes of Health, and the Pennington Biomedical Research Foundation.

Conceptual framework that illustrates how contextual risk factors shape individual risk factors, which ultimately give rise to disease.

Adapted from Daniel et al. (Health & Place, 2008) and Glass & McAtee (Soc. Sci. Med., 2006).
FOCUS: The goal of this laboratory is to develop information on the relationships between behaviors, biomedical traits, and chronic disease risk in children and adults.

Obesity is one of the most pernicious medical conditions affecting populations around the world. Rates of overweight have been increasingly globally for over a generation, and in many countries, including the United States, rates now exceed 60% in adults. Onset in childhood is increasing and occurring increasingly early in growth and development. The numerous medical conditions associated with overweight and obesity include cardiovascular disease, stroke, diabetes, many cancers, and musculoskeletal disorders.

The U.S. Army, cognizant of the degree to which obesity might impact society in general and its own recruitment base in particular, has funded research into the roots of this condition’s development throughout childhood and into early adulthood. The Troop Recruit Improvement (TRIM) Study is a multicenter effort that will extensively examine the interactions of body composition, physiological, genetic, social, psychological, and economic factors relating to the development of obesity in children, adolescents, and young adults. Pennington Biomedical is one of four clinical sites gathering data to clarify these relationships. Currently in Phase I (pilot), data on smaller samples of children and adolescents are being gathered in 2011 to finalize data collection protocols and set the stage for the full study to begin in 2012.

Phase II will begin the intensive examination of approximately 1,700 youths from 3 states. These participants will be followed annually for up to four years and will submit data in the areas outlined above. Information collected will not only characterize individual children and youths, but will also yield information on the social and economic environments in which they reside, including less commonly examined issues such as food security and availability and seasonal/cyclical factors related to growth, development, and body weight. Data on neighborhood, school, and community characteristics will also be gathered.

The result will be the most extensive picture of the development of overweight ever created and will be invaluable in informing interventions and preventive programs aimed at reducing the current public health burden of overweight.

Research in this laboratory is supported by grants from the U.S. Department of Defense.
FOCUS: The goal of this laboratory is to use research methods to determine how to improve the cost-effectiveness of health care delivery.

Improving cost-effectiveness of health care delivery requires improving the health care cost/quality tradeoff. The Healthcare Quality Improvement (HQI) Laboratory pursues this goal using several methods: (1) redesigning care delivery algorithms, (2) evaluating how to incorporate new technologies into existing care delivery algorithms, (3) designing quality improvement programs and projects, and (4) using informatics coupled with research methods to define and test improvement hypotheses. This work is done largely in conjunction with the LSU Health Care Services Division (LSUHCSD) and its hospitals and clinics at seven major Louisiana population centers.

A recent example, with final analysis still in progress, was a “pragmatic trial” to assess the effectiveness of home tele-monitoring for heart failure patients in reducing adverse events (emergency department visits and inpatient admissions.) Inpatient stays by heart failure patients are a major cost component in American health care, and each such admission represents a potentially avoidable high-risk health event. The HQI Laboratory designed this study in conjunction with Dr. Lee Arcement (study P.I.), an LSUHCSD cardiologist and clinical lead for the division’s heart failure disease management program. The study, done at four LSUHCSD sites, randomized heart failure patients to either home tele-monitoring or usual care. Home tele-monitoring subjects had daily monitoring data (such as weight and blood pressure) automatically forwarded to a nurse care coordinator for daily review. Results suggest that such home tele-monitoring may reduce inpatient admissions of heart failure patients by 60% (see figure.) The improvement may be accompanied by a modest increase in the number of primary care visits per person.

A major emphasis of the HQI Laboratory is the use of health informatics to improve cost-effectiveness. The HQI Laboratory uses the LSUHCSD’s clinical data warehouse (called DMED) to analytically support and evaluate the division’s disease management and population health programs, including programs for adult diabetes, asthma, HIV, chronic kidney disease, heart failure, tobacco control, weight management, hypertension, cancer screening, and medical home development. The HQI Laboratory has developed a “drilling platform,” an electronic interface that allows rapid summarization of program results at the site, clinic, and physician level and that supports case-mix adjustment and subgroup analysis. The HQI Laboratory also has created L-DMED, a limited clinical data warehouse, accessible by authorized epidemiological researchers. L-DMED has been extensively used by the Chronic Disease Epidemiology Laboratory (Dr. Gang Hu) at Pennington Biomedical.

In addition, a largely latent opportunity lies in using very detailed health informatics information to generate more focused hypotheses regarding health outcomes improvement. The HQI Laboratory is now pursuing this approach to develop projects in the following areas: (1) creating a cost-effective algorithm for screening for diabetes and prediabetes (in conjunction with the Chronic Disease Epidemiology Laboratory), (2) incorporating retinal imaging into diabetic eye exam protocols, (3) defining targeted hypotheses for reducing tobacco use, and (4) developing an instrument to assess patient perceptions of medical home experiences.

Research in this laboratory is supported by an ongoing contract with LSUHCSD. The Heart Failure Tele-monitoring study was funded by a grant to LSU from the Louisiana Legislature.

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Tele-monitoring Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total person-years of exposure</td>
<td>33.8</td>
<td>33</td>
</tr>
<tr>
<td>Emergency Department (ED) Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of ED events</td>
<td>58</td>
<td>47</td>
</tr>
<tr>
<td>ED events per person-year</td>
<td>1.72</td>
<td>1.42</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.00</td>
<td>0.83 (p-value = .477)</td>
</tr>
<tr>
<td>Inpatient Admissions (IP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of IP events</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>IP events per person-year</td>
<td>0.77</td>
<td>0.30</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.00</td>
<td>0.39 (p-value = .037)</td>
</tr>
<tr>
<td>Primary Care &amp; Chronic Disease Clinic Visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Clinic Visits</td>
<td>208</td>
<td>253</td>
</tr>
<tr>
<td>Clinic visits per person-year</td>
<td>6.15</td>
<td>7.67</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.00</td>
<td>1.25 (p-value = .058)</td>
</tr>
</tbody>
</table>

Effect of home tele-monitoring program on utilization outcomes among heart failure patients.
FOCUS: Nutritional epidemiology includes all studies of the relationship between diet and health in human populations. Another goal of this laboratory is to provide nutrition education and counseling that improve diet and health.

The Delta Obesity Prevention Research Unit (OPRU) – Strategies to Improve Health in the Delta: Pennington Biomedical has been part of an ongoing collaborative, multiyear research effort to design, carry out, and evaluate interventions directed at improving nutrition in the impoverished and disadvantaged Lower Delta region of Arkansas, Louisiana, and Mississippi. We have been collecting dietary intake information on children in rural Arkansas prior to the start and upon completion of summer camps from 2007 through 2010. The camps provided lunch and snacks for students aged 6 through 13 years and included nutrition education lessons. It was observed that dietary intakes improved among the children due to an emphasis on fruits, vegetables, dairy, and whole grains.

Other efforts from our team have been focused on working with leadership in Arkansas on strategies to improve adherence to the Dietary Guidelines for Americans, specifically on fruits, vegetables, whole grains, and dairy, within an adult population. The three states are involved in this project, which has used focus groups and nutrition education to promote healthier diets.

Dietary Counseling Activities: Several projects at Pennington Biomedical involve dietary counseling efforts.

- The Diabetes Prevention Project Outcomes Study (DPPOS) follows individuals from DPP who have successfully made lifestyle changes; this project will continue until 2015.
- The Look AHEAD trial focuses on lifestyle changes in a population of diabetic individuals.
- The POUNDS LOST trial tested the weight loss effects of four diet treatments varying in protein and fat; subjects were asked to follow structured meal plans or exchange options in order to adhere to the dietary targets.
- The Weight Loss Maintenance (WLM) trial was designed to determine how weight loss achieved in phase 1 of intensive lifestyle change sessions can be best sustained through a second phase, a 30-month period of either personal contact or Internet efforts; the project included a two-year unfunded extension. Dietary changes resulting from the WLM trial were published in the December 2011 volume of the Journal of the American Dietetic Association. Nutritional Epidemiology Laboratory research dietitians/interventionists played key roles by conducting both group and individual sessions utilizing nutrition information and behavior change messages.

Soldier Nutritional Epidemiology: Since 1996, nine studies have been supported in collaboration with the U.S. Army Research Institute of Environmental Medicine (USARIEM). Camp Mackall, NC, was the site of a Special Forces study titled “Energy Expenditure and Physiological Strain in Special Forces Candidates and Cadre,” conducted in two phases during late August and early October 2009. In 2009, Fort Bragg, NC, initiated a study in its dining facilities titled “Testing the Efficacy of Modifying Serving Practices in Military Dining Facilities to Enhance Healthy Nutrition in Soldiers.” The study included 10 dining facilities, with half receiving intervention initially and the remainder after six months. Staff from the Nutritional Epidemiology Lab supported these efforts by using food photography to capture soldiers’ intakes during three time points: baseline prior to intervention (September 2009), 6 months following initial intervention (March 2010), and after 12 months (September 2010).

Research in this laboratory is supported by grants from the U.S. Department of Agriculture, the National Institutes of Health, and the U.S. Army.
**FOCUS:** The goal of this laboratory is to investigate the effects of physical activity, fitness, and obesity on morbidity and mortality and to quantify their impact on population health.

It is clear that physical activity and obesity are intricately linked in their associations with numerous health conditions. Several questions remain about the shape of the dose-response relationship between physical activity and health, how physical activity interacts with obesity and other risk factors in predicting health outcomes, the effect on health of sedentary behaviors such as sitting and watching television versus moderate or vigorous physical activity, and how much and which types of physical activity should be recommended for optimal health benefits. Beyond these basic questions, we have much to learn about gender and ethnic differences in physical activity, obesity, and health.

We are actively collaborating on several projects designed to unlock answers to the questions above, including the Canadian Physical Activity Longitudinal Study (PALS), the Bogalusa Heart Study, InSight, the Pennington Center Longitudinal Study (PCLS), and the National Health and Nutrition Examination Survey. The PCLS represents a cohort of volunteers who have participated in clinical studies at Pennington Biomedical. This cohort was established to better characterize the health of the population and to follow subjects over time for the development of a variety of health problems. This study holds the promise of providing important information on the role of physical activity, nutrition, obesity and other lifestyle behaviors on the future health of the population, particularly in Louisiana.

Research in this laboratory is supported by the National Institutes of Health, the U.S. Department of Agriculture, the Canadian Institutes for Health Research, the Heart and Stroke Foundation of Canada, and the Pennington Biomedical Research Foundation.

Men and women differ in their level of body fatness for a given body mass index (BMI) or body adiposity index (BAI), as shown by this figure from a scientific paper that used data from the PCLS and was published in the Journal of the American Medical Association (JAMA 2011;306(8):828-830). This paper challenged the assertion that BAI is a superior measure of body fat compared to BMI.
**FOCUS:** The goal of this laboratory is to study the measurement of and motivation for walking behaviors in relation to important health outcomes.

The science supporting the health benefits of a physically active lifestyle across the life span is strong. Of all types of physical activity behaviors, ambulatory activity (most obviously walking, but also any lower limb locomotion) is probably the single most important to measure and promote. Walking for exercise is consistently the most frequently reported leisure-time physical activity. In addition, walking is the foremost form of human-powered personal transportation, a part of many nonautomated chores, and a functional aspect of almost all types of personal mobility.

The Walking Behavior Laboratory has established itself as a world leader in the objective monitoring of walking behaviors using accelerometers and pedometers to capture steps per day. For example, we have recently led the writing of three international consensus articles focused on “how many steps per day are enough?” in children/adolescents, adults, and older adults/special populations. With the growing awareness of the detrimental effects of an overly sedentary lifestyle, we are expanding our research to also answer “how many steps per day are too few?” in relation to several important health outcomes.

Steps per day is a measurement representing physical activity volume, and it has been criticized for lacking a description of intensity of movement. Physical activity guidelines worldwide include an element of intensity in their recommendations. In the past year, we have begun to focus on the assessment and analysis of patterns of minute-by-minute cadence (steps per minute), alone and together with steps per day, as a means of getting at intensity. Cadence increases with speed of walking and intensity, and so the study of cadence under free-living conditions represents a simple pattern-recognition strategy. Puttering can be discriminated from walking, and running can be identified with reasonable ease in data sets based on objectively monitored physical activity. In this next year, we will be investigating the relationship between time spent at different cadence levels and important health outcomes, including body composition, diabetes, and overall cardiometabolic health.

To achieve the lab’s mission, we employ a broad range of quantitative and qualitative methods, tap into existing data sets, and seek funding to support original research studies. We have adopted measurement technologies including an electronic walkway that allows us to instantaneously capture research participants’ gait speed, stride lengths, and cadence. We are conducting studies to elucidate the relationship between different cadences and energy expenditure in adults, older adults, and children in order to better estimate energy expenditure of walking in free-living conditions. We have recently received an American Heart Association award to support our WALKMORE study of the relative impacts of two pedometer-based walking interventions (one focused on accumulating more steps per day and the other on steps per day + cadence) in overweight/obese, postmenopausal women with elevated blood pressure. WALKMORE will inform public health messages related to improving blood pressure in a population at increased risk of cardiovascular disease.

Research in this laboratory is supported by grants from the American Heart Association, the U.S. Department of Agriculture, and the National Institutes of Health.
The 2011 installment of Louisiana’s Report Card on Physical Activity and Health for Children and Youth is the fourth annual edition of the Report Card, which is guided by a Research Advisory Committee composed of members from across the state.
THE DIVISION OF EDUCATION administers programs in three major areas: (1) training the next generation of scientists, (2) producing scientific symposia that focus on Pennington Biomedical’s research efforts and attract world-renowned scientists to our Center and (3) organizing professional and community education programs to engage the citizens of Louisiana and the state’s medical community, as well as to provide educational outreach to the general public.

Postdoctoral Training Programs
The Division directs training programs for Pennington Biomedical’s postdoctoral fellows. These programs are designed to train fellows to become productive research scientists capable of establishing independent scientific careers in biomedical research. Many of our fellows are sponsored by NIH Institutional Postdoctoral Training Grants. One of these grants is funded by the National Institute of Diabetes and Digestive and Kidney Diseases and trains fellows to conduct studies that investigate genetic, molecular, behavioral and population aspects of obesity. The other grant from the National Center of Complementary and Alternative Medicine provides training in research skills to identify new plant compounds that may impact metabolic syndrome and its related disorders including diabetes. In addition to research collaboration with faculty mentors, postdoctoral fellows also attend graduate nutrition seminars, participate in workshops on grant proposal writing, enjoy presentations by Center faculty and visiting scientists, and participate in responsible conduct of research seminars and data presentation sessions.

Predoctoral Training
Students from Louisiana universities and medical schools receive hands-on experience in research and laboratory skills each year at Pennington Biomedical, and the Division assists in the placement, training, and tracking of student trainees. The Division of Education recently teamed with LSU Health Sciences...
LSU Agricultural Center

The Division of Education continues its successful partnership with the LSU Agricultural Center and its Division of Education, the Louisiana Cooperative Extension Service. The objective of the partnership is to provide an effective, efficient means of disseminating the latest health and nutrition information to the people of Louisiana. PowerPoint presentations and booklets suitable for use by extension agents, school teachers and the public are contained in the “Pennington Nutrition Series,” a downloadable collection on the LSU Ag Center and Pennington Biomedical Research Center web sites.

LSU Health Care Services

Overweight and obesity are extremely prevalent among patients attending public teaching hospitals and their affiliated medical clinics in Louisiana. The Division of Education partners with the LSU Health Care Services Division to provide weight management instruction to the faculty and staff of the state’s public medical clinics. This initiative includes training in proven, low cost patient-directed weight management techniques, counseling methods and program evaluation.

Future Goals

In order to promote the training of future biomedical scientists, the Division of Education plans to expand programs for predoctoral trainees, expand our role in medical education to promote the next generation of physician scientists, and to reach out to younger academically gifted Louisiana students in hopes of encouraging them to consider careers in biomedical research. We will achieve these new initiatives while enhancing our existing training opportunities for postdoctoral fellows and continuing to produce high quality scientific symposia despite the growing challenge of acquiring the necessary funding for such endeavors. We will continue to serve the citizens of Louisiana by alerting them to new discoveries of Pennington Biomedical and offering new opportunities to participate in the continued success of our Center.
OVERVIEW OF CORE SERVICES

The Pennington Biomedical Research Center provides its researchers with state-of-the-art core services designed to improve efficiency, timeliness and precision of vital technical procedures needed across research boundaries. Core services are divided into three areas: clinical, basic, and population science. The Clinical Cores provide full support for clinical research studies and trials beginning with protocol development, IRB submission, and budgeting and contract assistance. Clinical services include participant recruitment, phlebotomy, biological specimen collection, processing and analysis, exercise testing, dietary assessment, and psychological assessment. The Center also offers both inpatient and outpatient options for trials performed here. Additional clinical services include preparation of meals by the metabolic kitchen, data collection and storage in medical records, medication preparation in the pharmacy, ingestive behavior assessments, imaging procedures using both MRI and DXA and assessments of metabolism in the metabolic chambers. The Basic Science Cores provide researchers with access to cutting edge technology and very focused technical procedures to further their research interests. Basic services include microscopy and imaging of cells and tissues, cell culture facilities, comparative biology, animal metabolism and animal behavior. Additional services include the area of genomics, proteomics and metabolomics, as well as transgenics. The Population Science Cores are directed at providing researchers with access to statistical and database expertise. In addition, the Library and Information Center offers reference, interlibrary loan processing, and bibliographic instruction among other information services.
MISSION: The mission of this core is to facilitate the assessment of metabolism and behavior in small animal models.

This core provides the tools and technical support for investigators to assess a wide range of metabolic and behavioral characteristics of laboratory rodents. For measuring metabolism, highly specialized equipment provides continuous monitoring of the exchange of oxygen and carbon dioxide to generate estimates of energy expenditure and respiratory quotient (carbohydrate vs. fat metabolism) over time, as well as locomotor activity and food and water intake. This year, the core was able to upgrade and expand this technology to provide simultaneous monitoring for 24 animals in a new state-of-art system (see figure). Using other automated apparatuses, feeding behavior can be measured to estimate meal size and feeding bout frequency across daily periods (circadian rhythms). Body composition (fat and lean content) can be measured noninvasively using an NMR machine designed for small animals. A battery of behavioral tests is also available using specially designed equipment. Measures of motor performance include locomotion, balance, gait, and endurance. Motivational measures include hunger, thirst, and anxiety. Specialized apparatuses for measuring cognition include various mazes for assessing spatial learning and memory, classical (Pavlovian) conditioning, and operant conditioning (Skinner boxes). Core staff assist investigators in designing experiments and analyzing data, as well as provide training in using the equipment.

This core is supported by the Nutrition Obesity Research Center funded by the National Institute of Diabetes and Digestive and Kidney Diseases.

MISSION: The mission of this core is to provide biostatistics and data management expertise and resources to enhance reliable and objective research at Pennington Biomedical Research Center.

The Biostatistics and Data Management Core seeks collaborations that lead to a smooth transition from hypothesis formulation to efficient research study design and execution through quality-controlled data management, statistical analysis, and summary presentations. Our overarching goal is to create electronic databases that accurately describe research outcomes and provide state-of-the-art statistical techniques for the objective interpretation of research findings that are captured in the observed data.

The biostatistics team offers expertise to ensure rigorous statistical integrity of research in Basic, Population, and Clinical Sciences. The faculty is strongly encouraged to maintain current expertise through continuing education and to pursue independent research in statistical theory and methods relevant to the Pennington Biomedical mission.

The data management team serves as a comprehensive clinical data-coordinating facility. Their primary responsibility is the continuing development of a proprietary Web-based portal to the clinical research database. The team interfaces with researchers to ensure the efficient and accurate transfer of data from observation to electronic files for storage and analysis; monitors the data processing throughout each study; and provides investigators with study-specific data sets via Web-based desktop data access. The team has developed custom applications for expedited creation of study-specific data sets that may contain both Pennington data and non-Pennington data. This development and data storage paradigm allows the team to work with both intramural and extramural researchers.
MISSION: The mission of this core is to provide state-of-the-art bioimaging-, histological-, and flow cytometry-related instrumentation and support to facilitate data collection and analysis by current and future Pennington Biomedical PIs and their staff.

The Cell Biology and Cell Imaging Core (CBBC) is loosely divided into three sections—imaging, histology/specimen preparation, and analytical/flow cytometry. The imaging section includes the necessary platforms for confocal microscopy, two-photon confocal microscopy, 3D imaging, brightfield imaging, epifluorescent imaging, live cell imaging, ratiometric imaging, total internal reflection fluorescence (TIRF) techniques, and whole slide scanning. The confocal system, the TIRF platform, and one epifluorescence system are capable of live-cell imaging techniques involving the maintenance of proper temperature and CO₂ concentration.

The histology/specimen preparation section of the core houses all the necessary equipment for tissue processing, sectioning, and staining needed by Pennington Biomedical researchers. The CBBC provides access to an automated tissue processor, cryostats, rotary microtomes, a sliding microtome, a vibratome, and autostainers for both traditional stains and immunohistochemical stains. In addition, the core provides access to a laser microdissection system for the precise collection of single cells or whole tissues from sectioned materials.

The analytical/flow cytometry section includes a fluorometric plate reader equipped with a robotic fluidic system for advanced kinetic studies in multiwell plate formats, a four-color analytical flow cytometer, and a high-speed cell sorter housed in a BSLII lamellar flow hood.

Training is available on almost all of the platforms within the CBBC, and staff are available for assistance in the development of experimental protocols and in data collection, analysis, and interpretation.

This core is supported by the Center of Biomedical Research Excellence and the Nutrition Obesity Research Center funded by the National Institutes of Health.

MISSION: The mission of this core is to provide cell culture facilities, equipment, and expertise to investigators requiring such services.

The Cell Culture Core is equipped with four certified Biological Safety Cabinets, four humidified CO₂ incubators, a liquid nitrogen dewar for cell sample cryopreservation, phase contrast microscopy with image capture capability, and support equipment (pH meter, balance, centrifuges, refrigeration, freezers). All equipment is operated with emergency power backup in the event of power failure. A closed room is available for any viral transduction or radioactive isotope studies that would require further isolation. The facility is maintained in a controlled access environment and is available to all Pennington Biomedical laboratories and outside entities on a fee-for-service basis. The Cell Culture Core staff maintains and monitors the instruments on a regular basis to insure their accuracy for use for cell culture experiments. In addition, the staff is available to assist investigators with any questions regarding cell culture experimental design and conduct. The facility is open for use 24 hours per day and on weekends. All prospective users are required to undergo certification in blood-borne pathogen safety regulations prior to authorization for entry and operation. Training in specific cell culture techniques or processes can be provided on an “as requested” basis.

* To provide more efficiency, the Cell Culture Core has recently merged with the Cell Biology and Cell Imaging Core. The combined core is now under the sole direction of Dr. David Burk.
MISSION: The mission of this core is to develop innovative methodology, provide accurate and timely test results, and foster a climate of personal and professional achievement while promoting health and wellness through nutritional research.

The Clinical Chemistry Core offers a comprehensive test menu ranging from routine screening assays to highly complex esoteric tests. The core provides services in the following areas: phlebotomy, accessioning, chemistry, hematology, urinalysis, special chemistry, and point-of-care testing. We also provide long-term specimen storage and maintain a comprehensive management system of specimens and data. During the past year, over 5,000 venipunctures and 350,000 assays were performed. The core performs more than 275 different clinical assays to support clinical trials, basic research, the U.S. Army Research Institute of Environmental Medicine, and contracting clients.

The laboratory follows rigorous quality control assurance practices and is certified by the Health Care Financing Administration and the College of American Pathologists. The laboratory also participates in the Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute lipid standardization program. All medical technologists and phlebotomists are certified by the Louisiana State Board of Medical Examiners.

The laboratory continues to provide method development for novel biomarkers. New assays developed during 2010-2011 include the following: superoxide dismutase, reduced and oxidized glutathione, cadmium, glutathione peroxidase, total antioxidant status, and high-molecular-weight adiponectin.

This core is supported by grant(s) from the National Institutes of Health, the U.S. Department of Defense, and numerous public and private sponsors.

MISSION: The mission of this core is to provide the highest quality animal housing space, animal husbandry and veterinary care, training, and technical support for scientists using animal models.

The Comparative Biology Core (CBC) is a 38,000-square-foot service unit providing laboratory animal housing, receiving, and quarantine facilities and animal procedural, behavioral testing, surgical, and diet preparatory laboratories for use by Pennington Biomedical scientists.

The CBC’s accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care International represents the “gold standard” for laboratory animal care, highlighting our commitment to the highest quality laboratory animal care and use program. The CBC fully endorses and complies with the National Institutes of Health Public Health Service Policy on Humane Care and Use of Laboratory Animals, The Guide for the Care and Use of Laboratory Animals, and the U.S. Department of Agriculture Animal Welfare Act and Regulations. These documents define our responsibility for the proper care and use of laboratory animals. Pennington Biomedical’s Institutional Animal Care and Use Committee, composed of scientists, a veterinarian, and a community member, reviews and must approve all laboratory animal care and use.

Training is vital to ensure the highest quality animal care and to keep staff current on all applicable laws and regulations. All employees who work with laboratory animals must attend animal care and use training covering a broad range of topics including institutional and governmental policies, laboratory animal biomedethology, and occupational health and safety. Ongoing training for laboratory animal care technicians is based on course materials developed by the American Association for Laboratory Animal Science.
The mission of this core is to provide accurate information on dietary intakes of research study participants who keep food records, food frequency questionnaires, and/or dietary recalls. This core also designs menus meeting specific nutrient targets.

Pennington Biomedical’s nutrient analysis system is Moore’s Extended Nutrient Database (MENu), named after its benefactor Margaret C. Moore. Primary data sets used are from the U.S. Department of Agriculture (USDA). The total count of foods and recipes contained in MENu’s food composition files numbers 27,107, from the following data sources:

- USDA Nutrient Database for Standard Reference, Release 23 (September 2010)
- USDA Food and Nutrient Database for Dietary Studies 4.1 (August 2010)
- Supplementary information from the scientific literature or other reliable food composition tables
- User-defined foods, allowing the input of nutrient data for foods needed in menus or recipes for which an appropriate food match cannot be found otherwise
- Recipes input by users of the system at Pennington Biomedical, using a unique recipe calculation system

Food Diary Program. Several research protocols use the Food Diary Program, which utilizes the MENu food composition files to analyze dietary intakes of individuals. In 2009-2010, 20,406 lines of data on dietary intake were processed.

Food Frequencies. Some studies collect food frequency questionnaires (FFQs) to capture intakes over a longer period of time. Currently converted to a scannable questionnaire, the Block Food Frequency Questionnaire (1992) is being used, with results exported electronically; approximately 1,085 FFQs were processed during the past two years. Online versions of this and current National Cancer Institute (NCI) questionnaires are in development.

The mission of this core is to perform reliable and reproducible measurements of energy expenditure and substrate oxidation in humans using indirect calorimetry.

The Energy Metabolism Core daily operations are overseen by Crystal Traylor, N.P., whereas Drs. Eric Ravussin and Leanne Redman provide scientific oversight of all assessments, instrumentation, and measurement quality control.

The core utilizes indirect calorimetry to measure energy expenditure. We have 13 portable bedside metabolic carts (Deltatrac II™ and MAX-II) in service, which allow for measurements of energy expenditure and substrate oxidation under resting conditions. Using these devices, we can also measure acute and chronic changes in energy metabolism in response to thermogenic compounds and ambient temperature, as well as the response to various dietary and exercise treatments.

Pennington Biomedical currently has two whole-room calorimeters, or metabolic chambers. The room calorimeters are used to assess energy expenditure over 24 hours, as well as components of energy expenditure such as sleeping metabolic rate, spontaneous physical activity, and the thermic response to meals. The customized software platform outputs minute-by-minute data also allowing for the assessment of acute effects. Each chamber has an approximate volume of 27,000 L and was designed to provide a pleasant ambiance for study participants.

Within the next year, the Energy Metabolism Core will undergo substantial renovations. We will acquire new space to house a metabolic rate suite and two additional room calorimeters, one with a similar size of 27,000 L and one smaller (10,000 L) with the capacity to modify ambient temperature, which will allow for environmental studies. This work will be conducted mostly by Mr. Tyler Clement, our Biomedical Engineer.

Additionally, the core provides measurement of core body temperature, heart rate variability, and skin temperature by infrared imaging. Approximately 750 metabolic cart measurements and 150 metabolic chamber measurements are performed annually by the Energy Metabolism Core.

This core is supported by grant from National Institutes of Health, U.S. Department of Agriculture, and industry sponsors.
**Core Services**

**Genomics**

**MISSION:** This core seeks to achieve high-quality and cost-effective research data production by providing state-of-the-art expertise, consultation, training, instrumentation, and services for qualitative and quantitative analysis of DNA, RNA, and protein to investigators at Pennington Biomedical and the biomedical research community of Louisiana.

The Genomics Core offers next-generation sequencing services including genomic DNA and exome sequencing, gene expression profiling, small RNA detection, methylation, and chromatin immunoprecipitation (ChIP) analysis using a Life Technologies Applied Biosystems 5500xl SOLiD™ platform and auxiliary equipment. Bioinformatics support is available through a contract with Geospiza. Microarray service is provided using the Illumina BeadArray scanner. Bioinformatics tools to analyze data generated on the high-throughput platforms include Illumina GenomeStudio, Geospiza GeneSifter®, JMP® Genomics, and Acumenta Literature Lab™ software.

Classical DNA sequencing and fragment analysis is performed on two Applied Biosystems 3130xl genetic analyzers. For nucleic acid fragment detection, four Applied Biosystems 7900HT sequence detection systems equipped with 96 well, 384 well, and low-density array blocks are available to perform quantitative PCR. Two pipetting robots, a Beckman Coulter Biomek FX and a PerkinElmer MultiPROBE® II, support robotic liquid handling for high-throughput experiments.

This core is supported by the National Institutes of Health.

**Exercise Testing**

**MISSION:** The mission of this core is to provide accurate, precise, and reliable assessment of physiologic, cardiopulmonary, and muscular strength parameters of exercise performance. The primary aim of the Fitness Center is to provide accurate exercise monitoring for studies requiring specific exercise interventions and for the exercise portion of our Corporate Wellness Program for Pennington Biomedical employees.

The Exercise Testing Core serves the needs of clinical investigators who wish to characterize the cardiopulmonary and strength capacity of their research populations. The goal of the core is to assist investigators with the design and implementation of testing protocols to best facilitate the testing needs of their studies.

The core is equipped with a ParvoMedics TrueOne® metabolic cart for the performance of VO₂max testing, a custom Lode Valiant treadmill with a “double-wide” (105 cm; 41.3 inches) and extra long (200 cm; 78.7 inches) treadmill running surface, and a Lode Excalibur Sport bicycle ergometer. The core also includes a Biodex isokinetic strength dynamometer to perform constant velocity strength testing.

Our Valiant Treadmill has a zero starting speed and acceleration capabilities ranging from 0.2 to 40 km/h (0.124 to 24.8 mph) and is capable of imposing both positive (+25%) and negative/downhill (-10%) running grades while accommodating patient weights up to 340 kg (750 lb). The Lode Excalibur Sport ergometer is capable of singular wattage increments ranging from 0 to 1000 W. The Biodex system interfaces with computer microprocessors to measure torque, power, and endurance for resistance throughout a joint’s range of motion in most musculoskeletal joint areas. In 2009, we added the ability to perform muscle biopsies in association with exercise testing and exercise performance.

**Director:**
Conrad Earnest, Ph.D., FACSM

**Staff:**
Melissa Lupo, B.S.

**Director:**
J. Michael Salbaum, Ph.D., Associate Professor

**Staff:**
Susan Newman, B.S.; Richard Carmouche B.S.; Diana Holmes, M.S.
MISSION: The core provides state-of-the-art imaging instrumentation which allows turnkey solutions for clinical investigators who need high-quality measures of body composition and function.

This core places in the hands of researchers a variety of instrumentation and technical services including the following:

- Hologic® QDR-4500A and GE iDXA dual energy X-ray absorptiometers (DXA) for the measurement of whole-body composition and site-specific bone mineral density
- Oasis™-based coordination of multicenter DXA studies
- An EchoMRI™ for whole-body nuclear magnetic resonance (NMR) body composition
- A Toshiba Aplio SSA-280 ultrasound/Doppler for cardiac and general purpose imaging, carotid ultrasonography, and studies of post-ischemic reactive hyperemia (brachial artery flow-mediated dilatation)
- An EndoPAT2000 for measurement of peripheral arterial tone
- Access to a 64-slice computed tomography (CT) scanner at the Baton Rouge General Medical Center Bluebonnet campus
- Assistance with special projects requiring image analysis of CT, magnetic resonance imaging, or ultrasound images, including multicenter clinical trials

The core also includes a magnetic resonance imaging (MRI) and spectroscopy (MRS) and functional MRI (fMRI) lab. The lab consists of a GE 3.0T Signa® EXCITE MR scanner, a series of specialized coils and instrumentation for MRS and fMRI, and clinical facilities oriented toward patient comfort and convenience. In addition to a variety of body image scans, this instrument allows researchers to noninvasively make the following measures of biochemistry in situ without biopsies:

- Proton spectroscopy for the measurement of intrahepatic and intramyocellular lipids
- Phosphorus spectroscopy to measure post-ischemic and exercise phosphocreatine recovery rates (resting and maximal ATP synthesis)
- fMRI with appropriate visual stimulation paradigms

The measurement of resting ATP turnover rates is complemented by optical spectroscopy. This technique allows researchers to directly measure oxygen consumption in skeletal muscle. When combined with resting ATP turnover rates, the mitochondrial coupling ratio or P/O can be directly measured for the first time in intact muscle.

MISSION: The Inpatient Clinic serves the needs of clinical investigators for the conduct of advanced clinical end points in studies of obesity, diabetes, and metabolism.

The unit consists of:

- Seven rooms, with two beds each, for overnight clinical stays and procedures; these rooms have been recently renovated and are comfortably furnished with large windows, private bath facilities, and telephones
- Two dedicated rooms for euglycemic hyperinsulinemic clamps
- Procedure room for oral glucose tolerance testing, IV glucose tolerance testing, pharmacokinetic studies, and other related procedures
- Dedicated biopsy room for adipose tissue and skeletal muscle biopsies
- Satellite clinical chemistry sample-processing and -accessioning room
- Room dedicated to the measurement of food intake and macronutrient selection
- Fully equipped Inpatient Clinic/Eating Laboratory Metabolic Kitchen
- Lounge/sunroom for volunteers where they can watch TV/DVDs, surf the Internet, and play games while admitted to the inpatient for specific research protocols
- Large nursing station that includes a remote pharmacy, Internet/intranet access, and work table
- Psychology data collection area for questionnaire completion on PCs

Immediately adjacent facilities: DXA, echocardiography, ultrasound, 3T magnetic resonance imaging (MRI) and spectroscopy (MRS), and pulmonary function and exercise testing units

The unit is staffed 24 hours a day, 7 days a week.
MISSION: The mission of the Library and Information Center is to serve the Pennington Biomedical students, faculty, staff, and the Baton Rouge community by providing access to the information resources needed to support and develop learning, teaching, and research at the Center.

The Pennington Library and Information Center services are designed to anticipate and respond to the information needs of all Pennington Center faculty and staff. The Library also provides services to the local community by providing limited access to health information resources and services.

Staffed by a director and assistant librarian, the library continues to offer reference, information services, interlibrary loan processing, and bibliographic instruction to all employees and is accessible to them twenty-four hours a day, seven days a week. Access to a specialized print and electronic resource collection concentrated in the medical field is provided. In addition to this collection, the library annually provides approximately 2500 requested informational items through various document delivery methods. The library is a renewing member of the National Network of Libraries of Medicine and LOUIS Louisiana Library Network.

Library databases include Medline (via PubMed and EbscoHost), the Science/Social Science/Arts & Humanities Citation Indexes and Journal Citation Reports Index (via ISI), and Agricola, Medline Full-Text, PsycINFO, Biological and Social Science Abstracts (via EbscoHost). Library staff provides instruction and support for these resources in addition to EndNote, Reference Manager and other programs accessible through the PBRC network. Wireless connectivity and a computer lab are also available, comprised of four computer workstations with hardware (color and b&w printers, scanners) as well as a variety of software.

The Pennington Library and Information Center now offers several new programs that combine traditional services with emerging technologies. They include a laptop/electronic reader checkout and an active paperback exchange. The library also provides a custom poster printing service for research poster presentations and other signage as needed. Development of the existing Faculty Publication Database into a complete electronic and print archive is in progress; new documents and photographs are being organized and added as they become available.

Research in this laboratory is funded by grant(s) from the National Institutes of Health, the U.S. Department of Defense, and numerous public and private sponsors.
MISSION: The Outpatient Clinic supports clinical trials by screening volunteers and collecting research data. Screening involves visits in the clinic for those who pass the initial telephone screening by the Recruitment Core.

The Outpatient Clinic is on the first and second floors of the new four-floor Pennington Biomedical Clinical Research Building, which occupies 90,000 square feet of space. There are 18 examination rooms, 2 electrocardiogram/procedure rooms, 3 private interview rooms, a phlebotomy laboratory with 6 phlebotomy chairs, a room for measuring height and weight, and a locked pharmacy storage room. There is a medical records library with three offices, administrative and physician office space, three recruiting offices, and reception/waiting areas.

The Imaging/MRS Core is also on the first floor and has dual energy X-ray absorptiometry (DXA), nuclear magnetic resonance (NMR), optical spectroscopy, and ultrasound rooms. There is also an Exercise Testing Core for testing strength and fitness, including locker facilities. The second floor has an eating laboratory core and office space.

The Outpatient Clinic employs 44 people: a clinic director, two physicians, a physician assistant, eleven nurse coordinators, eleven study coordinators, five dietitians, a project coordinator, a medical records librarian with two assistants, four secretarial personnel, a data entry supervisor, a postdoctoral fellow, and three part-time pharmacists.

In 2010, there were 13,032 telephone screenings, 2,483 screening visits, and 1,790 subjects randomized into clinical trials. There were 39 new clinical trials with funding from the federal government, industry, and foundations. The Outpatient Clinic participates in multicenter trials and collaborates with industry to develop new products. Most of the studies performed at Pennington Biomedical relate to obesity or its associated complications, including diabetes, abnormal fat metabolism, high blood pressure, and atherosclerotic vascular disease. We are now developing new research programs in aging and sleep abnormalities.
The mission of this core is to provide scientific and technical expertise and resources to enable researchers to apply proteomics and metabolomics for biomedical and biological studies.

The Proteomics and Metabolomics Core provides investigators at Pennington Biomedical and around the world with an array of cutting-edge tools and technologies to investigate the causes of diseases. The facility specializes in the analysis of biological molecules (peptides, proteins, lipids, and small molecules) from tissues, blood, urine, and cell cultures. The Proteomics and Metabolomics Core facility utilizes powerful separation technologies such as multidimensional liquid chromatography in conjunction with mass spectrometric detection to identify, quantify, and characterize biological molecules. These tools enable measurement of changes in thousands of molecules in a single experiment in order to learn which are important for a particular disease. These tools also can be used for more detailed investigation of one or more biological molecules that have been found to be important for a particular disease. These measurements are used to understand the causes of diseases, to understand the mechanisms by which treatments for diseases are effective, and to identify molecules that can be used for diagnosis and prognosis of diseases.

The facility is equipped with five mass spectrometers, seven liquid chromatography systems, and several robotic workstations. The core also maintains a variety of software packages to provide bioinformatics support for both global and targeted proteomics and metabolomics applications. The core staff provides a significant amount of consulting regarding analytical techniques and works with scientists to develop new experimental methods.

**MISSION:** The goal of this core is to provide recruitment services for clinical trials to accelerate participant accrual rates.

The Recruiting Core is dedicated to promoting clinical trials to the public. Since the formalization of the core in 2007, much advancement has taken place to improve the efficacy and efficiency of recruiting. Our goal is to accelerate recruitment by establishing innovative methods of advertisement, increasing available resources, and developing tools to streamline the accrual process. Traditional advertisement mediums that are utilized include newspaper, television, and direct mailing. Meanwhile, more novel methods have been employed, including online and email advertisements. An advertisement-tracking system provides the necessary metrics to measure efficacy and facilitate market testing.

The core is equipped with a Uniform Call Distributor (UCD)-enabled call center and is operated by a team of six full-time recruiters. A UCD system expands the capability of a traditional phone system by processing large volumes of phone calls and distributing them evenly across available recruiters. During periods when the volume of calls exceeds the number of available recruiters, callers are directed to a voicemail system. Information from that system is subsequently inputted into an electronic message-tracking application, developed to expedite and track follow-up. One of the tools developed to enhance the recruiting process is the electronic phone screen system, which allows recruiters to screen potential participants while seamlessly matching them to alternative clinical trials in the event that they do not meet the criteria for the study for which they originally called.

In 2010 and 2011, the Recruiting Core conducted over 21,000 phone screens and scheduled over 2,600 screening visits.
The Research Kitchen Core is located on the second floor of the Clinical Research Building. It is a state-of-the-art facility that is equipped to provide quality service and is ideal for conducting simultaneous study protocols. Approximately 225 meals per day can be prepared in the facility. The core’s dietitians use a nutritional analysis program to precisely plan menus and recipes to meet the requirements of each study protocol. The Research Kitchen is integrated into the clinic scheduling system at Pennington Biomedical, and its dietitians work directly with principal investigators as they plan research and design study protocols. The Research Kitchen works closely with the Inpatient Clinic and Ingestive Behavior Laboratory, providing meals to these entities, collecting food intake data by weighing food provision and plate waste, and entering these data into the Center’s Central Database.

The core employs a director who oversees menu planning, food production, and daily management of the operation, while research dietitians are responsible for managing the dietary component of specific study protocols. Research specialists and a food service worker prepare and serve the research-designated diets. Meal monitors sit with participants during meal times to ensure that participants are being compliant. The Research Kitchen receives oversight by a users committee.

The Transgenic Core currently produces genetically engineered mice for faculty at Pennington Biomedical, as well as investigators at other institutions. The core utilizes pronuclear microinjection and embryonic stem cell technologies to control gene expression in mice. We strive to provide services at prices below those that are commercially available. The unique feature that we offer over most other cores is a turnkey service for generating knockout mice at a price well below commercial cost. By having a full-time person devoted to the design and construction of the targeting vector, we have created an efficient, money-saving service for Pennington Biomedical investigators.

Pennington Biomedical has an Association for Assessment and Accreditation of Laboratory Animal Care International-approved animal facility capable of housing and providing care for the number of mice necessary for transgenic work. The barrier portion of the animal facility has 3,000 square feet for transgenic use capable of housing 6,000 mice. There is a 400-square-foot wet lab within the barrier for embryo manipulation.

Microinjection of mutant mouse embryonic stem cells into mouse blastocysts.
The Pennington Biomedical Research Center has maintained its capability of expanding and growing its scientific, clinical, and population science research efforts over the past several years of economic recession. Now in the third year of a five year $71 million capital construction and renovation campaign, a new 90,000 sq ft Clinical Research Center has recently opened and a state of the art 30,000 sq ft Biomedical Imaging Center is soon to be completed. In all, over 320,000 sq ft of new and renovated space position Pennington Biomedical to remain current and competitive in the research arena both nationally and internationally.

Funding for the center has remained relatively stable despite shrinking state appropriations due to the variety of funding sources utilized - federal grants, private grants and contracts, and state research grants. Additionally, the Pennington Biomedical Research Foundation and the Pennington Medical Foundation provide funding for periodic capital projects and ongoing operations. With such diversified funding sources, Pennington Biomedical has been able to maintain a high level of productivity and research activity in the face of the difficult economic environment.

**Federal Grants**

Pennington Biomedical is a continuing success story in attaining federal research funding and has consistently been in the $20 million range for federal awards over the last three years. A large portion of this federal funding comes from the National Institutes of Health (NIH) grants through a highly competitive review process, and the Pennington Biomedical’s research scientists are extremely successful in competing with top researchers across the country.

The United States Department of Defense also continues its long-standing research relationship with the Pennington Biomedical Research Center. In past years, this research has delved into a number of facets of military nutrition and fitness. This relationship continues to be very important to the growth and success of the center with the recent award of a $6 million dollar grant to research optimal war fighter nutrition.

**Private Research Grants and Contracts**

Pennington Biomedical has long been recognized by private industry as a premier clinical and basic research institute, resulting in private grants and contracts established with pharmaceutical companies, the food industry, non-profit health organizations such as the American Diabetes Association, the American Heart Association and the American Cancer Society, and various other businesses and not-for-profit entities. Current researchers have been increasingly successful in obtaining industry awards and the level of private grants and contracts recently exceeded $10 million annually.

**State Appropriations**

Unrestricted state dollars are used to fund pilot studies that result in new grants and contracts, as seed money to recruit new research faculty and to build new research programs at the Pennington Biomedical. The state of Louisiana receives a return on this investment through an inflow of research dollars from sources outside of the state while also creating new jobs and new wealth in Louisiana.

In the last fiscal year, Pennington Biomedical received approximately $14 million in unrestricted state funding, down from a peak of $17 million three years ago.

**Outlook for the Future**

Shrinking state appropriations have challenged the Pennington Biomedical Research Center to creatively expand its horizons to leverage the unique human and physical resources at its disposal. With state of the art facilities and world class research faculty, the major goal and focus will be to generate new partnerships, programs and revenue streams that will enable Pennington Biomedical to remain financially secure and successful in realizing its vision for the future.
Computing Services provides exceptional technical support in cutting edge technologies, collaborative tools and customized application development.

Computing Services’ focus is on supporting every facet of the research and business operations at the Center. It provides support through its four functional groups: Administrative Computing, Nutritional Computing, Technical Support and Education, and Infrastructure.

Computing Services keeps abreast of new technological advances and places a high value on opportunities to integrate them into our technology offerings in order to increase collaborative opportunities for our faculty and decrease the burden for administrative staff. By enriching the computing environment, we are able to improve overall efficiency and enhance the Center’s research activities. We work continuously to identify the information technology needs of our researchers, and design and implement timely technological solutions to meet these needs. We also place much emphasis on ensuring the most competent support possible, by the technical training of our staff. We are proud to be associated with the science produced by our institution and gladly welcome the opportunity to join in the Center’s pursuit of excellence.

Facilities Management provides operation and maintenance services for the entire Pennington Biomedical Research Center campus.

The department is charged with responsibilities for the interior environmental control of the facility; building maintenance and equipment repairs; utility services; grounds maintenance; custodial services; reception and mailing services; shipping and receiving; property control; management of the on-site Residence Center; and security. Facilities Management also provides overall project design supervision and monitors construction activity for facility additions and renovations.

Presently, department personnel are administering and supervising the design and implementation of more than $50 million in Capital Outlay construction projects. The receiving department processes all deliveries made to the Center and is responsible for shipping, receiving, and delivering all packages, and for tagging and tracking all moveable equipment with a value of $1,000 or more. All requests for furniture moves and office personnel relocations are also coordinated through this department.

The security department is responsible for the safety and well being of employees, visitors and the protection of property. Security officers are responsible for providing coverage on a twenty four hour basis throughout the year and for the issuing and monitoring of ID badges and parking tags for employees, external contractors and visitors.
**FOCUS:** Fiscal Operations provides sound fiscal management of the Center’s financial assets, ensures compliance with Federal and State laws and regulations, enables timely procurement and delivery of goods and services, and oversees a multitude of business-related functions and services.

Fiscal Operations managers provide individualized financial management of research and clinical funding procured by the Pennington Biomedical faculty. Detailed management of accounting and reporting requirements of grants and contracts by Fiscal Operations affords them the opportunity to focus on the science of their funded research.

The management services provided by Fiscal Operations include payroll, purchasing, accounts payable, post-award financial management, contracts audit, budget preparation and monitoring, travel reimbursement audit, and collection of university revenues. Fiscal Operations also prepares all financial accounting and reporting for the Pennington Biomedical Research Center relative to all state, federal, and industry funding.

**FOCUS:** Human Resource Management is committed to providing Pennington Biomedical with a qualified, trained workforce by working as a partner with management to recruit and retain a highly qualified diverse workforce.

The department provides efficient and effective support services to management in such areas as recruitment, employment, benefits, immigration, reporting, and retention and reward of faculty and staff.

Developing and implementing all policies, procedures, and programs which promote a positive, productive and fair work environment for faculty and staff, and designing fair, competitive benefit and compensation programs as appropriate are large key components of the department’s activities. The HRM department is responsible for overseeing all personnel and employee benefit programs offered to faculty and staff as part of the LSU System, including all health, dental, vision, term life, accidental death and dismemberment, long term care and long term disability insurance offerings, the flexible spending and dependent care spending account options, the tuition exemption program, retirement planning options, and provision of an employee assistance program.

Human Resources Management is also dedicated to ensuring compliance with all federal, state, and local employment laws.
FOCUS: Intellectual Property, Legal and Regulatory Affairs (IPLRA) oversees activities involving economic development, commercialization of research, legal, regulatory and compliance functions for the entire center.

The economic development mission of the Office of IPLRA is to commercialize Pennington Biomedical’s intellectual property, new inventions and discoveries, including patents and copyrights, to license these technologies and to develop business partnerships in the United States and worldwide. IPLRA also functions as the compliance office for Pennington Biomedical and as the liaison to other regulatory offices and programs at the Center.

IPLRA is responsible for HIPAA Compliance and works closely with the Institutional Review Board (IRB), the Biosafety Committee, and all other compliance components.

FOCUS: Sponsored Projects provides information, advice, and assistance to faculty and staff in the acquisition and administration of externally funded projects.

Pre-award and non-financial post award management of sponsored research and clinical trials, as well as provision of current information on funding opportunities, sponsor requirements, and state and federal regulations allows Sponsored Projects to enhance the competitiveness of Pennington Biomedical researchers.

The services provided by Sponsored Projects include proposal review and approval, budget development, contract preparation and negotiation, reporting, subrecipient monitoring, post award modifications, and interpretation of sponsor regulations and requirements. Pennington Biomedical researchers are also assisted in locating funding opportunities, preparing and processing proposal information, and administering awarded projects. The Sponsored Projects staff serves as liaisons with representatives for grants awarded by federal, state, and local government agencies, as well as for research and clinical trial projects funded through private corporations and foundations. Sponsored Projects works closely with Intellectual Property, Legal and Regulatory Affairs and Fiscal Operations to support and facilitate proper stewardship of external funding.
At Pennington Biomedical Research Center, our new mission is to discover the triggers of chronic diseases through innovative research that improves human health across the lifespan.
“In addition to our own researchers, Pennington Biomedical benefits from the talents, abilities and experience of over 85 adjunct faculty. These adjunct faculty members represent more than 30 universities and research institutes from around the State of Louisiana and the world.”

— Steven B. Heymsfield, M.D., Executive Director
<table>
<thead>
<tr>
<th>Adjunct Employee</th>
<th>PBRC Title</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>George Argyropoulos, Ph.D.</td>
<td>Associate Professor</td>
<td>Weis Research Institute</td>
</tr>
<tr>
<td>David Baker, Ph.D., D.V.M.</td>
<td>Professor</td>
<td>Louisiana State University School of Veterinary Medicine</td>
</tr>
<tr>
<td>Lydia Bazzano, Ph.D.</td>
<td>Assistant Professor</td>
<td>Tulane University School of Public Health and Tropical Medicine</td>
</tr>
<tr>
<td>Eric Drake Bellanger, M.D.</td>
<td>Instructor</td>
<td>Advanced Videoscope Surgery</td>
</tr>
<tr>
<td>Peter H. Bennett, MD, FRCP</td>
<td>Professor</td>
<td>The National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health</td>
</tr>
<tr>
<td>Gerald Berenson, M.D.</td>
<td>Professor</td>
<td>Tulane University</td>
</tr>
<tr>
<td>Steven Blair, P.E.D</td>
<td>Professor</td>
<td>University of South Carolina</td>
</tr>
<tr>
<td>John F. Bolter, M.D.</td>
<td>Professor</td>
<td>The NeuroMedical Center</td>
</tr>
<tr>
<td>Leon Bombet, M.D.*</td>
<td>Instructor</td>
<td>The Baton Rouge Clinic</td>
</tr>
<tr>
<td>Sandra Brown, Ph.D.</td>
<td>Professor</td>
<td>Southern University</td>
</tr>
<tr>
<td>Bruce Bunnell, Ph.D.</td>
<td>Professor</td>
<td>Tulane University</td>
</tr>
<tr>
<td>Thomas Burris, Ph.D.</td>
<td>Professor</td>
<td>Scripps Research</td>
</tr>
<tr>
<td>John T. Caprio, Ph.D.</td>
<td>Professor</td>
<td>Louisiana State University</td>
</tr>
<tr>
<td>Stuart Chalew, M.D.</td>
<td>Professor</td>
<td>Children's Hospital</td>
</tr>
<tr>
<td>Wei Chen, M.D., Ph.D.</td>
<td>Professor</td>
<td>Tulane University</td>
</tr>
<tr>
<td>Paul Ronald Clisham, M.D.</td>
<td>Assistant Professor</td>
<td>Tulane University</td>
</tr>
<tr>
<td>Deborah A. Cohen, M.D., M.P.H.</td>
<td>Professor</td>
<td>Rand Corporation</td>
</tr>
<tr>
<td>Lisa A. Colvin, Ph.D., FACSM</td>
<td>Professor</td>
<td>University of Louisiana - Monroe</td>
</tr>
<tr>
<td>Vinod Dasa, M.D.</td>
<td>Assistant Professor</td>
<td>Ochsner Medical Center, LSU Health Sciences Center</td>
</tr>
<tr>
<td>Daniel DiLorenzo, M.D., Ph.D.</td>
<td>Assistant Professor</td>
<td>DiLorenzo Biomedical, LLC</td>
</tr>
<tr>
<td>Robert Dubin, M.D.</td>
<td>Associate Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Karen Elkind-Hirsch, Ph.D.</td>
<td>Professor</td>
<td>Woman's Health Research Institute</td>
</tr>
<tr>
<td>John W. Finley, Ph.D.</td>
<td>Professor</td>
<td>Louisiana State University Agricultural Center</td>
</tr>
<tr>
<td>Anne Foundas, M.D.</td>
<td>Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Joseph Francis, Ph.D.</td>
<td>Associate Professor</td>
<td>Louisiana State University School of Veterinary Medicine</td>
</tr>
<tr>
<td>Warren Fraser, M.D.</td>
<td>Instructor</td>
<td>Caring Clinic of Louisiana</td>
</tr>
<tr>
<td>Patrick W. Gahan, M.D.</td>
<td>Associate Professor</td>
<td>Lake Senior Care Center</td>
</tr>
<tr>
<td>Earl James Garitty, M.D.</td>
<td>Instructor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Julia George, J.D.</td>
<td>Instructor</td>
<td>Louisiana Department of Culture, Recreation and Tourism</td>
</tr>
</tbody>
</table>

* deceased
<table>
<thead>
<tr>
<th>Adjunct Employee</th>
<th>PBRC Title</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>David Glancy, M.D.</td>
<td>Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Stewart Gordon, M.D.</td>
<td>Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Jimmy Guidry, M.D.</td>
<td>Assistant Professor</td>
<td>Louisiana Department of Health &amp; Hospitals</td>
</tr>
<tr>
<td>Thomas Guillot, M.D.</td>
<td>Assistant Professor</td>
<td>Our Lady of the Lake</td>
</tr>
<tr>
<td>Barbara Hasek, Ph.D.</td>
<td>Instructor</td>
<td>Baton Rouge Community College</td>
</tr>
<tr>
<td>Mark Hausmann, M.D.</td>
<td>Associate Professor</td>
<td>The Surgeons Group of Baton Rouge</td>
</tr>
<tr>
<td>Mark Heiman, Ph.D.</td>
<td>Associate Professor</td>
<td>NuMe Health</td>
</tr>
<tr>
<td>Julie Holden, M.D.</td>
<td>Instructor</td>
<td>Tulane University</td>
</tr>
<tr>
<td>Houchun Harry Hu, Ph.D.</td>
<td>Assistant Professor</td>
<td>University of Southern California</td>
</tr>
<tr>
<td>Glenn Jones, Ph.D.</td>
<td>Associate Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Anita S. Kablinger, M.D.</td>
<td>Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Michael Keenan, Ph.D.</td>
<td>Associate Professor</td>
<td>Louisiana State University</td>
</tr>
<tr>
<td>Betty Kennedy, Ph.D.</td>
<td>Instructor</td>
<td>Louisiana School Boards Association</td>
</tr>
<tr>
<td>Leslie Kozak, Ph.D.</td>
<td>Professor</td>
<td>Polish Academy of Sciences</td>
</tr>
<tr>
<td>Carol Lammi-Keefe, Ph.D.</td>
<td>Professor</td>
<td>Louisiana State University</td>
</tr>
<tr>
<td>Carl J. Lavie, M.D.</td>
<td>Professor</td>
<td>John Oschner Heart and Vascular Institute</td>
</tr>
<tr>
<td>Karl LeBlanc, M.D.</td>
<td>Professor</td>
<td>The Surgeons Group of Baton Rouge</td>
</tr>
<tr>
<td>Monique M. LeBlanc, Ph.D.</td>
<td>Instructor</td>
<td>Southeastern Louisiana University</td>
</tr>
<tr>
<td>Michael Lefevre, Ph.D.</td>
<td>Professor</td>
<td>Utah State University</td>
</tr>
<tr>
<td>Natalie Leonard, Ph.D.</td>
<td>Instructor</td>
<td>Our Lady of the Lake College</td>
</tr>
<tr>
<td>Lilian Levitan, Ph.D.</td>
<td>Instructor</td>
<td>The National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health</td>
</tr>
<tr>
<td>Zhijun Liu, Ph.D.</td>
<td>Professor</td>
<td>Louisiana State University Agricultural Center</td>
</tr>
<tr>
<td>Mandi Lopez, Ph.D., D.V.M.</td>
<td>Associate Professor</td>
<td>Louisiana State University School of Veterinary Medicine</td>
</tr>
<tr>
<td>Jennifer Lovejoy, Ph.D.</td>
<td>Professor</td>
<td>Alere Wellbeing, Inc.</td>
</tr>
<tr>
<td>Ronald Luftig, Ph.D.</td>
<td>Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Lan Chi Luu, Ph.D.</td>
<td>Instructor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Nathan Markward, Ph.D.</td>
<td>Assistant Professor</td>
<td>Blue Cross/Blue Shield of Louisiana</td>
</tr>
<tr>
<td>Pamela Martin, Ph.D.</td>
<td>Assistant Professor</td>
<td>Behavioral Medicine</td>
</tr>
<tr>
<td>Roy Martin, Ph.D.</td>
<td>Professor</td>
<td>University of California - Davis</td>
</tr>
<tr>
<td>Adjunct Employee</td>
<td>PBRC Title</td>
<td>Institution</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Kenneth Matthews II, Ph.D.</td>
<td>Associate Professor</td>
<td>Louisiana State University</td>
</tr>
<tr>
<td>Leslie McLaughlin, Ph.D., D.V.M.</td>
<td>Assistant Professor</td>
<td>Louisiana State University School of Veterinary Medicine</td>
</tr>
<tr>
<td>Steve Nelson, M.D.</td>
<td>Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Augusto Ochoa, M.D.</td>
<td>Associate Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>John T. Paige, M.D.</td>
<td>Associate Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Curtis Phifer, Ph.D.</td>
<td>Professor</td>
<td>Northwestern State University</td>
</tr>
<tr>
<td>Angelo Pietrobelli, M.D.</td>
<td>Associate Professor</td>
<td>Verona University Medical School</td>
</tr>
<tr>
<td>Stefany Primeaux, Ph.D.</td>
<td>Assistant Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Ilya Raskin, Ph.D.</td>
<td>Professor</td>
<td>Rutgers University</td>
</tr>
<tr>
<td>David Ribnicky, Ph.D.</td>
<td>Professor</td>
<td>Rutgers University</td>
</tr>
<tr>
<td>Edward Richards III, J.D. M.P.H.</td>
<td>Professor</td>
<td>Louisiana State University Paul M. Hebert Law Center</td>
</tr>
<tr>
<td>Paulo Rodriguez, Ph.D.</td>
<td>Instructor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Wei Shen, M.D.</td>
<td>Assistant Professor</td>
<td>Columbia University</td>
</tr>
<tr>
<td>Lars Sjostrom, M.D.</td>
<td>Professor</td>
<td>Goteborg University</td>
</tr>
<tr>
<td>Steve Smith, M.D.</td>
<td>Professor</td>
<td>Translational Research Institute</td>
</tr>
<tr>
<td>Melinda Sothern, Ph.D.</td>
<td>Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Sathanur Srinivasan, Ph.D.</td>
<td>Professor</td>
<td>Tulane University</td>
</tr>
<tr>
<td>Laura K., Stewart, Ph.D.</td>
<td>Assistant Professor</td>
<td>Louisiana State University</td>
</tr>
<tr>
<td>Diana Thomas, Ph.D.</td>
<td>Professor</td>
<td>Montclair State University</td>
</tr>
<tr>
<td>Lisa Tussing-Humphreys, Ph.D., R.D.</td>
<td>Instructor</td>
<td>Southern Regional Research Center – USDA</td>
</tr>
<tr>
<td>Gabriel Uwaifo, M.D.</td>
<td>Associate Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Julia Volaufova, Ph.D.</td>
<td>Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Michaela Vossen, Ph.D.</td>
<td>Instructor</td>
<td>Medistat GmbH</td>
</tr>
<tr>
<td>Michael Welsh, Ph.D.</td>
<td>Associate Professor</td>
<td>Louisiana State University</td>
</tr>
<tr>
<td>Brooke Whisenhut, Ph.D.</td>
<td>Assistant Professor</td>
<td>Missouri State University</td>
</tr>
<tr>
<td>Marney White, Ph.D.</td>
<td>Assistant Professor</td>
<td>Yale University</td>
</tr>
<tr>
<td>Donald Williamson, Ph.D.</td>
<td>Professor</td>
<td>Louisiana State University</td>
</tr>
<tr>
<td>Eugene Woltering, M.D.</td>
<td>Professor</td>
<td>Louisiana State University Health Sciences Center</td>
</tr>
<tr>
<td>Jolene Zheng, Ph.D.</td>
<td>Assistant Professor</td>
<td>Louisiana State University - Agricultural Center</td>
</tr>
</tbody>
</table>
PUBLICATIONS

SECOND EDITION

Physical Activity and Obesity

Claude Bouchard
Peter T. Katzmarzyk
editors

PENNINGTON BIOMEDICAL RESEARCH CENTER


Aronne LJ, Rogers RC, Van Meter MJ and Hermann GE. Co-localization of TRHR1 and LepRb receptors on neurons in the hindbrain of the rat. Brain Res 2010; 1355:70-85.

Barnes MJ, Argyropoulos G and Bray GA. Preference for a high fat diet, but not hyperphagia following activation of mu opioid receptors is blocked in AgRP knockout mice. Brain Res 2010; 1345:146-55.


Camhi SM, Stefanick ML, Katzmarzyk PT and Young DR. Metabolic syndrome and changes in body fat from a low-fat diet and/or exercise randomized controlled trial. Obesity (Silver Spring) 2010; 18(3):548-54.

Camhi SM, Stefanick ML, Ridker PM, and Young DR. Changes in C-reactive protein from low-fat diet and/or physical activity in men and women with and without metabolic syndrome. Metabolism 2010; 59(1):54-61.


Deitulis JA, Liu LF, Belury MA, Rim JS, Shin S and Lee K. Betat(3)-

Dixit VD. Thymic fatness and approaches to enhance thymopoietic


Dorsey KB, Thornton JC, Heymsfield SB and Gallagher D. Greater lean tissue and skeletal muscle mass are associated with higher bone mineral content in children. Nutr Metab (Lond) 2010; 7:41.


Hu G. Total cholesterol and the risk of Parkinson’s disease: a review for some new findings. *Parkinsons Dis* 2010; 2010:836962.


Jackson AW, Lee DC, Sui X, Morrow JR, Jr., Church TS, Maslow AL and Blair SN. Muscular strength is inversely related to prevalence and incidence of obesity in adult men. *Obesity (Silver Spring)* 2010; 18(10):1988-95.


Katzmarzyk PT. Physical activity, sedentary behavior, and health: paradigm paralysis or paradigm shift? *Diabetes* 2010; 59(11):2717-25.


Primeaux SD, Barnes MJ, Braymer HD and Bray GA. Sensitivity to the satiating effects of exendin 4 is decreased in obesity-prone Osborne-Mendel rats compared to obesity-resistant SSB/PI rats. *Int J Obes (Lond)* 2010; 34(9):1427-33.


Sutton GM, Centanni AV and Butler AA. Protein malnutrition during pregnancy in C57BL/6J mice results in offspring with altered circadian physiology before obesity. *Endocrinology* 2010; 151(4):1570-80.


Adams CE, Myers VH, Barbera B and Brantley PJ. The role of fear of negative evaluation in predicting depression and quality of life four years after bariatric surgery in women. *Psychology 2011*; 2:150-54.


Lecoultre V, Ravussin E and Redman LM. The fall in leptin concentration is a major determinant of the metabolic adaptation induced by caloric restriction independently of the changes in leptin circadian rhythms. *J Clin Endocrinol Metab* 2011; 96(9):E1512-6.


Shin AC, Townsend RL, Patterson LM and Berthoud HR. “Liking” and “wanting” of sweet and oily food stimuli as affected by high-fat diet-induced obesity, weight loss, leptin, and genetic predisposition. Am J Physiol Regul Integr Comp Physiol 2011; 301(5):R1267-80.


Yu JM, Wu X, Gimble JM, Guan X, Freitas MA and Bunnell BA. Age-related changes in mesenchymal stem cells derived from rhesus macaque bone marrow. *Aging Cell* 2011; 10(1):66-79.


OUR SUPPORTERS

PENNINGTON MEDICAL FOUNDATION

Board of Trustees:

Paula Pennington de la Bretonne, Chair

Jake L. Netterville, Vice Chairman

G. Lee Griffin
Charles Lamar
Richard Lipsey
John V. Lombardi, Ph.D.
Claude B. Pennington III
Daryl B. Pennington, Sr.
Raymond G. “Skipper” Post
William B. Richardson, Ph.D.
Larry H. Hollier, M.D.
Christel C. Slaughter, Ph.D.

Ex-Officio

Steven Heymsfield, M.D.
Executive Director, Pennington
Biomedical Research Center

Secretary

William Hodgkins

President and
Chief Executive Officer

William L. Silvia, Jr.
Dear Friends,

The Trustees of the Pennington Medical Foundation have faithfully fulfilled the intentions of my grandparents by being astute stewards of the funds they provided for the development of the Pennington Biomedical Research Center into a world leader in the field of diabetes and obesity research. Through careful management, the Foundation has provided over $165 million in program support for Pennington Biomedical since its inception. In the current fiscal year, the Foundation will provide over $3 million to assist the Center in accomplishing its mission.

Over the years since the original donation, the funds provided by the Foundation have resulted in the construction and equipping of over one-half million square feet of research and support space. In addition, the Foundation has provided Pennington Biomedical with vital funding for endowed research scientists, start-up packages for research faculty, unrestricted development funds for its Executive Director, and numerous other support opportunities for which state funds were unavailable.

Recently, the Foundation has focused on assisting Pennington Biomedical in developing a technology transfer and commercialization program. The Foundation has provided funds for leading experts in the field of intellectual property to visit the Center and work with Foundation and Center staff to develop programs designed to bring the scientific discoveries of the Center to the public marketplace. This is extraordinarily important from two perspectives. First, by bringing discoveries from the research and clinical laboratories to the public, peoples’ lives are improved. Chronic diseases are prevented or managed in ways which were previously unknown. Second, the commercialization of technologies provides potentially significant revenue streams that are exceedingly important in these stressful economic times. Through the leadership of Governor Jindal and the Legislature, the state funded a new Clinical Research Building, Imaging Center, and the renovation of existing clinical research space into a childhood obesity center. As these facilities become available, opportunities to put innovative ideas into action for the benefit of Louisiana’s citizens will accelerate.

On a sad note, this year marks the passing of Dr. Allen Copping. Dr. Copping and I served together as Trustees of the Foundation since its inception in 1980. Dr. Copping was passionate about the Pennington Biomedical Research Center. He shared my grandfather’s vision and, as both a Trustee and more importantly, as President of the Louisiana State University System, he was instrumental in guiding and protecting the Center during precarious fiscal times. Dr. Copping always considered the Pennington Biomedical Research Center to be one of his grandest accomplishments. We all will miss his wit, wisdom, gentle direction and advice.

Sincerely,

Paula Pennington de la Bretonne

Chair
Includes members from January 1, 2010 until December 31, 2011

Board of Directors

PENNINGTON BIOMEDICAL RESEARCH FOUNDATION

Officers
Tim A. Barfield, Jr.
Chairman
John B. Noland
Immediate Past-Chair
J. Gerard “Jerry” Jolly
Vice-Chair
C. Brent McCoy
Treasurer
Annette D. Barton
Secretary

Directors
Clay M. Allen
J. Herbert Boydstun
J.S. “Si” Brown, III
J. Terrell Brown
Joseph “Jay” H. Campbell, Jr.
Maxine CORMIER
Robert W. Daigle
Paula P. de la Bretonne
Paul M. Haygood
C. Kris Kirkpatrick
Luther “Luke” C. Kissam, IV
Charles A. Landry
Carl S. Luikart, M.D
Kevin R. Lyle
Myron E. Moorehead, M.D.
Elizabeth “Betsy” S. Nalty
George D. Nelson, Jr.
Nanette Noland
Kevin P. Reilly, Jr.
Kevin P. Reilly, Sr.
Elizabeth Querbes Sammons
John Spain

Ex-Officio Directors
Steven B. Heymsfield, M.D.
Executive Director, Pennington Biomedical Research Center
John V. Lombardi, Ph.D.
President, LSU System
Melvin “Kip” Holden
Mayor-President, East Baton Rouge Parish
Adam Knapp
President/CEO, Baton Rouge Area Chamber
Janet L. Olson
Chair, Annual Fund for Excellence 2010-2011
David A. Winkler
Chair, Annual Fund for Excellence 2011-2012
Jennifer G. Winstead
President/CEO, Pennington Biomedical Research Foundation
J. Brad Jewell
Chief Financial Officer, Pennington Biomedical Research Foundation

* Includes members from January 1, 2010 until December 31, 2011
Dear Friends,

As chairman of the Pennington Biomedical Research Foundation, I am pleased to share that once again the generosity of our donors has contributed to helping the Pennington Biomedical Research Center continue its work to lead the world in eliminating chronic diseases.

Private donations help to enable Pennington Biomedical retain important scientific leaders and advance research. These philanthropic gifts are vital and help to support pilot projects, endow chairs and professorships, and invest in the health and well-being of citizens, locally and worldwide. Our donors also helped to make targeted recruitments of key research faculty in 2010 and 2011, and provided bridge funding to existing scientists that allowed their research to proceed while competing for outside funding.

The research taking place at the Pennington Biomedical Research Center is more important than ever. We are grateful to the individuals, companies, and foundations that are helping Pennington Biomedical fulfill its mission of discovering the triggers of chronic diseases through innovative research that improves human health across the lifespan.

Sincerely,

Tim Barfield
Chairman of the Board
ENDOWED CHAIRS
(AS OF DECEMBER 31, 2011)

Claude B. Pennington, Jr. Endowed Chair
Donor:  C.B. “Doc” Pennington
Eminent Scholar: Jacqueline Stephens, Ph.D.

United Companies/Harris J. Chustz Endowed Chair
Donor: United Companies Financial Corporation
Eminent Scholar:  Abba Kastin, M.D., Ph.D.

Hibernia National Bank/Edward G. Schlieder Endowed Chair
Donors: Edward G. Schlieder Educational Foundation and Capital One, formerly Hibernia National Bank
Eminent Scholar:  Jeffrey Keller, Ph.D.

George A. Bray, Jr. Endowed Super Chair in Nutrition
Donor:  Pennington Medical Foundation
Eminent Scholar:  Steven Heymsfield, M.D.

Douglas L. Gordon Endowed Chair in Diabetes and Metabolism
Donor:  Edward G. Schlieder Educational Foundation
Eminent Scholar:  Eric Ravussin, Ph.D.

LPFA Endowed Chair in Nutrition
Donor:  Louisiana Public Facilities Authority
Eminent Scholar:  Peter Katzmarzyk, Ph.D.

Marie Edana Corcoran Endowed Chair in Pediatric Obesity and Diabetes
Donor:  Our Lady of the Lake Foundation
Eminent Scholar: Under Recruitment

Peggy M. Pennington Cole Endowed Chair in Maternal Biology and the Risk of Obesity
Donors: Irene W. & C.B. Pennington Foundation and the Community Foundation for Southeastern Michigan
Eminent Scholar:  Claudia Kappen, Ph.D.

Johns S. McIlhenny Endowed Chair in Health Wisdom
Donor:  Coypu Foundation Trust
Eminent Scholar:  Timothy Church, M.D., M.P.H., Ph.D.

John W. Barton, Sr. Endowed Chair in Genetics and Nutrition
Donors: Various (Friends and Family of John W. Barton, Sr.)
Eminent Scholar:  Claude Bouchard, Ph.D.

Fairfax Foster Bailey Endowed Chair in Heart Disease Prevention
Donors:  Laura and James J. Bailey III, Virginia and John B. Noland, and P. Foster Bailey
Eminent Scholar: Under Recruitment

ENDOWED PROFESSORSHIPS
(AS OF DECEMBER 31, 2011)

Douglas L. Manship, Sr. Endowed Professorship in Diabetes
Donor: Douglas L. Manship, Sr.
Eminent Scholar:  William Cefalu, M.D.

John Stauffer McIlhenny Endowed Professorship in Nutrition
Donor:  Coypu Foundation Trust
Eminent Scholar:  Phillip Brantley, Ph.D.

George H. Bray Endowed Professorship
Donors:  George and Mitzi Bray and Friends
Eminent Scholar:  Hans-Rudolf Berthoud, Ph.D.

John S. McIlhenny Endowed Professorship in Nutritional Neuroscience
Donor:  Coypu Foundation Trust
Eminent Scholar:  Richard Rogers, Ph.D.
Our Donors – Honoring Lifetime Giving

**PENNINGTON SOCIETY**
$1,000,000 and above

*Irene W. and *C.B. Pennington
Baton Rouge Area Foundation
*Imogene N. Brown
  *in memory of L. Heidel Brown
Community Foundation for
Southeastern Michigan
Coypu Foundation Trust
Edward G. Schlieder Educational
Foundation
Irene W. and C.B. Pennington
Foundation
Virginia B. and John B. Noland
Our Lady of the Lake Foundation

**PRESIDENT’S CIRCLE**
$500,000 and above

Alta and John Franks Foundation
Bailey and Noland Families
  *Laura and James J. Bailey III
  *Virginia B. and John B. Noland
*P. Foster Bailey
John W. Barton, Sr.
Capital One
  *formerly Hibernia National Bank
The Coca-Cola Company
Entergy Corporation
JP Morgan Chase Bank
  *formerly Bank One, City National Bank,
  *Premier Bank and LNB
Louisiana Public Facilities Authority
United Companies Financial Corporation/
  Harris J. Chustz

**PREEMINENT BENEFACCTOR**
$250,000 and above

Blue Cross and Blue Shield of Louisiana
Charles Lamar Family
The Reilly Family Foundation

**PREMIER BENEFACCTOR**
$100,000 and above

Albemarle Foundation
Amedisys, Inc.
Loretta M. and Edward M. Downey
Eli Lilly and Company
Anonymous
Gordon & Mary Cain Foundation
Hancock Bank and Trust Company
  of Louisiana
Dr. William Hansel
Knoll Pharmaceutical – BASF Corporation
Lamar Advertising Company
Pat and Don Lyle
Ruth and *Charles W. McCoy
*Margaret C. Moore
Our Lady of the Lake Regional
  Medical Center
*Bert S. and Sue Turner

**PHILANTHROPIST**
$50,000 and above

Patsy and Lawrence D. Adcock
Amylin Pharmaceuticals, Inc.
Laura and James J. Bailey III
Nan and Tim Barfield
Annette D. Barton
Mitzi and George A. Bray, M.D.
Mary Kay and J. Terrell Brown
Centers for Obesity Research & Education
CIGNA Foundation
Mr. and Mrs. Dudley W. Coates
Columbia Medical Center of Baton Rouge
Lev Dawson
Dr. Jacques and Paula P. de la Bretonne
ExxonMobil
General Health System
Guaranty Corporation
Anne and Bill Hise
Hovey S. Simon - Uniroyal Chemical
  Company Fund
D. Benjamin Kleinpeter
Charles and Josephine Lamar
  Memorial Fund
  *Mr. and Mrs. Bill Dixon
  *Mr. and Mrs. Charles W. Lamar III
Mr. and Mrs. Charles W. Lamar III
Louisiana Ballooning Foundation
Kevin R. Lyle
*Douglas L. Manship, Sr.
Mars, Incorporated
Medical University of South Carolina
The Milford Wampold Support
  Foundation
Nutrition 21, Inc.
Ochsner Medical Center of Baton Rouge
Anonymous
Phenex Pharmaceuticals AG
Phytomedics, Inc.
*Norma Jean Raiford
Roche Laboratories, Inc.
RoyOMartin
Slim Fast Foods Company
John G. Turner and Jerry G. Fischer
University of Colorado Foundation, Inc.
Westlake Partners
Woman's Hospital

**PARTNER**
$25,000 and above

The Advocate
AgriTech Company, Inc.
Ajinomoto
American Medical Assoc. -
  Educational Research Foundation
Baton Rouge Coca-Cola
Nan and Herb Boydstun
Buquet & Leblanc, Inc.
Digestive Health Foundation of Louisiana
The Dow Chemical Company
Sylvia and Gene Duke
Anonymous
The John Galt Fund
Mr. and Mrs. John H. Hernandez
The John W. Barton Family Foundation
Kellogg Company
Kraft Foods North America, Inc.
Latter & Blum, Inc. / C.J. Brown Realtors
Long Law Firm, LLP
Louisiana Charities Trust
McMains Foundation
Milton J. Womack, Inc.
Anonymous
Noesis Data, LLC
Nanette Noland
Orentreich Foundation for the
  Advancement of Science
Joanie and Allen Penniman
The Pew Charitable Trusts
Pfizer, Inc.
Placid Refining Company, LLC
Steve Hicks/ Provident Resources Group
Jerry* and Chuck Schwing
The Shaw Group Inc.
Page and William L. Silvia, Jr.
The Josef Sternberg Memorial Fund
Moo and Martin Svendson

* Deceased
<table>
<thead>
<tr>
<th>Donor Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takeda Pharmaceuticals North America, Inc.</td>
</tr>
<tr>
<td>Kay and Roland M. Toups</td>
</tr>
<tr>
<td>Turner Industries Group, LLC</td>
</tr>
<tr>
<td>Anonymous</td>
</tr>
<tr>
<td>W.R. Grace &amp; Company</td>
</tr>
<tr>
<td>WHLC Architecture</td>
</tr>
<tr>
<td>Margaret C. and *Milton J. Womack</td>
</tr>
<tr>
<td>Joanna Wurtele</td>
</tr>
<tr>
<td><strong>PATRON</strong> $10,000 and above</td>
</tr>
<tr>
<td>Anne and Herschel Abbott</td>
</tr>
<tr>
<td>ABIC International Consultants</td>
</tr>
<tr>
<td>Adams and Reese, LLP</td>
</tr>
<tr>
<td>Allen &amp; Gooch, A Law Corporation</td>
</tr>
<tr>
<td>America on the Move</td>
</tr>
<tr>
<td>Amgen, Inc.</td>
</tr>
<tr>
<td>Arthur J. Gallagher Risk Management Services, Inc.</td>
</tr>
<tr>
<td>Associated Food Stores</td>
</tr>
<tr>
<td>Anonymous</td>
</tr>
<tr>
<td>Anonymous</td>
</tr>
<tr>
<td>Baton Rouge General Medical Center</td>
</tr>
<tr>
<td>Dr. Drake E. Bellanger</td>
</tr>
<tr>
<td>Jeanie and David Bondy</td>
</tr>
<tr>
<td>Dr. Claude Bouchard and Monique Chagnon</td>
</tr>
<tr>
<td>Mrs. Jane T. Boyce</td>
</tr>
<tr>
<td>H. Douglas Braymer, Ph. D.</td>
</tr>
<tr>
<td>Marilyn Braymer</td>
</tr>
<tr>
<td>Breazeale, Sachse &amp; Wilson, LLP</td>
</tr>
<tr>
<td>Bruce Foods Corporation</td>
</tr>
<tr>
<td>Business First Bank of Baton Rouge</td>
</tr>
<tr>
<td>Drs. Laura and William M. Cassidy</td>
</tr>
<tr>
<td>The Children’s Hospital</td>
</tr>
<tr>
<td>Maxine Cormier</td>
</tr>
<tr>
<td>Corporate Management of Baton Rouge, Inc.</td>
</tr>
<tr>
<td>Aglonie and Michael S. DiVincenti, Jr.</td>
</tr>
<tr>
<td>Edgen Murray Corporation</td>
</tr>
<tr>
<td>Kathryn and David M. Ellison, Jr.</td>
</tr>
<tr>
<td>Equitas Capital Advisors, LLC</td>
</tr>
<tr>
<td>Pam and Charles Fisher</td>
</tr>
<tr>
<td>Lynnette and Tommy Frazer</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>*Patricia and *Robert S. Greer, Sr.</td>
</tr>
<tr>
<td>Barrie and Lee Griffin</td>
</tr>
<tr>
<td>Guaranty Broadcasting Company of Baton Rouge, LLC</td>
</tr>
<tr>
<td>Ava and Cordell Haymon</td>
</tr>
<tr>
<td>Cindy and John Hill, Jr.</td>
</tr>
<tr>
<td>Richard and Debra Hise</td>
</tr>
<tr>
<td>Investar Bank</td>
</tr>
<tr>
<td>J.B. James Construction</td>
</tr>
<tr>
<td>Jean H. Curet Fund for Medical Research</td>
</tr>
<tr>
<td>Dr. and Mrs. Sheldon A. Johnson</td>
</tr>
<tr>
<td>Donna and Jerry Jolly</td>
</tr>
<tr>
<td>Jones Walker</td>
</tr>
<tr>
<td>Margo and Roy G. Kadair, M.D.</td>
</tr>
<tr>
<td>KPMG, LLP</td>
</tr>
<tr>
<td>Anonymous</td>
</tr>
<tr>
<td>Anne C. and Walter E. Legett, Jr.</td>
</tr>
<tr>
<td>Susan and Richard Lipsey</td>
</tr>
<tr>
<td>Louisiana Diabetes Foundation, Favre &amp; Lipe Research Fund</td>
</tr>
<tr>
<td>Louisiana Machinery</td>
</tr>
<tr>
<td>Maggie and Jonathan Martin</td>
</tr>
<tr>
<td>Dr. and Mrs. Roy J. Martin</td>
</tr>
<tr>
<td>Mary Bird Perkins Cancer Center</td>
</tr>
<tr>
<td>Brent McCoy</td>
</tr>
<tr>
<td>*John S. McIlhenny</td>
</tr>
<tr>
<td>Phyllis and Lee McLaurin</td>
</tr>
<tr>
<td>McNeil Nutritionalns</td>
</tr>
<tr>
<td>Merck &amp; Co., Inc.</td>
</tr>
<tr>
<td>The Merice “Boo” Johnson Grigsby Foundation</td>
</tr>
<tr>
<td>Merrill Lynch</td>
</tr>
<tr>
<td>Miss Teen USA - Miss Universe Organization</td>
</tr>
<tr>
<td>National Dairy Council</td>
</tr>
<tr>
<td>Mr. James M. Nolan</td>
</tr>
<tr>
<td>The Nanette Nolan Foundation</td>
</tr>
<tr>
<td>North American Association for the Study of Obesity</td>
</tr>
<tr>
<td>Novo Nordisk, Inc.</td>
</tr>
<tr>
<td>Pamlab, LLC</td>
</tr>
<tr>
<td>Performance Contractors, Inc.</td>
</tr>
<tr>
<td>Claudia and Gary Phillips</td>
</tr>
<tr>
<td>Post Architects</td>
</tr>
<tr>
<td>Bryan and Raymond G. Post, Jr.</td>
</tr>
<tr>
<td>Postlethwaite &amp; Netterville, APAC</td>
</tr>
<tr>
<td>Mr. and Mrs. Kevin P. Reilly, Jr.</td>
</tr>
<tr>
<td>Donna H. Ryan, M.D. and Edwin Lupberger</td>
</tr>
<tr>
<td>Janice and Frank Sadler</td>
</tr>
<tr>
<td>Servier Amerique</td>
</tr>
<tr>
<td>Steven R. Smith, M. D. and Joffa Braymer, M.D.</td>
</tr>
<tr>
<td>*Mr. and Mrs. Joe D. Smith</td>
</tr>
<tr>
<td>Source Capital, LLC</td>
</tr>
<tr>
<td>St. James Place</td>
</tr>
<tr>
<td>Mr. and Mrs. Leonard Sullivan</td>
</tr>
<tr>
<td>Taylor Porter Law Firm</td>
</tr>
<tr>
<td>*Ida and *J. Frank Terrell, Jr.</td>
</tr>
<tr>
<td>*Charlotte M. Thompson</td>
</tr>
<tr>
<td>U.S. Army Research Institute of Environmental Medicine</td>
</tr>
<tr>
<td>University Club Plantation</td>
</tr>
<tr>
<td>USDA</td>
</tr>
<tr>
<td>WBRZ-TV Channel 2</td>
</tr>
<tr>
<td>Whole Foods Market, Inc.</td>
</tr>
<tr>
<td>Ann Wilkinson</td>
</tr>
<tr>
<td>William E. Montan Charitable Trust</td>
</tr>
<tr>
<td>Jennifer and Chuck Winstead</td>
</tr>
<tr>
<td>*Barbara Womack</td>
</tr>
<tr>
<td>William H. Wright, Jr.</td>
</tr>
<tr>
<td>Margaret C. Womack Hart</td>
</tr>
<tr>
<td><strong>PACESETTER</strong> $5,000 and above</td>
</tr>
<tr>
<td>Anonymous</td>
</tr>
<tr>
<td>The Alma Lee and H. N. Saurage, Jr. Fund</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists</td>
</tr>
<tr>
<td>Analytic Stress</td>
</tr>
<tr>
<td>Arthritis Foundation</td>
</tr>
<tr>
<td>Princeton and Dadie Bardwell</td>
</tr>
<tr>
<td>Barrett, Vernon &amp; Montgomery, LLC</td>
</tr>
<tr>
<td>Peggy and John Barton, Jr.</td>
</tr>
<tr>
<td>Mary Scott Barton</td>
</tr>
<tr>
<td>Baton Rouge Cardiology Center</td>
</tr>
<tr>
<td>Bernhard Brothers Mechanical Contractors</td>
</tr>
<tr>
<td>Jeanelle Beskin</td>
</tr>
<tr>
<td>Melanie and John Boyce</td>
</tr>
<tr>
<td>*Mrs. Ruth S. Calhoun</td>
</tr>
<tr>
<td>Rosemary and John S. Campbell, Jr.</td>
</tr>
<tr>
<td>Mr. and Mrs. J.H. Campbell, Jr.</td>
</tr>
<tr>
<td>Campus Federal Credit Union</td>
</tr>
<tr>
<td>Catalyst Pharmaceutical Partners, Inc.</td>
</tr>
<tr>
<td>Elizabeth and William Cefalu</td>
</tr>
<tr>
<td>Catherine Champagne, Ph.D., R.D.</td>
</tr>
<tr>
<td>Patricia L. Cheramie</td>
</tr>
<tr>
<td>*City Social Magazine</td>
</tr>
<tr>
<td>Clear Channel Communications</td>
</tr>
<tr>
<td>Community Health Charities of LA and MS</td>
</tr>
<tr>
<td>Covidienn</td>
</tr>
<tr>
<td>Crestar Financial Corporation</td>
</tr>
</tbody>
</table>

*Deceased
Louis D. Curet
Daniel T. Calongne and Associates
*George A. Daniels
deGravelles & Associates
Mr. Michael T. Delahaye
*Mrs. Eleanor J. Eldredge
Juliet S. Dougerty
Ethicon Endo-Surgery, Inc.
Evans-Graves Engineers, Inc.
Ms. Stephanie Ferry
Sharon and Jack H. Field, Jr.
Mary Barnett Fruhan
General Mills
Grady Crawford Construction Co., Inc.
Bob Greer Family
Gupta/Mittal Family: Alok and Sunita Gupta
Anonymous
Dr. Richard C. Rogers and Dr. Gerlinda Hermann
Dr. and Mrs. Steven B. Heymsfield
Dr. and Mrs. Richard M. Hill
William R. and Marilyn S. Holman
IBERIABANK
Donald and Kitty Ingram
In Vitrogen Corporation
Dr. Anne Rossi Jarrett
Julie and Leonard R. Nachman II
Nestle S.A.
Orexigen Therapeutics, Inc.
*Hermann Moyse, Jr.
Julie and Leonard R. Nachman II
Nestle’ S.A.
Phelps Dunbar, LLP
Mary Olive Pierson
Jim and Shannon Poche’
Proctor & Gamble Company
Real Estate Management Services Group, LLC
Renal Associates of Baton Rouge, LLC
Ragan and Virginia Richard
Dr. Jennifer C. Rood and Mr. Michael Rood
Beverly and Rory Russell
Mr. and Mrs. Chris Sammons
Schwab Charitable Fund
Frank and Marcy Simoneaux
Christel C. and William S. Slaughter III
Mr. and Mrs. Lee Solomon, Solomon Family Foundation
Southeastern Cardiovascular Consultants, LLC
Stuart & Company General Contractors, LLC
Ralph and Margi Underwood
Unilever Corporate Research
WAFB-TV Channel 9
Nancy and Gerald L. Walter, Jr.
Weight Watchers International, Inc.
Willis-Knighton Health System
David and Anne Winkler
Bobby and Marsha Yarborough
Janet and John A. Young

* Deceased