

Two Decades of Discovery



TIME FOR DISCOVERIES
20 Years

“Given the growth experienced by the Pennington Biomedical Research Center during the relatively short time it has been operational, we can predict that it will become one of the premier research institutions in the country.”

Claude Bouchard, Ph.D.

Executive Director

Pennington Biomedical Research Center

Foreword	3	<i>Autonomic Neuroscience Laboratory</i>	76
Message from the Executive Director	4	<i>Blood-Brain Barrier Laboratory – I</i>	77
Vision 2010 – A Status Report	9	<i>Blood-Brain Barrier Laboratory – II</i>	78
Two Decades of Discovery	12-25	<i>Neurobehavior Laboratory</i>	79
<i>Remembering “Doc”</i>	13	<i>Neurobiology and Nutrition Laboratory – I</i>	80
<i>“The Biggest and Best Nutrition Research Center”</i>	14	<i>Neurobiology and Nutrition Laboratory – II</i>	81
<i>Timeline</i>	16	<i>Neurosignaling Laboratory</i>	82
Twenty Years of Community Support	28-31	<i>Neurotrauma and Nutrition Laboratory</i>	83
<i>Pennington Medical Foundation</i>	28	<i>Nutritional Neuroscience and Aging Laboratory</i>	84
<i>Pennington Biomedical Research Center</i>	30	<i>Adipocyte Signaling Laboratory</i>	85
Status of Research Programs	32-46	<i>Endocrinology Laboratory</i>	86
BASIC RESEARCH	33	<i>John C. McIlhenny Skeletal Muscle Physiology Laboratory</i>	87
<i>Division of Experimental Obesity</i>	35	<i>Nuclear Receptor Biology Laboratory</i>	88
<i>Division of Functional Foods</i>	37	<i>Protein Structural Biology</i>	89
<i>Division of Nutrition and the Brain</i>	39	<i>Maternal Biology</i>	90
CLINICAL RESEARCH	40	<i>Epigenetics and Nuclear Reprogramming Laboratory</i>	91
<i>Division of Clinical Obesity and the Metabolic Syndrome</i>	42	<i>Regenerative Biology Laboratory</i>	92
<i>Division of Nutrition and Chronic Diseases</i>	43	<i>Stem Cell Biology Laboratory</i>	93
<i>Division of Health and Performance Enhancement (HaPE)</i>	45	<i>Ubiquitin Biology Laboratory</i>	94
POPULATION SCIENCE	46	Clinical Research Unit Reports	96-106
Division of Education	48-50	<i>Behavioral Medicine Laboratory</i>	98
Centers of Excellence	52-57	<i>Health Psychology Laboratory</i>	99
<i>Clinical Nutrition Research Unit</i>	53	<i>Woman’s Health, Eating Behavior and</i>	
<i>Center for Botanicals and Metabolic Syndrome</i>	55	<i>Smoking Cessation Program</i>	100
<i>COBRE - Center of Biomedical Research Excellence</i>	57	<i>Ingestive Behavior Laboratory</i>	101
Basic Research Laboratory Reports	58-94	<i>Exercise Biology Laboratory</i>	102
<i>DNA Damage and Repair Laboratory</i>	60	<i>Human Physiology Laboratory</i>	103
<i>The William Hansel Cancer Prevention Laboratory</i>	61	<i>Preventive Medicine Laboratory</i>	104
<i>Antioxidant and Gene Regulation Laboratory</i>	62	<i>Diet, Physical Activity and Behavior Modification Trials</i>	105
<i>John C. McIlhenny Botanical Research Laboratory</i>	63	<i>Pharmacology-Based Clinical Trials</i>	106
<i>Mechanisms of Diabetes Complications Laboratory</i>	64	Population Science Laboratory Reports	108-113
<i>Gene-Nutrient Interactions Laboratory</i>	65	<i>Chronic Disease Epidemiology and Health Delivery</i>	110
<i>Dietary Obesity Laboratory</i>	66	<i>Clinical Epidemiology</i>	111
<i>Functional Genomics Laboratory</i>	67	<i>Nutritional Epidemiology</i>	112
<i>Infection and Obesity Laboratory</i>	68	<i>Physical Activity Epidemiology Laboratory</i>	113
<i>Neuroendocrine Immunology Laboratory</i>	69	Core Services	114-125
<i>Energy Balance</i>	70	BASIC RESEARCH CORES	115-118
<i>Human Genomics Laboratory</i>	71	<i>Animal Metabolism and Behavior</i>	115
<i>Molecular Genetics and Thermogenesis Laboratory</i>	72	<i>Cell Biology and Cell Imaging</i>	115
<i>Neuropeptides Laboratory</i>	73	<i>Cell Culture</i>	116
<i>Regulation of Gene Expression</i>	74	<i>Comparative Biology</i>	116
<i>Taste Genetics Laboratory</i>	75	<i>Genomics Facility</i>	117
		<i>Proteomics</i>	117
		<i>Transgenic</i>	118

(Continued on the next page)

CLINICAL RESEARCH CORES 118-125

<i>Biostatistics and Data Management</i>	118
<i>Clinical Chemistry</i>	119
<i>Dietary Assessment and Food Analysis</i>	120
<i>Exercise Testing</i>	120
<i>Imaging</i>	121
<i>Inpatient Unit</i>	121
<i>Library and Information Center</i>	122
<i>Mass Spectrometry</i>	122
<i>Metabolic Chambers</i>	123
<i>Outpatient Clinic</i>	124
<i>Recruitment</i>	125
<i>Research Kitchen</i>	125

Administrative Services and Finance 126-134

<i>Message from the Associate Executive Director for Administration and Finance</i>	127
<i>Communications</i>	129
<i>Computing Services</i>	130
<i>Facilities Management</i>	131
<i>Fiscal Operations</i>	132
<i>Human Resource Management</i>	132
<i>Intellectual Property, Legal and Regulatory Affairs</i>	133
<i>Sponsored Projects</i>	135

Adjuncts and Honors 136-141

<i>Adjunct Faculty</i>	137
<i>Faculty Emeritus</i>	139
<i>Doctorate Honoris Causa</i>	140

Journal Articles and Publications 142-161

<i>Journal Articles 2006 through 2007</i>	143
<i>Books and Chapters 2006 through 2007</i>	159

Our Supporters 162-171

<i>A Message from our Chair – Pennington Medical Foundation</i> ..	163
<i>PMF Board of Trustees and Staff</i>	164
<i>A Message from our Chair – Pennington Biomedical Research Foundation</i>	165
<i>PBRF Board of Directors and Staff</i>	166
<i>Endowed Chairs and Professorships</i>	167
<i>Our Donors – Honoring Lifetime Giving</i>	168

Foreword

This year, 2008, marks the 20th Anniversary of the opening of the Pennington Biomedical Research Center. During these two decades, our successes have been closely tied to the support of many. We are sincerely indebted to former LSU System Presidents Allen Copping, D.D.S., and William Jenkins, Ph.D., as well as former Executive Vice-President Mr. William Silvia, who now serves as Chief Financial Officer of the Pennington Medical Foundation. We are also thankful to other vice-presidents of the LSU System and members of the LSU Board of Supervisors for supporting our mission and encouraging the growth of the Pennington Biomedical Research Center during our 20 year history. We look forward as well to a strong relationship with our new system president, John Lombardi, Ph.D.

I would like to express our gratitude to former Governor Mike Foster for his support, and former Governor Kathleen Babineaux-Blanco, former President of the Senate, Dr. Donald Hines, and former Speaker of the House, Mr. Joe Salter, for their support, particularly their work in the 2007 legislative session to place sufficient funds in the state budget to begin construction of a much needed clinical research facility and for the increase in our regular state appropriation. I am thankful also to the former Commissioner of Administration, Mr. Jerry Luke LeBlanc. And, of course, we are thankful that Governor Bobby Jindal was a supporter of our Center even before taking office, and we look forward to working closely with him and his new administration. We are also grateful to the Louisiana Board of Regents and to the Commissioner of Higher Education, Dr. T. Joseph Savoie, for the confidence they have expressed in the future of the Pennington Biomedical Research Center.

In recent times, we have benefitted from the tremendous support of our city's business and political leaders. I'd like to thank Stephen Moret, former President and CEO of the Baton Rouge Area Chamber. Under his leadership, the Chamber placed the Center's legislative funding at the top of its priority list. John Davies, President and CEO of The Baton Rouge Area Foundation, which was with us even before we officially opened our doors, has continued to express his strong support for the Center and its mission. Finally, our current Mayor, Melvin "Kip" Holden, has taken a personal interest in the Center, and we are grateful for his commitment to PBRC.

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, leads a

group of professionals whose management skills have resulted in the steady growth of our endowment. They 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. Likewise, Mr. John Noland, Chairman of the Board, and Ms. Jennifer Winstead, President and CEO of the Pennington Biomedical Research Foundation, and their fellow board members are fully engaged in the task of creating endowed chairs and professorships and raising unrestricted funds as well. 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, our heartfelt gratitude and thanks.

The progress we have made during these 20 years would not have been possible without the dedication of our faculty, staff and management team. Their devotion to our research and education makes the Pennington Biomedical Research Center an inspiring place to work.

We will be forever grateful and thankful to the late Claude B. "Doc" Pennington and his wife, the late Irene Pennington, for their vision and generosity. Actively working to reach and enlarge their original vision are their grandchildren Paula, Daryl and Claude. The Pennington family has created in Baton Rouge a center of excellence focused on discovery, prevention of diseases, promotion of a high quality of life and economic development. Their continued generosity has captured the attention of their city, state and nation and garnered the praise and admiration of scientists around the world.

Our mission remains: to promote healthier lives through research and education in nutrition and preventive medicine. What has changed, significantly, is the breadth and depth with which we are achieving our mission. In this report, you will discover a spectrum of research projects, discoveries and related publications about which we could only dream two decades ago. To learn more about our Center, please visit www.pbrc.edu. If you would like to learn more about supporting our mission, please visit the website of the Pennington Biomedical Research Foundation at: www.penningtonfoundation.org.



Claude Bouchard, Ph.D.
Executive Director

A Message from the Executive Director



Claude Bouchard, Ph.D.
Executive Director

This year, 2008, will bring our Center to a true milestone: two decades of “improving the health of future generations” through research on nutrition and preventive medicine. The vision of a Louisiana entrepreneur sparked the effort that converted 234 acres of experimental farmland into a vibrant research center; now the home of more than 90 full-time researchers and 450 support staff from more than 20 nationalities. On those farm acres now sit specialized facilities totaling more than 500,000 square feet, of which nearly 400,000 are dedicated to wet laboratories and other research units. Soon, we will expand our clinical research space by about 90,000 square feet. When “Doc” Pennington bestowed a sizeable gift to the LSU System to create the Center, his sole direction was to build a world class institution. I believe that with the strong support of the LSU System, the state of Louisiana and the citizens of our region, we have exceeded Doc’s vision.

In this special 20th anniversary edition of our *Scientific Report*, you’ll read a brief history of the Center itself and a history of the community support that, in large part, made this success possible. You will also find a description of the various laboratories and research programs of the Center as well as of the core facilities that provide cutting-edge technologies and high quality support to our research enterprise. You can also find information on the challenges and opportunities, and the economic impact potential of the Center as we are poised to experience a phase of rapid growth.

Twenty Years of Discovery

Scientists at the Pennington Biomedical Research Center carry out research in three broad areas of inquiry: basic, clinical and population science. This range of research activities allows us to foster basic science discoveries,

promote clinical applications and encourage the translation of our findings and those of others to the population at large. It takes time to build high quality research teams, and it typically requires enormous resources. Our basic science and clinical research programs were initiated almost 20 years ago. In contrast, our population science effort is only two years old.

Several discoveries have been made by our scientists over the years and many of the advances in science made by others would not have been made in a timely manner if our scientists had not contributed some important observations or facts to the knowledge base. We believe that it is important in the context of this report to survey the important discoveries and other advances that have been made by the scientists of PBRC. The following paragraphs provide a partial list of such discoveries/advances.

Basic Science

- Discovery of a novel gene product involved in translating signals from the brain to the periphery and associated with the level of accumulation of adipose tissue.
- Discovery of a new secreted protein influencing fat deposition and obesity-related metabolic disorders including fatty liver disease and insulin resistance.
- Discovery of a property of stem cells isolated from an adipose tissue depot that allows them to convert to bone cells when grown on a bone promoting scaffold.
- Discovery that a gene in a human adenovirus associated with obesity induces fat cells to multiply and increases fat storage.
- Discovery that genetically identical laboratory animals raised in a similar environment can vary considerably in their level of adiposity.

Clinical Research

- Discovery that caloric restriction in non-obese adults improves biomarkers of aging including metabolic rates, body temperature, insulin level, markers of inflammation and other systems.
- Discovery that physical activity protects against the tendency to store excessive amounts of fat in the presence of a diet rich in fat.
- Demonstration together with 21 academic sites that type 2 diabetes can be prevented in high risk individuals: loss of 7% of body weight and 150 minutes of physical activity per week producing a 58% reduction in the rate of conversion to diabetes.
- Discovery that the cardiovascular and metabolic response to regular exercise is highly individualized and that several genes determine the benefits to be accrued from a physically active lifestyle.
- Demonstration that insulin can be inhaled and absorbed through the lungs instead of by an injection in order to control blood glucose in diabetics.

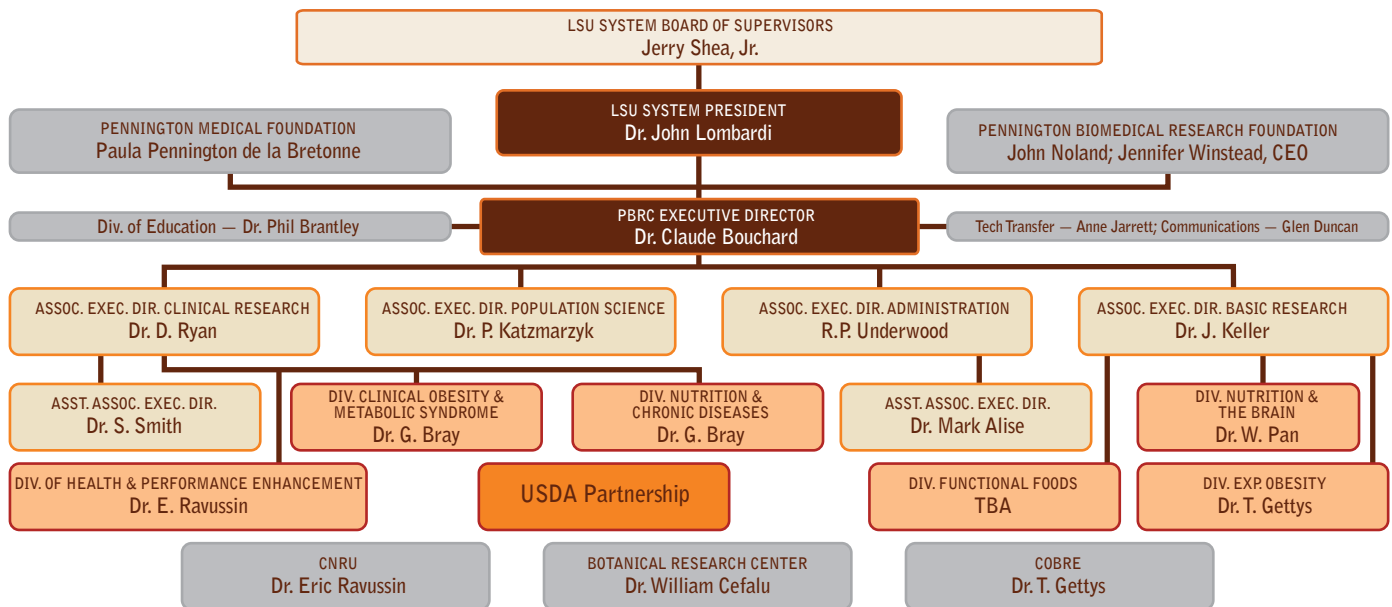
Population Science

- Reported that food insecurity with hunger is higher in the lower Mississippi River Delta than in other parts of the United States.

- Reported that Louisiana schoolchildren, measured in 17 school systems, have among the highest rates of overweight and obesity in the United States.
- Demonstrated that obesity in both black and white children predicts the development of health problems in adulthood.
- Demonstrated the efficacy of an environmental approach to induce behavioral changes in physical activity and eating habits among elementary school children.
- Demonstrated the efficacy of internet-based programs for weight loss.

Organizational Chart of PBRC

By the end of the 2007 calendar year, the Pennington Biomedical Research Center employed about 600 people, including 90 faculty. The scientists are grouped among 50 laboratories covering basic, clinical and population research areas. Moreover the research enterprise of the Center is supported by the resources of 19 core facilities. Eight programmatic areas cut across the individual interests of the scientists and the mission of each laboratory. These program areas are embodied in six research Divisions and three NIH-funded centers. These entities are depicted on the Organizational Chart and are the focus of short reports later in this publication.



50 LABORATORIES AND 19 CORE FACILITIES

A Message from the Executive Director

External Advisory Board 2006

Every two years, a group of distinguished scientists visits PBRC to advise the leadership of the Center and its management team on strategic choices, long term planning issues and other big picture questions. The reports of the External Advisory Board have been very useful over the years and have played a key role in shaping the development of the Center. The last visit of the Board took place in April 2006 and its composition is defined below.

Phillip Gorden, M.D. – CHAIR

NIDDK/NIH - Clinical Endocrinology Branch

Harvey Anderson, Ph.D.

University of Toronto

Steven N. Blair, P.E.D.

Cooper Institute for Aerobics Research

Barbara Corkey, Ph.D.

Boston University School of Medicine

Richard J. Deckelbaum, M.D.,

Columbia University

Karl E. Friedl, Ph.D.

U.S. Army Research Institute of Environmental Medicine

Richard Havel, M.D.

University of California at San Francisco

Norman K. Hollenberg, M.D., Ph.D.

Brigham and Women's Hospital

Edward S. Horton, M.D.

Joslin Diabetes Center

Stephen Woods, Ph.D.

University of Cincinnati

Van S. Hubbard, M.D., Ph.D.

NIDDK/NIH and DHHS

Economic Impact

Other reports in this document will contain more detail on the economic impact of PBRC. For the moment, let me emphasize that over the last 20 years, the State of Louisiana has invested \$131 million in the Center. This has been complemented by contributions totaling \$152 million from the Pennington Medical Foundation and the Pennington Biomedical Research Foundation, \$213 million in federal

grants, and \$119 million in contracts from the private sector. As revealed by these numbers, the Center is an excellent example of a successful partnership between public and private entities.

Among the activities of PBRC that contribute to our economy, one needs to include the technological transfer portfolio and the creation of start-up companies. After a slow growth during the first 15 years of operations, the Center has experienced steady growth in this area over the last five years. We expect to see a surge in activities in this department over the next decade.

The Challenges We Face

To continue its expansion and be successful, the Center needs to address a number of issues. The most important challenge is that of the research space. PBRC needs more space for its basic science program, for its imaging core, and for its comparative biology activities. It also needs a new physical plant, parking facilities and resources to renovate its existing clinical research space and undertake maintenance on its oldest buildings.

Competition for the best minds has always been very keen. In the case of PBRC, there are now a few institutions that are attempting to emulate its success, and a number of these institutions have a much larger endowment than we do. It is therefore imperative that we continue to be in a position to offer high quality employment opportunities to faculty candidates and generous start-up funds to launch new research enterprises at PBRC.

Since 2000, the Center has committed more than \$15 million to recruit new scientists and clinical investigators. It will be necessary to devote even more resources to recruit the best and brightest minds in the coming years if PBRC is to meet expectations. This is a critical investment particularly in an environment where the level of federal funding for scientific research is not increasing to any significant extent.

The Opportunities We Have

Despite all the challenges that we face as an institution, there are great opportunities ahead for the Center. First, we are in a very strong position as a result of the high quality of our faculty. For instance, each faculty at PBRC is on soft money and has to cover his or her salary from grants and contracts. In practice, when one considers the whole range of faculty from Instructors to Full Professors, including

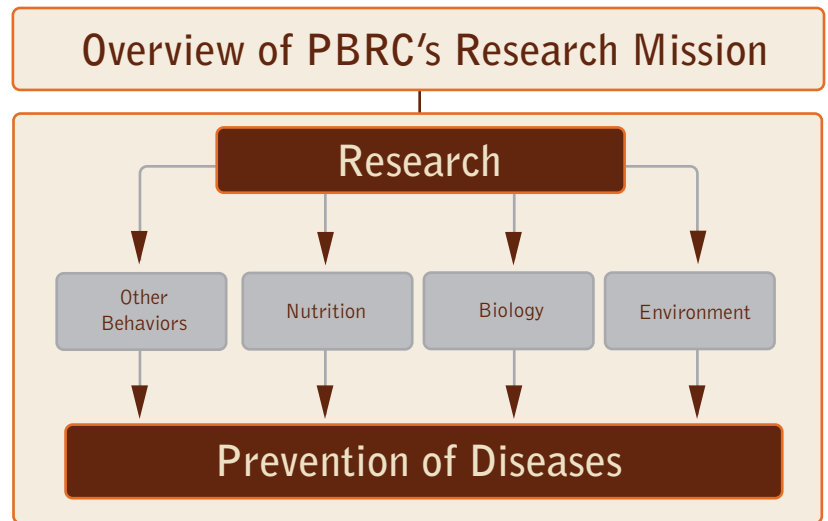
new arrivals, about 80-percent of salaries and benefits are covered by these sources. Moreover, PBRC does not offer full tenure. Most faculty and all postdoctoral fellows are on one-year, renewable contracts. About 40-percent of faculty is on a five-year rolling tenure system. These factors are greatly contributing to the success of the Center by placing an emphasis on productivity

Second, our portfolio of grants and contracts is strong for the number of scientists seeking these sources of external funding. For instance, we have about \$40 million in external grants and contracts for the current fiscal year with another \$70 million confirmed for subsequent years. Each PBRC scientist brings on average almost \$500,000 of external research funds every year. Third, PBRC's scientists have an above average productivity as shown by the fact that they published more than 400 scientific papers during the last academic year alone. Fourth, our scientists are influential in the world of science as evidenced by the more than 180,000 citations that their research has received in the scientific literature. Fifth, PBRC enjoys strong support not only from the LSU System Board of Supervisors but also from President John Lombardi and his associates. Sixth, the Center can count on the extraordinary support of the Baton Rouge Area Chamber, the Baton Rouge Area Foundation, the City of Baton Rouge and East Baton Rouge Parish. Seventh, the contributions of the board members of the Pennington Medical Foundation and of the Pennington Biomedical Research Foundation add enormously to the ability of the Center to strive for excellence.

In addition, the global field of disease prevention research is one that has a great future filled by exciting opportunities. Our strategy is to invest in cutting-edge basic science areas with the goal of contributing to the definition of the next generation of best practices in public health and preventive medicine. Nutrition remains one of the key research pipelines, but it is complemented by strong programs in other behavioral areas and in the biological sciences. This is illustrated in the above figure.

Strategic Position of PBRC

In its short history, PBRC has focused its clinical and population research programs on the characteristics of



a healthy diet, on the conditions under which a healthy weight can be maintained or recovered, and on the role of regular physical activity. Nutrients and other food compounds are also a strong research pursuit as we discover more about their biological and curative properties.

There are about 2.5 million deaths per year in the USA. Most of these deaths are attributable to common conditions such as heart disease, stroke, cancer, diabetes and obesity, to adverse lifestyle choices as exemplified by smoking, poor nutrition and a sedentary lifestyle, and to a lack of education or poverty. A substantial fraction of these deaths is preventable. Research programs designed to define the most efficacious prevention programs and how to deliver them effectively are going to play a major role in this regard.

As the population gets older with many more Americans living 80 years of age and beyond, 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 as we advance in age that presents the most meaningful opportunity for the Center to make unique contributions. Indeed, there is not one single cause accounting for the way we look and feel as we get older. It is evident that one's genes play a critical role, but nutrition and physical activity are also two important determinants of the decline in overall physical and cognitive independence and in well-being associated with aging.

Quality of life is extremely important, particularly as one gets older. In this regard, preventing morbidities and remaining free from disability are of the utmost importance. However, it would be shortsighted to focus only on the

A Message from the Executive Director

period after retirement to study the mechanisms and conditions under which the prevention of physical and mental deterioration can occur. Prevention should begin as early in life as possible and, as a result, the Center should continue to make important investments in developmental biology, maternal biology and pediatrics.

The following table identifies behavioral traits that are common in state-of-the-art preventive medicine approaches and new measures that stand a reasonable chance of being part of disease prevention strategies of the future. The Center has already invested heavily in some of these areas, including: genomics and genetics, functional foods and botanicals, neuroscience, epigenetic and in utero programming research, as well as stem cell and gene

Prevention of Diseases:

The PBRC Paradigm

State of the Art Prevention

- Smoking Cessation
- No illicit drugs
- Healthy diet
- Safe sex practices
- Regular exercise
- Proper hygiene
- Stress management
- An aspirin a day
- Healthy weight
- Fiber capsules
- Seat belt usage
- Vitamin supplements

Next Generation of Disease Prevention Measures

- All the preceding plus:
- Genomic-based prevention
- Targeted functional foods
- Specific pharmaco-preventative compounds
- Stem-cell based enhancement
- Targeted gene preventive measures

targeted research. As the table indicates, PBRC is investing strategically in areas of science that will likely shape the future of public health and individualized preventive medicine.

A Final Word

The Center will experience substantial growth during the next decade. Since we have already met almost all the goals of our Vision 2010 Strategic Plan, we need to set new priorities for the coming years. We will continue to recruit outstanding faculty, expand our research facilities, build increased capacity, and make growing contributions to the economy of the State of Louisiana.

Soon we will have seen our 20th year anniversary come and go. A number of activities are planned to highlight in 2008 the Center's contributions to science, nutrition, disease prevention and the regional economy. However, let us all recognize that the Pennington Biomedical Research Center is still a young institution that has the potential to make many more contributions and to become a major player on the international scene in nutrition and preventive medicine research if granted an adequate level of support.

Vision 2010 – a Status Report on the five-year Strategic Plan

“...the Pennington Biomedical Research Center will be the leading nutrition and preventive medicine research center.”


Claude Bouchard
Director
Pennington Biomedical
Research Center

Although looking back over our accomplishments is a wonderful way to chart our progress, we have chosen another as well...to set significant future goals and strive to reach or exceed them. In January, 2005 we released our five-year strategic plan, called Vision 2010. In it we called for significant growth in the breadth of our research, in our physical facilities and in our support functions. We opened with a bold new vision statement: “By the year 2010, the Pennington Biomedical Research Center will be the leading nutrition and preventive medicine research center recognized for the outstanding quality of its research, its contribution to scientific discovery, and its commitment to professional and public education initiatives.”

Our intent with the new strategic plan is to significantly raise our sights within our four long-term goals, which continue to guide us:

1. Build a world-class research center in nutrition and preventive medicine.
2. Generate cutting edge and influential research
3. Maximize the benefits of technological advances and new discoveries made at the Center
4. Contribute to the economic development of the State of Louisiana.

(Continued on the next page)



PENNINGTON BIOMEDICAL RESEARCH CENTER

A significant means to our ultimate success is to recruit senior researchers, successful in their fields and in their abilities to compete for large, competitive research grants, and to equip them with outstanding facilities. We have achieved a great deal of that part of our vision, including funding for a significant addition to our clinical research. In addition, we have made great strides by focusing on the ten priority areas we announced in January 2005. Here is short summation of those priorities and our progress under each.

Top Ten Priorities

1. Establish a Division of Nutrition and the Brain.

The Division has been created with Dr. Weihong Pan as Division Chief. The Division can count on the contributions of 17 scientists. Since the plan was launched in 2005, Drs. Don Ingram, Maria Barnes, and Stefany Primeaux have joined the ranks of this Division.

2. Expand comparative biology and enhance transgenic animal core.

Dr. Barry Robert has joined the Center and is the veterinarian responsible for the Comparative Biology facility. A 4,000 sq. ft. addition has been completed with funding from the NIH. However, much more space is needed to accommodate the growth of the basic science programs. More resources have been added to the Transgenic Core and Instructor Jingying Zhang has joined the Center.

3. Increase expertise in developmental biology and genetic epidemiology.

Our recruitment is completed for the Peggy M. Pennington Cole Chair in Maternal Biology (Dr. Claudia Kappen), and for other key areas such as developmental biology (Dr. Claudia Kruger), regulation of gene expression (Dr. Michael Salbaum), neuroendocrine immunology and aging (Dr. Vishwa Dixit), adipose tissue, (Dr. Yourka Tchoukalova), cell biology and cell imaging (Dr. David Burk), cell signaling (Dr. Tom Burris), neuroscience (Drs. Jolene Zheng, Paul Pistell, Rudolph Schicho, Tada Utsuki, Jun Zhou, Jeff Keller and Anna Bruce-Keller), neuropeptides and metabolism (Dr. Greg Sutton), cancer prevention, (Dr.

Sita Aggarwal) Additionally, Dr. Indu Kheterpal), joined the Center as Director of the Proteomics Core and leader of the structural protein biology laboratory.

4. Expand Clinical Research, Population Research and Imaging facilities.

Dr. Peter Katzmarzyk has joined the Center as our first associate executive director for Population Science. He is tasked with leading the way for new, broader research in this area. A new Magnetic Resonance Spectroscopy laboratory is now operational. A new 15,000 sq. ft. Population Science wing has been added to the Claude B. Pennington, Jr. building with the \$5 million cost underwritten by the Pennington Medical Foundation. It will house population science faculty and support staff. Additions to the faculty in population science include Dr. Ronald Horswell (biostatistics), Dr. Valerie Myers (clinical psychology), Dr. William Johnson (biostatistics), and Dr. Nathan Markward (genetic epidemiology).

The construction of a new 80,000 sq. ft. Clinical Research building remains the top priority for the Center. The Louisiana Legislature has set aside \$21 million available this year to build the bulk of the facility. We anticipate an additional \$ 4 to 5 million will be made available in the next fiscal year.

5. Increase expertise in pediatric obesity, aging, metabolic syndrome, physical activity and wellness, minority health behaviors and population health assessment.

Dr. Tim Church, public health, preventive medicine and physical activity specialist, has joined the faculty as the John S. McIlhenny Endowed Chair in Health Wisdom. We have successfully recruited other faculty in these areas: aging (Dr. Don Ingram), exercise testing and functional foods, (Dr. Conrad Earnest), and human physiology (Dr. Leanne Redman).

6. Secure NIH center grants and obtain designation and funding as a satellite of an NIH-funded GCRC.

Three federal grants have enabled us to establish centers of research excellence at PBRC. The Clinical Nutrition Research Unit (CNRU) central research theme is the maternal, pre-natal, peri-natal, and epigenetic network

of factors that may predispose to obesity and metabolic diseases. The Botanical Research Center (BRC) focuses on finding and testing botanical compounds that may prevent diabetes or serve as functional adjuncts in the treatment of diabetes and the metabolic syndrome. Additionally, we were awarded a five-year grant to establish a NIH-Center of Biological Research Excellence (COBRE) to support the mentoring of promising young faculty members.

Finally, we were able to secure a planning grant from NIH to allow us to devote PBRC resources to an application for a Louisiana state-wide NIH Clinical and Translational Science award. Our application is in development with the support of the three medical schools in Louisiana and other campuses. The goal is to establish a Louisiana Clinical & Translational Research Center.

7. Expand the postdoctoral program.

An additional position has been added to the existing NIH T-32 Training Grant for postdoctoral fellows. A second T-32 application has been submitted to NIH later this year and a revised training grant application in Botanicals has been submitted. The position of postdoctoral fellow has been more clearly defined at the Center. A structured series of lectures in nutrition science and metabolism, and seminars in research ethics and professional development as well as grant writing have been established.

8. Expand community and professional education efforts.

We have consolidated our symposium and conference activities and have received funds from the Coypu Foundation. Our collaboration with the LSU Agricultural Center in the dissemination of information on nutrition and health continues to expand.

9. Pursue partnerships to establish a wellness center with research-based wellness programs.

A feasibility study has been completed, and discussion is ongoing with potential partners and investors.

10. Expand the administrative and service resources to sustain the growth of the research and education programs.

The expansion is scaled to the progress made across the other priorities and to the general growth of PBRC. Fifteen positions have been added since 2005.

Summary of the financial progress underlying Vision 2010

A cornerstone of Vision 2010 is an increase in overall state support of the Center. Our five-year plan called for \$350 million in expenditures during the five-years of the plan, with our annual revenue growing from \$45 million in 2005 to \$65 million by 2010. The operating budget for the current fiscal year is \$61 million. The annual appropriation from the State of Louisiana is \$17 million, and assuming that this amount recurs in future years as is anticipated, the Center's state allocations will likely surpass the financial goals set forth in Vision 2010.

PBRC has a well-established history of bringing in \$3 to \$4 of external research funding for every dollar invested by the State of Louisiana, and we have every reason to believe that this performance will continue in the coming years.

A glimpse of the future

It is with high expectations that we move into the final years of Vision 2010, as we expect to begin construction on one of our greatest priorities: a new clinical research facility (mentioned above, priority 4.) This is a goal we set forth many years ago, and one that required a confluence of events: public awareness of the Center's mission, and support from the LSU System, the community, our legislature and the office of the Governor. Currently, we are poised to make even greater strides due to events unpredictable at the outset of the current five-year strategic plan. The newly elected Governor of Louisiana, Bobby Jindal, was a vocal supporter of the Center during his campaign and has appointed individuals to his cabinet who have been active supporters of PBRC in the past. Also, the state has enjoyed enhanced revenues sparked by the enormous post-hurricane Katrina re-building efforts. These events encourage us to seek significant support from the state that we have not sought in the past. We are proposing a major expansion of the Center that will take us into new areas of research, emphasizing disease prevention and economic development.



“In formulating the original foundation, my only instructions were that this should be the biggest and best nutrition research center in the country.”

Claude Bernard “Doc” Pennington,
Benefactor and founder of the Pennington Biomedical
Research Center

Two Decades of Discovery – Our History

Remembering “Doc”

(Reprinted from *The Pen*, October 2002)

Claude Bernard “Doc” Pennington, benefactor and founder of the Pennington Biomedical Research Center, was born at the turn of the 20th century in Chunky, Miss. As a young boy, he developed a passion for the oil industry when his family moved to Elton, La., near the site of the state’s first oil strike. His father ran a pharmacy and an eye and ear clinic there, and though Pennington made efforts to follow in his father’s footsteps, his heart never left Southwest Louisiana’s bucking oil fields.

Graduating from high school during World War I, Pennington enrolled in 1918 in the U.S. Naval Academy at Annapolis when the United States entered the war. When the war ended a year later, Pennington left the Naval Academy to attend Northwestern University in Chicago and graduated in 1920 with a degree in optometry from the Illinois College of Optometry. During his summer breaks, Pennington returned as often as he could to Louisiana and worked as a roughneck on oil wells.

In the early 20s, he met and married Irene Wells, his wife for the next 76 years, and soon the couple had a son, C. B. Pennington, Jr. “Doc” joined his father’s clinic in 1925, which had moved from Elton to Baton Rouge. While not a certified physician, Pennington obtained his nickname, Doc, during the short time he worked with his dad. His career as an optometrist lasted only one year. When his father died in 1926, Pennington closed the clinic doors, headed for the oil fields and never looked back.

“Doc” entered the oil industry buying and selling gas leases for Shell, Texaco and other major oil companies, but soon found that he wanted to run his own operation. So, he leveraged his own oil and gas leases and founded Pennington Oil Company. His entrepreneurial instincts paid off in 1952 when his team drilled a then unheard of 10,000 feet and struck oil across the Mississippi River in what would become known as Lobdell Field, La.

Five years after his strike, Pennington acquired 2,000 acres of land in the now famous Tuscaloosa Trend near Port Hudson, La. He paid \$400,000 for the Mount Pleasant Plantation property, and his ambitious hopes to drill and strike oil established Pennington as one of the country’s biggest wildcatters. The year 1957 also held

tragedy for “Doc.” His 35-year-old son and only child, C. B. Jr., and employee of Pennington Oil Company, was killed in a drilling accident on an oil field near Jackson, La. In his memory, the Pennington family established the Irene W. and C. B. Pennington Foundation, which has made considerable donations to Southeastern Louisiana University, their son’s alma mater, among numerous other need-based organizations.

Twenty years after buying the Mount Pleasant Plantation property, Pennington struck the largest inland U.S. oil discovery in the second half of the 20th century. A pioneer in the development of the Tuscaloosa Trend, “Doc” struck oil after drilling several dry wells and kept striking oil. Other companies came in, drilled and helped open the trend, and soon 10 working wells had been drilled. With an estimated \$4 billion in reserves, each well produced as much as \$100,000 a day, and Pennington had an interest in them all. At the age of 77, “Doc” had made a fortune that would leave a mark on Louisiana for decades.

In January of 1980, “Doc” provided a \$125 million grant in a trust to Louisiana State University for the construction of the Pennington Biomedical Research Center. At the time, it was said to be the single largest donation in history by a private individual to an American university. In 1988, Pennington was inducted to the LSU Alumni Association Hall of Distinction in recognition of his generous donation to the university system. “Doc” has also supported other Baton Rouge institutions by donating to the YMCA, Boy Scouts of America, Girl Scouts of America, the United Way and the East Baton Rouge School System.

At the time of his death in 1997, *Forbes Magazine* estimated Pennington’s worth at more than \$550 million. For many years, Pennington was the only person in Louisiana to be named as one of “The Forbes Four Hundred,” an annual ranking of the 400 richest people in America. Little is known of Pennington’s personal life. He valued his privacy and rarely granted interviews or appeared in public. His wife, Irene, his three grandchildren and 10 great-grandchildren survived him.

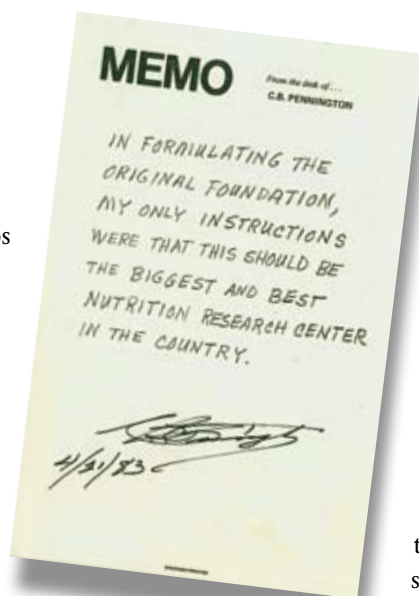
Two Decades of Discovery – Our History

“The biggest and best nutrition research center in the country”

In 1980, “Doc’s” gift to the LSU System to create the Pennington Biomedical Research Center took the form of a foundation named the Pennington Medical Foundation. When he created the foundation and drafted its mission he said simply, *“In formulating the original foundation, my only instructions were that this should be the biggest and best nutrition research center in the country.”*

The President of the LSU System at the time was Allen Copping, D.D.S., who formed an advisory group to oversee the construction of the facility and the ultimate hiring of an executive director, research corps and staff. A team of researchers and physicians from the LSU Health Science Center in New Orleans examined existing research facilities and led in the design of the new Center, which was to be built on a former experimental farm on Perkins Road operated by the LSU Agriculture Center. “Doc” and his wife Irene, along with Dr. Copping ceremonially broke ground in 1984 to start a two-year construction project to create the finest research facility of its kind. Construction was finished in 1986. William Pryor, Ph.D., of LSU was appointed interim director in 1988, and the search for a full-time director began in earnest. It was a long process requiring a jump-start from a group of community leaders. To guarantee a salary and sufficient resources for a world-class leader to come aboard, the Baton Rouge Area Foundation pledged to provide a competitive salary and a small group of LSU system researchers and leaders won two start-up grants from the US Department of Agriculture and the U.S. Army.

George Bray, M.D., after a long recruiting process, became the Center’s first executive director. In 1989, he arrived to survey his new post: 223,000 feet of newly completed, yet almost empty basic science laboratories,



clinics and administrative offices. Dr. Bray’s task was to lure world-class researchers and funding to an unknown research center built with a portion of Doc Pennington’s generous donation to the LSU System. The remainder of the donation was placed in trust for future growth. Bray immediately began to recruit researchers in the basic sciences and looked to quickly open a clinical trial component, inviting residents of the Baton Rouge area to participate in research that would lead to new, medicinal diets, physical activity regimens and the testing of new drugs and food products.

In his decade of leadership, Dr. Bray built a faculty and technical staff, witnessed and participated in the publication of hundreds of books, chapters and peer-reviewed papers, touched the lives of thousands of clinical participants and oversaw a second construction phase – a 93,000 foot complex comprising a conference center, guest lodge and exercise research facility financed by the Pennington Medical Foundation. The growth and expansion, though funded mainly by the trust, could have occurred only through significant growth in funding from state, federal and private sources. Dr. Bray also led the Center to clearly define its Mission – “to promote healthier lives through research and education in nutrition and preventive medicine.” Under Dr. Bray, the Center also achieved an important status – that of a separate campus of the LSU System over which Dr. Bray assumed the equivalent status of chancellor. When asked how he knew this would be a key to success, he replied, “because it was the best way to provide the administrative and academic flexibility needed to develop the institute as a center of excellence.”

In 1999, having previously served as a member of the Center’s external board of advisors, Claude Bouchard, Ph.D., of the Université Laval in Quebec, Canada, became the Center’s second executive director. At that time, Dr. Bouchard introduced a strategic planning process, calling for significant, cutting-edge growth. The Center launched in early 2000, a bold, comprehensive plan, Vision 2005, to meet ambitious long-term goals: 1. build a world-class research center in nutrition and preventive medicine; 2. generate cutting-edge and influential research; 3. maximize the benefits of technological advances and new discoveries made at the Center; and 4. contribute to the economic

development of the State of Louisiana. The Center would reach these goals with a series of activities built on recruiting competent and highly productive scientists, building a strong postdoctoral program, and providing first-class laboratory facilities and state-of-the-art equipment.

Under the first five-year strategic plan, Dr. Bouchard undertook a third phase of significant expansion. At the end of 2003, the Center opened a new, five-story, 187,000 sq. ft. Basic Science Laboratory Building, and new researchers began to move in.

The center was organized around four research priorities, which led to the establishment of four research divisions based on subject matter: Obesity, Functional Foods, Nutrition and Chronic Diseases and Health and Performance Enhancement. Subsequently, the Division of Obesity was split into a Division of Experimental Obesity and a Division of Clinical Obesity and Metabolic Syndrome. This organization allowed researchers to interact within and across divisions to lead the way in development of knowledge within all of them. Shortly after, Dr. Bouchard created a Division of Education to share knowledge of the Center with colleagues around the world, and Bouchard created a means to identify, capture and nurture proprietary knowledge that might lead to marketability and private sector funding of the Center's intellectual property.

Dr. Bouchard oversaw remarkable growth during his second five-year strategic plan, Vision 2010, which will carry the Center to January 1, 2010. During this time span, the Center won three large, national research grants to establish centers of excellence in topic areas. These grants, nicknamed "Center Grants," now fund a specialized diabetes research effort (the Center for Botanicals and Metabolic Syndrome), an effort in the epigenetic causes of obesity and diabetes (The Clinical Nutrition Research Center) and a junior faculty mentoring program (The COBRE grant).


The field of Population Science at the Center has also grown quickly, prompting the addition of a new executive position, the associate executive director of Population Science, filled by the arrival in late 2007 of Dr. Peter Katzmarzyk.

The Center also had to turn a very big corner in 2007 to determine how to fund future construction. Historically, Doc's original endowment – in the Pennington Medical Foundation – had been a valuable and effective means of securing financing for new construction. Prior to 2007, every building on campus had been built or financed with private funding or Center generated funds. In 2007 that changed when the Center approached the Louisiana legislature with a first-ever request for construction funds. The Center requested \$25 million and received a substantial portion of that, allowing construction of a priority project to begin in 2008.

At the close of 2007, Center leaders and staff undertook the planning of a series of events to recognize 2008 as the Center's 20th year, including a scientific conference on the "The 20 Most Significant Advances in Obesity Research, Prevention and Treatment," as well as a statewide public health conference on childhood obesity, and a business and economic forum on the future of science and the Center in the local economy.







This year, 2008, marks the 20th Anniversary of the opening of the Pennington Biomedical Research Center. During these two decades, our success has been immense in “improving the health of future generations” through research on nutrition and preventive medicine. This timeline displays a brief history of the center itself and a history of the community support that, in large part, made this success possible.

1957

Called by the Chicago Tribune "the best real estate transaction since Peter Minuit bought Manhattan Island from the Indians in 1624 for \$24 in beads, trinkets and cloth," Doc acquires 2,000 acres of land near Port Hudson called Mt. Pleasant Plantation. Pennington had approached the owner, 93-year-old Edward Eagle Brown, chairman of the board of the First Chicago Bank, proposing to lease the land. Brown refused, offering instead to sell. Reportedly, when Pennington responded that he did not have the money, \$400,000, Brown himself lent Doc the full purchase price.

1977-79

Amoco, leasing the acreage from Doc Pennington, strikes pay dirt, hitting the "Tuscaloosa Trend" in Port Hudson field.

August 16:

Doc's only son, Claude Bernard Pennington, Jr., dies in an oilfield accident, leaving a young wife, Peggy, and three children—Paula, Claude, III, and Daryl.

Claude B. Pennington and Irene Wells are married.

1921

Doc goes independent, striking his first oil well in Lobdell Field near Baton Rouge.

1952

1900 Claude Bernard Pennington is born in Chunky, Mississippi on March 30.

1926

C.B. "Doc" Pennington, Baton Rouge Optometrist decides to change careers, turning to the oil business.



At age 80, Doc Pennington and his wife, Irene W. Pennington, pledge \$125 million to Louisiana State University, which at the time is the largest single gift to an institution of higher learning.

1980

Louisiana State University Medical Center awards Doc an honorary Doctor of Science degree.

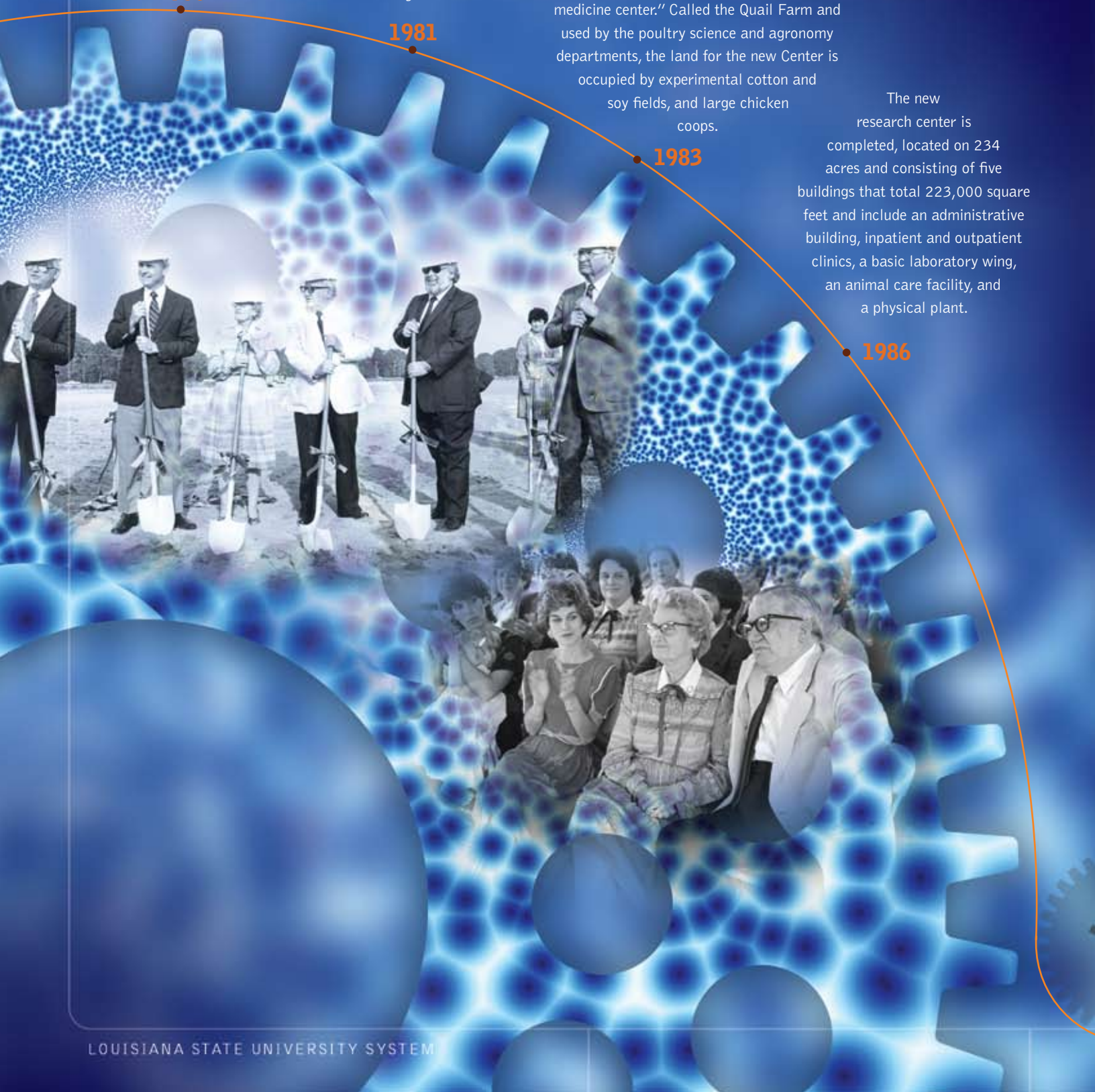
1981

April 21 :
Allen Copping, David Treen, Doc and Irene Pennington, Board of Supervisors Chairman Sheldon D. Beychok, and the immediate past president of the LSU system, Dr. Martin D. Woodin, symbolically break ground on what Pennington said will become "the country's biggest and best nutrition and preventive medicine center." Called the Quail Farm and used by the poultry science and agronomy departments, the land for the new Center is occupied by experimental cotton and soy fields, and large chicken coops.

1983

The new research center is completed, located on 234 acres and consisting of five buildings that total 223,000 square feet and include an administrative building, inpatient and outpatient clinics, a basic laboratory wing, an animal care facility, and a physical plant.

1986



Dr. Bray announces the first clinical research team, led by **Dr. Donna Ryan**, the Center's first associate executive director for clinical research.

The Louisiana Legislature commits to a \$5 million annual appropriation for operations. The PBRF receives sufficient funds to create the Center's first endowed chair, the Claude B. Pennington, Jr Chair.

The first of ten meetings called "Frontiers in Nutrition" is held at the Center. The meetings eventually result in a 10-volume set of the collective presentations entitled **Pennington Center Nutrition Series**, published by LSU Press. PBRC becomes a separate campus of the LSU System in fiscal year 1990-91, and Dr. Bray's position as executive director is granted the same status as chancellor.



LSU (Baton Rouge) awards C.B. "Doc" Pennington Honorary Doctor of Science. The Centers' first clinical volunteers enroll in an investigation of the effects of dietary patterns in overweight women. The trial is under the direction of LSU professor of psychology, Dr. Don Williamson, and his graduate student, Candy Lawson.

The study examines the effects of eating habits on body weight and metabolism.

1991

1990

March:

LSU Boyd Professor William Pryor, of the LSU Chemistry and Biochemistry departments, is named interim director of the Center. Louisiana Governor Buddy Roemer, announcing the appointment to the Baton Rouge Rotary Club, states the Pennington Biomedical Research Center will be open in 60 to 90 days. He promises state support of the Center. A handful of LSU scientists move into the Center.

November: After a two-year recruitment effort, George Bray, M.D., an internationally known specialist in obesity, diabetes and metabolism at the University of Southern California, is appointed the Center's first executive director. A grant from the Baton Rouge Area Foundation guarantees his salary.

December: With an assortment of funding from the Louisiana Public Facilities Authority, the U.S. Department of Defense, and individual and corporate gifts, a full-time executive director, and initial research teams, the Center is operational.

David York, Ph.D., becomes the Center's first head of basic research, leading the Experimental Obesity Research Program.

1988

U.S. Senator Bennett Johnston and Congresswoman

Lindy Boggs help guide a funding request through the halls of Washington, resulting in the U.S. Department of Agriculture awarding a grant of \$9.4 million for the purchase of equipment to outfit the first labs.

1989

1987

August: Baton Rouge business leaders form the Pennington Biomedical Research Foundation to solicit further private donations. In addition, the Baton Rouge Area Foundation provides critical funds when it commits about a third of its total resources, primarily to provide a sufficient salary to hire the Center's first executive director.



The Center

publishes its first scientific report, called the **Annual Report** and convenes its first external advisory committee composed of leading experts across the country. The Center receives its first pharmaceutical research grant. The first professorship, the Douglas L. Manship Professorship in diabetes, **1992** is created

The Nutrient Data Base Conference and North American Association for the Study of Obesity (NAASO) hold their annual meetings in the new conference and education center. NAASO is the premier organization in the country for the study of obesity.

U.S. Department of Agriculture funds a multi-center nutrition intervention study of the rural Mississippi River delta regions of Arkansas, Louisiana, and Mississippi. It is called The Lower Mississippi River Delta Nutrition and Health Initiative.

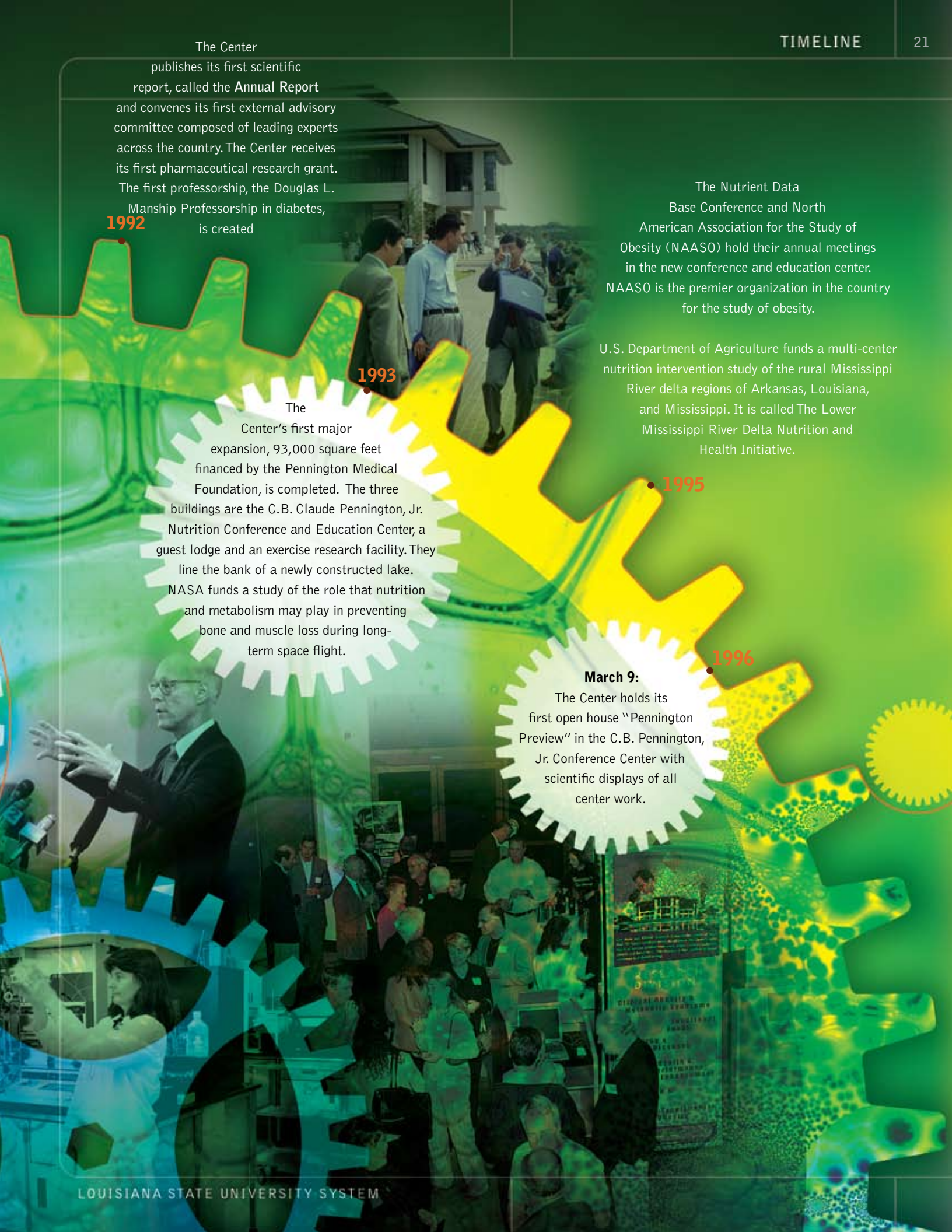
1993

The Center's first major expansion, 93,000 square feet financed by the Pennington Medical Foundation, is completed. The three buildings are the C.B. Claude Pennington, Jr. Nutrition Conference and Education Center, a guest lodge and an exercise research facility. They line the bank of a newly constructed lake. NASA funds a study of the role that nutrition and metabolism may play in preventing bone and muscle loss during long-term space flight.

1995

March 9: The Center holds its first open house "Pennington Preview" in the C.B. Pennington, Jr. Conference Center with scientific displays of all center work.

1996



After ten years on the job, the center's first executive director, Dr. George Bray, announces he is stepping aside to resume full-time research at the Center.

Total grants from NIH reach \$5.5 million and for the first time exceed state appropriations.

Allen Copping, D.D.S., who played a key role in creating the Center, steps down as LSU System president. William Jenkins, Ph.D., succeeds him.

August: Claude Bouchard, Ph.D., of the Université Laval in Quebec, becomes the center's second executive director and occupies the George A. Bray chair in Nutrition. He develops an agenda for growth, and begins work on the Center's first strategic plan.

1999 •



1997

Results from the NIH-funded study on diet and high blood pressure are published in the *New England Journal of Medicine*. The DASH Diet results are published and conclude the diet significantly lowers blood pressure.



1998

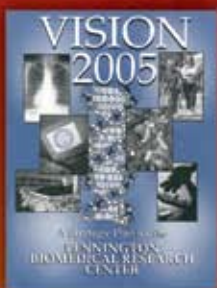
August 7, 1997: **C.B. "Doc" Pennington**, the Center's benefactor, passes away. He was 97.

PBRC goes live with its website, www.pbrc.edu. Among other benefits, the website improves recruiting for clinic and postdoc programs. PBRC holds an open house to celebrate the 10th anniversary of its opening.

The Board of Regents awards a five-year, \$6 million grant to Drs. David York and Leslie Kozak to discover genes associated with obesity.

Dr. Bouchard releases Vision 2005, the Center's first 5-year strategic plan, calling for a doubling in the budget, faculty and staff, including new construction to accommodate the expansion.

2000



The LSU Board of Supervisors approves plans for a new 180,000 square foot Basic Science Laboratory Building. The Pennington Medical Foundation provides bond funding for the new facility.

The Center and its 26 partners in the NIH-funded Diabetes Prevention Program (DPP) announce that at least 10 million Americans at high risk for type 2 Diabetes can sharply lower their chances of getting the disease through improved diet and exercise.

2002

The NIH awards a seven-year, \$12.4 million grant to study the possible benefits to aging of a long-term reduction of calories. The grant is awarded to Eric Ravussin, Ph.D., and is the largest NIH grant in the Center's 14 year history.

The Division of Education is created to accompany the research divisions, with Phillip Brantley, Ph.D., as director. The existing research divisions include Nutrition and Chronic Diseases, Health and Performance Enhancement, Obesity, and Functional Foods.

Growing clinical research necessitates use of trailers for temporary office space located on the upper parking deck.

In the Center's first economic "spin-off," Pennington Discoveries, Inc., an investment arm of the Pennington Biomedical Research Foundation, partners with a Swedish corporation to form Pennington Management of Clinical Trials (PMCT). The company specializes in the planning, participant recruitment, implementation and management of multi-center clinical trials.

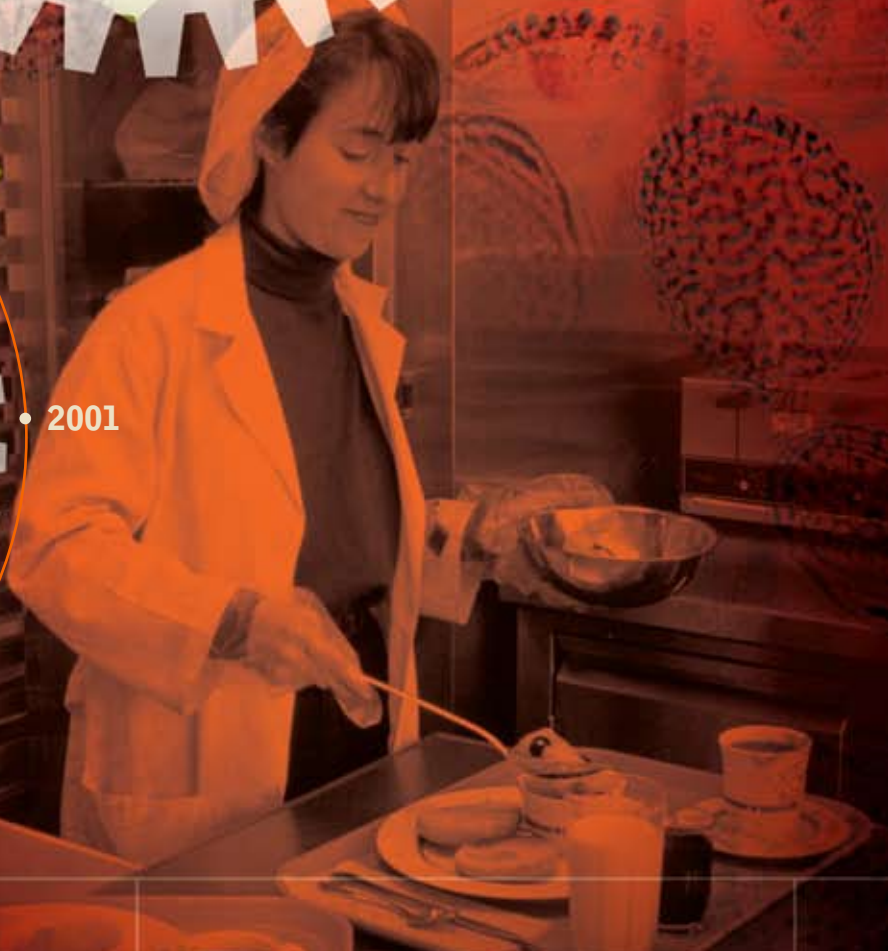
2003

Paula Pennington de la Bretonne, Doc's granddaughter, is named Chair of the Board of the Pennington Medical Foundation.



Irene Pennington, Doc's wife, passes away. She was 104 years old.

2001



2004

The 187,000 sq. ft. state-of-the-art Basic Science Laboratory building opens.

NuPotential is formed as a limited liability company and begins operations in PBRC.

The company, founded by Dr. Ken Eilertsen of the Center, produces reprogrammed cell lines. Cell reprogramming restores an existing cell to a state where it can differentiate into a new cell type. Reprogrammed cell lines have the potential to develop therapies for such afflictions as cardiovascular disease, Alzheimer's disease, diabetes, stroke and other degenerative diseases.

PBRC and the USDA sign a working agreement to begin USDA research on campus. This is regarded as the first step toward a broader partnership between the USDA and PBRC.

January: Both

Nature and Science in the same month feature manuscripts by Center researchers.

The Center releases Vision 2010, a five-year strategic plan presenting the Center's goal to be "the leading nutrition and preventive medicine research center." The plan calls for continued significant growth, including a new \$25 million clinical research building.



March: The Center establishes a new research division "Nutrition and the Brain" to be led by Richard Rogers, Ph.D.

April: William Cefalu, M.D., leads a team to win PBRC's first NIH Center Grant to establish a Center of Excellence in Botanicals and Metabolic Syndrome. In partnership with Rutgers University, the center is to focus on clinical and basic research into the conditions that lead to metabolic syndrome and type 2 diabetes and to determine whether plant extracts can effectively treat those conditions. A related grant from the Coypu Foundation allows the center to create its first named laboratory: The John S. McIlhenny Laboratory of Botanical Research.

July: Eric Ravussin, Ph.D., leads a team to win PBRC's second NIH Center Grant to establish a NIH-NIDDK Clinical Nutrition Research Unit to focus on prenatal causes of obesity. The theme is "Nutritional Programming: Environmental and Molecular Interactions".

August: The Center, in cooperation with the LSU Health Science Center, confers its first honorary doctorate (Honoris Causa Doctorate) to Douglas Coleman, Ph.D. for his groundbreaking research on obese and diabetic mice, which led to the discovery of leptin and its critical role in hunger and satiety.

September: Hurricane Katrina's destruction of New Orleans causes a temporary relocation of the LSU Health Science Center. Both classroom and research units of the LSU Medical School, Dental School and School of Allied Health move to PBRC, doubling the campus population with an influx of nearly 650 students and faculty.

A grant from center researcher William Hansel, PhD., and his nephew, Edward Downey, create the Center's second named laboratory; The William Hansel Laboratory of Cancer Prevention.

December: PBRC leaders and investors establish the first venture capital fund to finance development of early-stage Center discoveries. Called Themelios, the fund is established with a \$10 million initial investment from the Pennington Family Foundation.

2005



2007 •

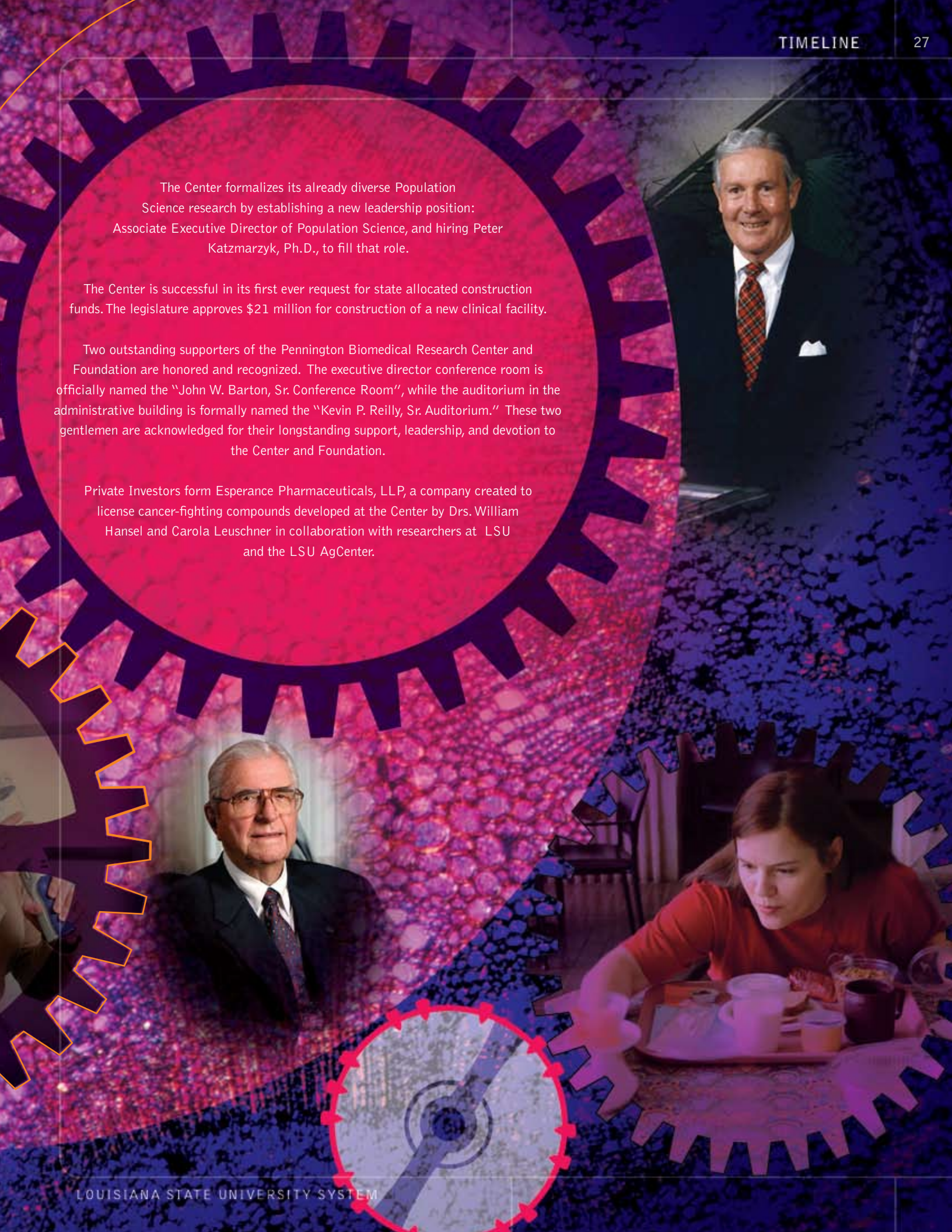
The Center Hosts the first international symposium on infectious obesity, the theory that a virus may cause some human obesity. The symposium is led by Center researcher Dr. Nikhil Dhurandhar, the first scientist to pose the theory, and the founder of the field of research he dubs "infectobesity."



2006 •

Portions of the former conference center are renovated, a new wing is added, and the name is changed to the Claude B. Pennington, Jr. Building. Researchers begin to move into what is now the new home of the Center's growing Population Science effort.





The Center formalizes its already diverse Population Science research by establishing a new leadership position: Associate Executive Director of Population Science, and hiring Peter Katzmarzyk, Ph.D., to fill that role.

The Center is successful in its first ever request for state allocated construction funds. The legislature approves \$21 million for construction of a new clinical facility.

Two outstanding supporters of the Pennington Biomedical Research Center and Foundation are honored and recognized. The executive director conference room is officially named the "John W. Barton, Sr. Conference Room", while the auditorium in the administrative building is formally named the "Kevin P. Reilly, Sr. Auditorium." These two gentlemen are acknowledged for their longstanding support, leadership, and devotion to the Center and Foundation.

Private Investors form Esperance Pharmaceuticals, LLP, a company created to license cancer-fighting compounds developed at the Center by Drs. William Hansel and Carola Leuschner in collaboration with researchers at LSU and the LSU AgCenter.



Twenty Years of Community Support—Pennington Medical Foundation



Pennington expansion through the years.

Pennington Medical Foundation The Beginning

January 30, 1980 - By Act of Donation in Trust, C. B. and Irene Pennington created and funded the Pennington Medical Foundation to build a research center in nutrition and preventive medicine.

The First Meeting of the Trustees of the Pennington Medical Foundation was held on April 17, 1980. The Trustees are stewards of the initial \$125 million gift and have overseen the construction of over 545,000 square feet of state-of-the-art research and support facilities. Since inception, the Pennington Medical Foundation has provided approximately \$145 million in support for facilities, equipment, and seed funding for investments in new programs and world class researchers.

“Few persons in history ever have the opportunity to truly alter the course of human events for millions of people for the better. And, even fewer avail themselves of the opportunity. Mr. and Mrs. Pennington did –and we will be eternally in their debt.”

Dr. Allen A. Copping
President Emeritus of the
LSU System



Trustees of the Pennington Medical Foundation: 1980 to present

Mr. John W. Barton, Sr.

Mr. John Bateman

Mrs. Paula P. de la Bretonne

Dr. Charles Beskin

Dr. H. Rouse Caffey

Mr. Robert R. Casey

Dr. Allen A. Copping

Dr. Douglas L. Gordon

Mr. G. Lee Griffin

Mr. C. Wayne Harmon

Dr. Larry H. Hollier

Dr. William L. Jenkins

Dr. Henry W. Jolly, Jr.

Mr. J. Luther Jordan, Jr.

Dr. John V. Lombardi

Mr. Tracey Mandart

Mr. J. W. Melancon

Mr. Jake L. Netterville

Mr. Claude B. Pennington, III

Mr. Daryl B. Pennington, Sr.

Mr. Raymond G. Post

Dr. William B. Richardson

Dr. Perry G. Rigby

Dr. John A. Rock

Dr. Mary Ella Sanders

Dr. Christel C. Slaughter

Dr. Mervin L. Trail

Mr. Richard S. White, Jr.

Mr. W.W. Williams

Dr. Martin D. Woodin

Founding Trustees



2004



2006

Pennington Today

“It was a particular pleasure for me to have Doc be able to live to see the result and promise of what he and Mrs. Pennington made possible. His contribution was not just his generosity, but his intuitive foresight and understanding of political practicalities that accompanied his gift.”

Dr. Charles Beskin

Former Chair of the Pennington Medical Foundation

Pennington The Future

“It is my joy and privilege to work with so many talented individuals to carry on my grandfather’s vision. With the very capable trustees we have, we will greatly exceed his dream to provide the knowledge and tools for us all to lead longer, healthier, more active lives.”

Paula Pennington de la Bretonne

Twenty Years of Community Support—Pennington Biomedical Research Foundation

Pennington Biomedical Research Foundation

The Pennington Biomedical Research Foundation was created in 1988 with Doc and Irene Pennington's encouragement, to foster support for the additional needs of the Center from broad-based private philanthropy, corporate support and state funding sources.

Charter PBRF board members played a vital role in the early days of PBRC, assisting in the search for the Executive



In 1988, the Baton Rouge Area Foundation made the grant to help fund the hiring of the Center's first executive director. John B. Noland, then chairman of BRAF, makes the presentation to Milton Womack, PBRF chairman, as Allen Copping, LSU System President, looks on.

philanthropic gift representing 60% of the named endowment. The remaining 40% is matched with funds provided by the Louisiana Board of Regents' Eminent Scholars Program. As of 2007, the Foundation's endowments are valued at approximately \$17.7 million and have provided more than \$3.8 million in support to PBRC since inception of the endowment program.

Identifying and developing volunteer leadership to support PBRC has always been a priority for the Pennington Biomedical Research Foundation. Early efforts

Director and generating much needed operating support to help open the Center.

The PBRF board quickly recognized the need to build an endowment of chairs and professorships to help the Center attract experienced research scientists. Today, the endowment includes 10 chairs, 1 super chair and 3 professorships.

Each endowment is created through a private

included the formation of the "docents" in 1992, a women's group led by Mitzi Bray, wife of Dr. George Bray (PBRC Executive Director from 1989 – 1999). The docents were the first ambassadors for the Center, leading tours, hosting receptions and introducing many members of the community to the exciting and emerging research at PBRC. Since then, hundreds of community citizens have volunteered to serve on committees ranging from fundraising activities and events to educational programs, such as the Irene W. Pennington Wellness Day for Women.



The Coypu Foundation Trust continues John S. McIlhenny's legacy of support for PBRC and PBRF. The Trustees gather at PBRC for the unveiling of McIlhenny's portrait.

In recent years, the Foundation's efforts have focused on generating unrestricted support for the Center, both through philanthropic support and encouraging increased investment from the state of Louisiana. Through this initiative, the Pennington Biomedical Research Foundation launched a successful governmental relations effort; the *Soaring to New Heights* fundraising event; the Pennington Council of 100, an annual leadership giving program; and a Named Gift program to permanently recognize the support of major donors and corporate partners. Cumulative support from the Foundation to the Center now exceeds \$15 million.

Since 2004, *Soaring to New Heights* has successfully raised funds for the Center. Volunteer committee members gather at the event in 2006.



Pennington Biomedical Research Foundation

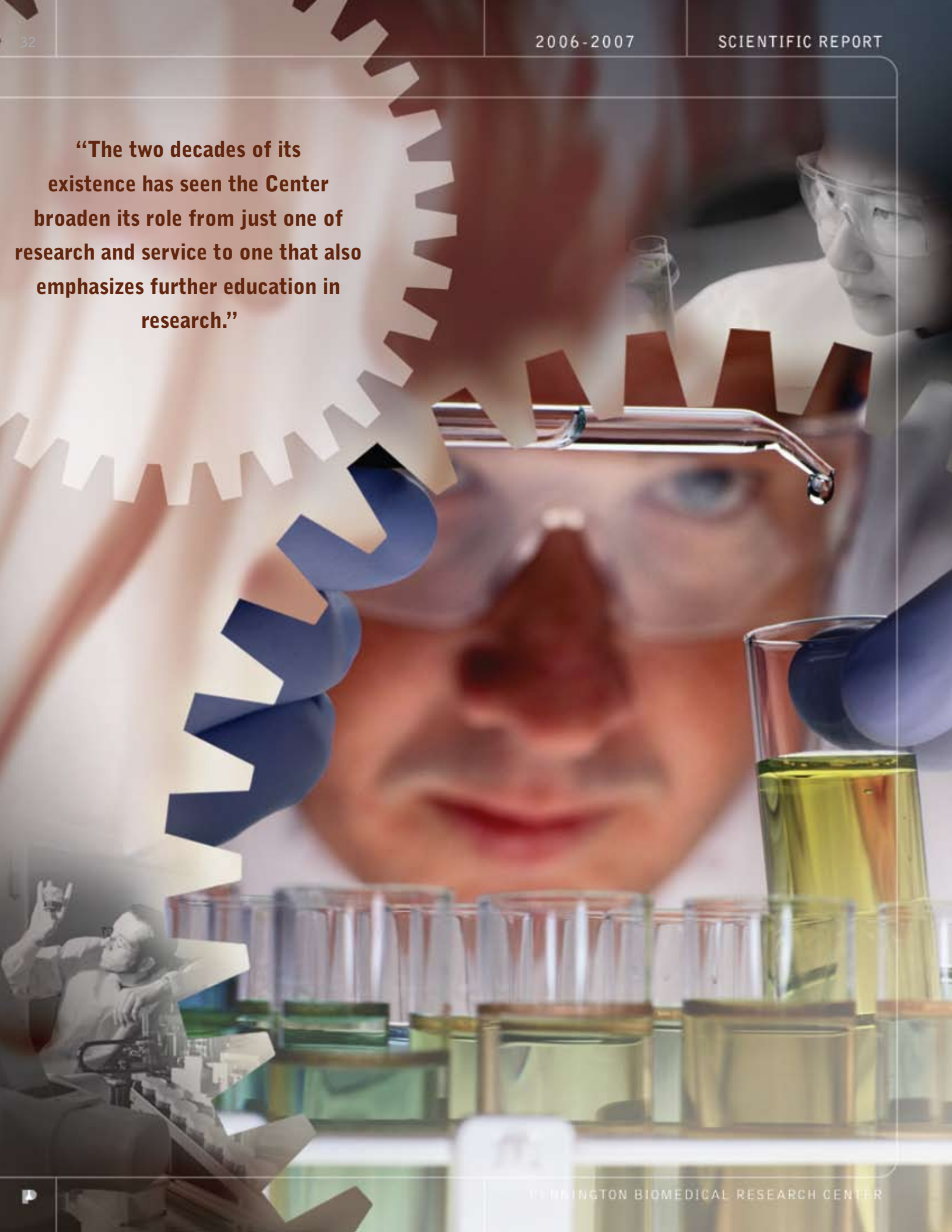
We gratefully acknowledge our board leadership from 1988 to 2007.

NAME	BOARD MEMBER SINCE	NAME	BOARD MEMBER SINCE
John W. Barton	Founding Member	*Irene W. Pennington	1996
Henry Goodrich	Founding Member	Robert Gaston	1998
* Robert S. Greer	Founding Member	*Donald J. Nalty	1998
* William H. LeBlanc	Founding Member	Paula P. de le Bretonne	2000
* Charles W. McCoy	Founding Member	James J. Bailey III	2001
Leonard R. Nachman	Founding Member	Joseph "Jay" H. Campbell, Jr.	2001
* Thomas P. Singletary	Founding Member	Thomas L. Frazer	2001
* J. Frank Terrell	Founding Member	Roy G. Kadair, M.D.	2001
David M. Walker	Founding Member	Charles A. Landry	2001
W.W. Williams	Founding Member	C. Brent McCoy	2001
* Milton J. Womack	Founding Member	James M. Nolan	2001
William H. Wright	Founding Member	John B. Noland	2001
Robert H. Barrow	1988	Kathryn M. Sullivan	2002
George A. Foster	1988	Annette D. Barton	2003
Roger A. Moser	1988	Patricia L. Cheramie	2003
Lawrence D. Adcock	1989	J.S. "Si" Brown, III	2004
William L. Senn	1989	Tim A. Barfield, Jr.	2005
Kevin P. Reilly, Sr.	1990	Madhu Beriwal	2005
J. Terrell Brown	1991	Maxine Cormier	2005
E. Gary Cook	1992	J. Gerard "Jerry" Jolly	2005
Edwin Lupberger	1993	Kevin R. Lyle	2005
Clyde Sasser	1993	Elizabeth "Betsy" S. Nalty	2005
Bert S. Turner	1993	J. Herbert Boydston	2006
Ann McMains	1994	Brace B. Godfrey, Jr.	2006
Richard F. Manship	1995	Carl S. Luikart, M.D.	2006
Thomas J. Moran	1995	Elizabeth Querbes Sammons	2006
Redfield E. Bryan	1996	Edward Ashworth	2007
Lev Dawson	1996		
Laura A. Leach	1996		
P.J. Mills	1996		
Nanette Noland	1996		

Founding Members

* Deceased

“The two decades of its existence has seen the Center broaden its role from just one of research and service to one that also emphasizes further education in research.”



Basic Research Programs



Jeff Keller, Ph.D.
Associate Executive
Director



Douglas Braymer Ph.D.
Interim Associate
Executive Director



Richard Rogers, Ph.D.
Immediate Past Assoc.
Executive Director

Background:

On the twentieth anniversary of the Center, it is appropriate to look at the development of Basic Sciences during the past two decades. The opening of the Center in 1988 occurred with four investigators working in the basic science laboratories Dr. Daniel Hwang, Dr. Chandan Prasad, Dr. Wayne Vedeckis and Dr. Daniel Church. The first Executive Director, Dr. George Bray, recruited Dr. David York from the University of Southampton as the Center's first Associate Executive Director for Basic Science. In 2005, Dr. Richard Rogers, a neuroscientist, assumed that position. The third Associate Executive Director for Basic Research, Jeff Keller, Ph.D., joined the Pennington Biomedical Research Center in late 2008. During the York/Rogers years, Basic Research grew from these original four to a present complement of fifty-nine scientists.

Organizational Growth – The last two years have been an eventful and successful time for the Center's Basic Science area. We have continued to grow with a faculty divided over three divisions: Experimental Obesity, Functional Foods and Nutrition and the Brain, all of which were held up for review by external advisory panels in late 2007. Within Basic Research, we also have seven Core facilities: Cell Culture; Comparative Biology; Genomics; Cell Biology and Cell Imaging; Animal Metabolism and Behavior; Proteomics; and Transgenics. The functionality of all the cores was reviewed in 2006, and cores were reorganized to allow them to operate more effectively and independently. Substantial institutional investment has been made in new instrumentation for the core facilities over the last two years. As a consequence, the cores have increased the productivity of the research programs by providing specialized instrumentation and technical assistance that are unmatched. Excellence in core instrumentation is essential to driving basic science progress.

Expansion of the cores and the basic science faculty was greatly assisted by the completion of the "new" Basic Sciences Building in 2004. This structure, which essentially doubled basic science research laboratory space is now filled to capacity. Plans are being made for the creation of an

additional Basic Science Building and Vivarium that will again double available laboratory space.

Funding Success

Nearly two decades ago, the Center's first grant came from the U.S. Department of Agriculture and provided \$9.4 million to equip laboratories. This was quickly followed by a grant of \$3.5 million from the Department of Defense to fund a program in Military Nutrition. Since those first successes, the amount of basic science grant support has steadily grown with the addition of two center grants (Botanical and CNRU) plus a COBRE grant. (You can read more about these significant center grants later in this report.) Basic Science acquired more than 25 million dollars in annual contract and grant funding in 2007. This is in addition to new programs funded by special legislative initiatives in Nutrition and Brain Development, Epigenetics, and Nuclear Reprogramming, totaling more than four million dollars per year.

Training

The two decades of its existence has seen the Center broaden its role from just one of research and service to one that also emphasizes further education in research. This has occurred through an ever growing emphasis on postdoctoral training, housing graduate students from other campuses to complete the research portion of their graduate degree and in the utilization of undergraduate student workers in the research programs. Basic Sciences has been involved in two NIH training grants and a T35 grant with the Veterinary School of LSU A&M. The addition of the COBRE grant has incremented our training mission to include the formal development of promising junior faculty.

Future Directions

The research direction of the Center has broadened considerably over 20 years. In 1988, research programs

were entirely focused on nutrition and obesity. By 1992 the mission had broadened to include cancer; in 1994, brain and behavior research were added and reproduction in 1996. Basic Sciences had refocused in 2004 to include nine different areas; stem cell biology, nutrient sensing, molecular genetics, human genomics, neuroscience, cancer, experimental obesity, bioinformatics and statistical genetics, and diabetes.

The 2006-2007 period has seen the Center broaden its expertise in the area of neuroscience. The addition to a stellar faculty (Drs. Berthoud, Rogers, Pan, Kastin, Travaglia, Hermann, Browning and Holmes) of Drs. Claudia Kappen, Michael Saulbaum, Donald Ingram, Vishwa Dixit, Jeff Keller and Annadora Bruce-Keller adds strength in new areas of developmental biology as well as aging and neurodegenerative disease research.

Over the last twenty years, Basic Science at PBRC has enjoyed enviable growth in funding, capabilities and recognition. As a result, it is presently poised to make a substantial positive impact on the economic development of Louisiana through expansion and commercialization of its scientific products. However, continued success of the Basic Science enterprise faces serious challenges for the future.

With the filling of practically all available basic science laboratory space, expansion of the basic science faculty will require the addition of a new Basic Science facility. The decline in the numbers of senior biomedical scientists in the U.S. makes recruitment of new Basic Science faculty more difficult than in the past. Addressing these problems will require redoubled commitment by the local community, the State and most particularly, the faculty to continue the success of the Pennington Biomedical Research Center.

Division of Experimental Obesity



Thomas Gettys, Ph.D.
Division Chief,
Experimental Obesity

Mission – to enhance understanding of the causes and consequences of obesity; and to use this understanding to promote new approaches to the treatment and prevention of obesity.

Obesity is most simply defined as accumulation of excess adipose tissue and the condition develops when energy intake chronically exceeds energy expenditure. A highly integrated set of regulatory systems function to maintain energy balance by continuously modifying energy intake and expenditure. Dysregulation of this homeostatic network compromises its ability to match energy intake and expenditure, setting up conditions which over time lead to excess accumulation of adipose tissue. The faculty of the Experimental Obesity Division are devoted to understanding the regulatory systems and communication networks which control energy balance.

A second unifying theme within our division is the extensive use of genetically modified animal models as *in vivo* approaches to explore how specific genes affect energy balance. These models include targeted gene disruption, transgenic over-expression, and naturally occurring mutations of specific genes. The common goal of these studies is to expand our understanding of how specific genes function to modify energy intake and/or expenditure. The reverse approach is also used in genetic mapping studies, where strain variation in specific components of energy balance is used to identify the genetic basis for phenotypic differences. A common feature of these studies is the extensive use of metabolic phenotyping to obtain longitudinal, noninvasive measures of energy expenditure, respiratory quotient, locomotor activity, and body composition. The Center has created and maintains state of the art metabolic phenotyping facilities within the Comparative Biology Core. Expertise in applying this technology to gain fundamental insights into the role of specific genes in energy balance represents a collective strength of the Experimental Obesity Division. During the last year, the Division committed additional resources to improve our systems used to monitor food intake

and expand our ability to use miniaturized implantable telemetry probes to measure heat production from specific organs. These investments have enhanced the ability of faculty within the Experimental Obesity Division to better understand how specific components of energy balance are being affected in the animal models that are central to the work in which we are engaged.

Faculty

The creation of the Nutrition and the Brain division in 2005 at PBRC involved redistribution of several faculty from Experimental Obesity into this new division. Given the multidisciplinary nature of work on obesity and energy balance, this redistribution has been beneficial in the sense that it has increased collaborative studies using complementary expertise found within each division. This has led to significant cross fertilization between the divisions with respect to ideas, experimental approaches, and technology. An important example is the expansion of imaging based approaches to study signaling events in cultured cells in real time. The value of these approaches has been embraced more broadly with the commitment of institutional resources, and coupled with support from our Center Grants (COBRE & CNRU), led to establishment of the Cell Biology & Bioimaging Core Facility. Key to establishment of this new Core was the recruitment of Dr. David Burk, an expert in confocal microscopy, to become the first Director of this facility. This valuable new facility is the product of collaborative thinking and a nimble institutional response to the powerful experimental approaches provided through application of this emerging technology. With the recruitment of Drs. Tom Burris and Vishwa Dixit to the Center this year, we have also expanded the Division's perspective and technical repertoire to include studies of nuclear receptor signaling and the links between energy balance and immunology. Dr. Burris is a recognized leader in nuclear receptor signaling, and given the key role of nuclear receptors in adipocyte differentiation and development, his addition will provide important

new expertise in this area. And Dr. Dixit's important observations concerning the role of ectopic fat deposition and its relation to function of the thymus provide a novel perspective on the implications of adipogenesis to thymic involution. A significant shared need for several Center Divisions is the recruitment of additional expertise in the area of mitochondrial biology. This need was also identified as a priority in our recent Center-wide strategic planning process. Recruitment of a cell biologist specializing in mitochondrial function is a priority for our Division in the coming year.

Resources and Support

The 16 faculty within the Experimental Obesity Division are supported by 19 extramural grants from NIH, USDA, and ADA, one training grant and three center grants from NIH. Junior faculty who obtained their initial independent funding in recent years will soon need to submit applications for continuation of funding. Our senior faculty face similar challenges and are also working to develop new funding. An important divisional goal in the next 2 years is to maintain and expand extramural support for our work. To meet this goal in the present funding climate, we have contracted with Dr. Israel Goldberg of Health Research Associates to provide intensive one on one grantsmanship support to divisional faculty. In the last NIH review cycle, three division faculty received high

priority scores that should translate into three new grants within the division. During the last year, the Center was also awarded a NIH Center of Biomedical Research Excellence (COBRE) grant entitled, "Mentoring Obesity & Diabetes Research in Louisiana". This new funding provides support to enhance research infrastructure at the Center and support four junior investigators making the transition to independent funding. The COBRE award complements the contributions of the CNRU and Botanicals Center to the Pennington Biomedical Research Center's core facilities by providing support to establish the Cell Biology and Bioimaging Core and expand the capabilities of the Genomics Core Facility. The additional resources from the CNRU to support the Transgenic Core will improve the ability of Divisional faculty to develop new genetically modified animal models and test hypotheses concerning the in vivo function of their genes of interest.

Division of Functional Foods



William Cefalu, M.D.



Jennifer Rood, Ph.D.

Mission - The overall goal of the Division of Functional Foods is to use cutting edge technologies to identify bioactive compounds that affect metabolic processes relevant to specific chronic diseases; discover the mechanistic basis of action for these compounds; and determine the health benefits of specific foods and food components in clinical studies.

Status Report

Functional foods are foods that, by virtue of physiologically active components, provide additional health benefits beyond that of meeting nutritional needs and may prevent disease. The Center's Functional Foods program has analyzed the healthful effects of foods and food products, such as individual fatty acids, plant sterols, phytoestrogens, a Mediterranean-style diet, dairy products, nuts, and rice and fish oils. At the core of an integrated Functional Foods research program is the application of cutting-edge technologies and clinical assessments to identify bioactive compounds that affect metabolic processes relevant to specific diseases, to discover the mechanistic basis of action for these compounds, and to determine their health benefits. Currently, there are 10 faculty members that provide effort in this Division and that examine the role healthy diet plays in the mitigation of chronic diseases such as cardiovascular disease, obesity, diabetes and cancer.

The Division contains three major interest groups:

- Non-digestible carbohydrates and intestinal function

- Plant bioactives and cell energy metabolism

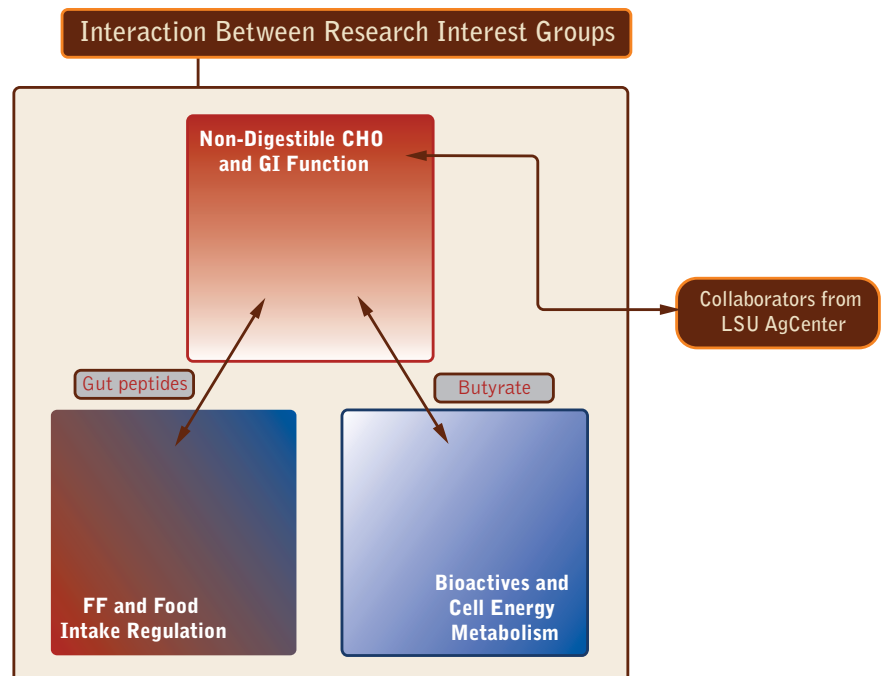
- Functional foods and food intake regulation

There is significant interaction between the three groups as depicted at right:

PBRC has established a strong research portfolio in the functional foods arena that is well balanced with respect to both discovery and mechanism oriented basic research and efficacy and application oriented clinical research.

“Regulation of Intestinal Cholesterol Absorption” is a National Institutes of Health (NIH) funded collaborative project between researchers here at the Center and Washington University. This five-year study addresses the role that minor components in vegetable oils play regulating plasma cholesterol levels. These studies have the potential to increase our options for the therapeutic reduction of plasma cholesterol levels in those at risk for cardiovascular disease.

A strength of our clinical program is that it continues to attract high quality, hypothesis driven, industry sponsored trials. In support of new product development, controlled feeding trials have examined the effects of novel food processing methods or unique combinations of ingredients



on cardiovascular disease-related endpoints. Other industry sponsored trials have examined the effects of herbs, herbal combinations, and/or novel food ingredients on features related to obesity. Indeed, the Center's reputation in the area of clinical obesity research continues to attract industry interest as companies seek to demonstrate the efficacy of weight loss or establish mechanisms of action for food products directed at weight management.

In 2005, the Division's basic science program was substantially expanded with the establishment of an NIH funded Botanical Research Center (see center report within this issue). This five-year program, in collaboration with the Division of Nutrition and Chronic Disease, pursues an integrated understanding of the molecular, cellular and physiological mechanisms by which select botanicals may modulate factors related to the development of obesity and insulin resistance. Importantly, the Botanical Research Center involves collaborations between PBRC, Rutgers University, and LSU Agricultural Centers, which allows our Division scientists to directly interact and work with leading scientists at other institutions.

The Botanical Research Center consists of three separate research projects, a training component to develop new scientists in the area of functional foods (including an active pilot study program) and a "discovery" component designed to identify new botanicals that may prove useful

in the management of the metabolic syndrome. As the Division looks to the future, it will be important continue building on strengths in the areas of carbohydrate and lipid metabolism and energy and food intake regulation. Important in this process is the continuing development of functional foods related research in other research divisions at the Center. This is greatly facilitated by pilot and feasibility grants funded through both the Botanical Research Center and PBRC institutional funds. Because of the modest size of this Division, it will remain a goal to continue to interact closely with the Center's other divisions on multiple research priorities through sharing expertise and technologies.

In future years, we will look to complement our existing faculty with additional appointments in areas of strategic importance. While traditional peer-reviewed grants provide the support base for the Division's research activities, our standard of excellence and growing national prominence will continue to attract significant additional private and industry support. A commitment to fundamental "discovery-based" research initiatives will open new avenues for exploration and afford novel opportunities for technology transfer. Through these activities, we will realize our combined vision focused on the continued development of a wholly integrated, nationally competitive, and internationally recognized research program.

Division of Nutrition and the Brain



Weihong Pan, M.D., Ph.D.
Division Chief

Mission - to conduct cutting-edge work on integrative neuroscience related to human nutrition, neuroendocrine regulation, and the healthy brain.

Status Report

History: The Division of Nutrition and the Brain was formed in 2005, headed by Dr. Richard C. Rogers, and passed on to Dr. Weihong Pan in 2006. In the beginning of PBRC, there were three neuroscientists: Drs. George Bray, David York, and Hans-Rudolf Berthoud. These senior investigators enjoy international reputations as neuroendocrinologists unraveling obesity disorders. Drs. Richard Rogers and Gerlinda Hermann joined the division in 2002. They added *in vivo* electrophysiological and *in vitro* imaging expertise to the list of tools available to the Center investigators. Dr. Roy Martin, also Chair of Human Nutrition on the main Louisiana State University Campus, arrived in 2002 to investigate nutrient detection mechanisms. Dr. Greg Holmes joined in 2003 and brought unique studies on gastric stasis and autonomic dysfunction after high-level spinal cord injury. In the same year, Dr. Christopher Morrison returned after completing his training related to hypothalamic regulation of nutritional homeostasis. This was followed by the group of Dr. R. Alberto Travagli and Kristeen Browning, who address the neuronal-pancreatic axis by use of whole animal physiology and *in vitro* neurophysiological techniques. The Blood-Brain Barrier Group (Dr. Abba J. Kastin and Dr. Weihong Pan) moved from New Orleans in 2004, bringing with them the journal *Peptides*. They remain the leading group in the world characterizing the transport of peptides and proteins across the blood-brain barrier in neuroinflammation and neuroendocrine-immunomodulation. Dr. Donald Ingram and Dr. Vishwa Dixit, both of whom relocated from NIH in 2007, provide expertise in aging, caloric restriction, behavioral analyses (Ingram) and immunology (Dixit). Most investigators actively collaborate with researchers in other Divisions as well as outside the institution.

Divisional activities: A research social is held monthly,

followed by interactive learning sessions. This year's format includes a journal club as well as talks by outside neuroscientists. The yearly award events include (1) grant applications by postdoctoral fellows, instructors, and assistant professors, with senior faculty and outside reviewers being the judge, and (2) first prizes for best performance, productivity, and team work. These events add a strong neuroscience component in addition to other institutional seminars and presentations.

Scope of research and aspects for future improvement:

During the past five years, research has extended from nutrient sensing (Martin, Travagli, Browning) and hypothalamic neuroendocrinology on feeding behavior (Berthoud, Morrison) to strokes. Drs. Rogers and Hermann are experts on the role of vagal afferents in cachexia, and recently showed new progress on chemokine regulation in the brainstem. Dr. Holmes studies the effects of spinal cord innervation on GI motility and gastric stasis after injury, a unique area largely ignored by the research community. Dr. Kastin and Dr. Pan address the integrative role of the blood-brain barrier in many physiological and pathological processes, and determine signal transmission by the cerebral endothelial cells in neuroinflammation. Dr. Dixit brings expertise in cellular immunology. Dr. Ingram is an authority in aging and caloric restriction, and has played a major role attracting more competitive researchers to join PBRC. Our newest addition, Dr. Indu Kheterpal, runs an efficient proteomics core which provides high-quality service to many researchers, and continues her own study on amyloid protein aggregation.

The divisional activities are designed to facilitate active discussions and apprenticeship in career advancement.

The outlook: We hope that the neuroscience division is becoming better and stronger. New expertise continues to arrive, and the overall quality of postdoctoral fellows has improved. Our goal is to address meaningful questions about the nervous system related to human health, and make significant contributions to the community.

Clinical Research



Donna Ryan, M.D.
Associate Executive Director
for Clinical Research

"It is the responsibility of those of us involved in today's biomedical research enterprise to translate the remarkable scientific innovations we are witnessing into health gains for the nation."

Elias A. Zerhouni, MD.
NEJM 2003 353;15 1621-3.

Clinical research is in the spotlight across the nation, as the academic biomedical research enterprise gears up to embrace the clinical and translational research agenda fostered by the National Institutes of Health, which is surely a harbinger of future direction for *all* biomedical research. There is a growing appreciation for the importance of clinical research, partly from enthusiasm for the new and powerful tools (genomics, proteomics and imaging technologies) applied at the bedside, but also a growing awareness of the limits inherent in the use of animal models. Both factors are driving the interest in advancing clinical research.

More than twenty years of progress in clinical research. The Pennington Biomedical Research Center is a model for clinical and translational research, since it houses basic, clinical and population research programs in one facility and is, thus, well-positioned for the research agenda for the twenty-first century. For this, credit goes first to the design committees from the LSUHSC in New Orleans, who 25 years ago envisioned a nutrition research institute without silos, but encompassing scientists at bench, bedside and in the community working across disciplinary boundaries to address nutrition issues. We must also credit the early inauguration of clinical research at PBRC, with the first study conducted in 1992. While this study might have had a modest scope – it was the evaluation of eating behavior in normal weight, overweight and obese individuals and was the basis for the doctoral thesis for Candy Lawson, PhD – this modest beginning enabled the initiation of the policies and procedures that form the basis of our clinical research enterprise today.

There has indeed been progress, as is attested in the chart, below. In just 16 years, we have conducted more than 300

research studies and enrolled more than 13,000 individuals. We have expanded our organization with the following cores:

- Outpatient Unit Core
- Inpatient Unit Core
- Recruiting Core
- Biostatistics & Data Management Core
- Clinical Chemistry Core
- Mass Spectrometry Laboratory
- Dietary Assessment Core
- Metabolic Assessment Core
- Research Kitchen Core
- Imaging Core

The productivity and organizational complexity of the clinic operation attests to the variety and number of disciplines that are required for clinical research. The incredible productivity of the inpatient and outpatient units reflects the contribution of a multidisciplinary team, including physicians, scientists, psychologists, dietitians, kinesiologists, study coordinators, nurses, phlebotomists, clinical chemists, pharmacists and many more disciplines.

The next twenty years of clinical research at Pennington Biomedical Research Center: We are already on the move. Ground will break in early 2008 on the new Clinical Research Building, a four story structure of 90,000 sq. ft., and we hope to occupy the new facility in early 2010. This will enable us to more than double our current outpatient clinic operations and expand our inpatient beds by 50%. We will reconfigure the "old" clinic to new uses, and are hoping to make this a pediatric nutrition research facility. We're not only growing on Perkins Road, however. In 2008, we will establish a satellite operation in cooperation with the Baton Rouge General Family Medicine Residency Program, a satellite in north Baton Rouge, and a satellite in Lafayette, in partnership with the University of Louisiana Lafayette School of Nursing.

We are not only expanding our operations at the Perkins Road campus and establishing satellites in Baton Rouge

and Lafayette, we will also expand our sphere of influence with others engaged in the clinical research enterprise in Louisiana. In 2006, we were awarded a planning grant to develop a clinical and translational science award application, and we have moved forward with a consortium effort in the Louisianan Clinical and Translational Science (LA CaTS) Center. The Center will have a home office on the fourth floor of our new clinic building, but will use the Louisiana Optical Network to link our partners – from New Orleans: LSU HSC and Tulane HSC, Xavier University of Louisiana, Ochsner Clinic Foundation; LSU HSC in Shreveport; and in Baton Rouge, LSU A&M and PBRC. The LA CaTS Center will enable the linkage of clinical research sites across the state and, using the Louisiana

Optical Network Initiative to provide the communications platform, spark a cohesive collaboration of those with like interests.

Having worked at the Center since 1989, I have personally witnessed its spectacular growth, and the establishment and flourishing of our clinical research. There are too many contributing individuals to thank here for their participation in the success of the clinical research enterprise, so their satisfaction, like mine, will come from observing the next twenty years which, I believe will not only equal but surpass these experiences. As long as we stay true to the original intent to bridge disciplines, to break down silos and to encourage and reward collaboration, then our success is assured.

Clinic Activity Report

YEAR	NO. OF TELEPHONE CONTACTS	NO. OF SCREENING VISITS	PERCENTAGE FEMALES	PERCENTAGE MINORITY	NO. ENROLLED IN STUDIES	PERCENTAGE FEMALES	PERCENTAGE MINORITY	STUDIES STARTED
1992	1962	771	67%	13%	255	61%	15%	5
1993	2543	1124	59%	20%	575	58%	20%	14
1994	3742	1423	49%	37%	451	57%	24%	15
1995	6020	2005	49%	52%	574	48%	22%	12
1996	4799	1432	54%	25%	628	44%	19%	13
1997	4261	1667	63%	32%	612	56%	23%	11
1998	5282	2218	68%	33%	783	73%	22%	23
1999	4537	1686	61%	26%	618	58%	22%	19
2000	5458	1933	76%	32%	731	69%	24%	25
2001	4432	1707	76%	39%	804	77%	37%	26
2002	4388	1836	69%	35%	999	69%	36%	24
2003	6224	2391	71%	41%	1394	72%	37%	28
2004	6741	2502	67%	44%	1429	66%	38%	37
2005	8576	3775	57%	39%	1723	64%	35%	18
2006	6984	2213	67%	39%	1189	68%	36%	35
2007	7192	1871	68%	43%	929	66%	36%	33
TOTAL	75,949	28,683			12,765			305

Division of Clinical Obesity and the Metabolic Syndrome



George Bray, M.D.
Division Chief, Clinical Obesity
and Metabolic Syndrome

Mission - to provide an academic home for professionals working on problems related to the clinical solution of obesity.

Status Report

The Division of Clinical Obesity and the Metabolic Syndrome was separated from the Division of Nutrition and Chronic Disease in 2002 to reflect the large program in clinical obesity, metabolism and behavioral medicine. Dr. Bray is Chief of the Division and Dr. Donald Williamson is the Deputy Chief. The faculty members assigned in part or wholly to the division include five Professors, five Associate Professors, five Assistant Professors and five Instructors. In most cases, these individuals also participate in other divisions. Several important awards have been made to members of the Division. Dr. Donald Williamson, Ph.D., has received a major award from the National Institutes of Health and the US Department of Agriculture to demonstrate that an intensive school based program, called LA Health, and reduce the risk of becoming overweight during school years. The nomination by Catherine Champagne, Ph.D., head the Center's Women's Nutrition Program, led to the election of George A. Bray, M.D. to an honorary membership in the American Dietetic Association. The completion of the new Population Science building in late 2006 added significantly to the space available for Population and Clinical Investigation. A new Clinical Science building is in the works. Dr. Steven Smith, M.D. has become an Assistant to Dr. Donna Ryan, the Association Executive Director for Clinical Science.

The two National Institutes of Health (NIH) center grants for a Clinical Nutrition Research Unit (CNRU), with Dr. Ravussin as the Principal Investigator, and a Botanical Research Center grant, funded to Dr. William Cefalu as principal investigator, both provide pilot and feasibility money (see center reports in this issue). Through funding from Professor Bouchard's office, the Division of Clinical Obesity and the Division of Health and Performance Enhancement awarded three Pilot and Feasibility grants

to complement those funded by the Center grants noted above. The Division of Clinical Obesity is well funded through a variety of external granting mechanisms. These include NIH funding of the following projects: 1) Diabetes Prevention Program Outcomes study (DPPOS); 2) Look AHEAD (Action for Health in Diabetics); 3) Weight Loss Maintenance Project (WLM); 4) Prevention of Obesity Using Novel Dietary Strategies (POUNDS Lost); 5) Healthy Transitions (Peri-menopausal study); 6) Prevention of Obesity after Smoking Cessation; 7) Health Improvement Program (HIP) for Teens; 8) Wise Mind; 9) CALERIE (Calorie Restriction); 10) a Clinical Nutrition Research Unit (CNRU). Three young investigators in this Division have received Career Development Awards from the National Institutes of Health on a competitive basis, indicating the high quality of the younger faculty members assigned to this Division.

The U.S. Department of Agriculture is funding studies on 1) Dietary Fat and Obesity; 2) The Delta Nutrition Intervention Research Initiative (DELTA NIRI); 3) Longitudinal Study of the predictors of obesity; and 4) Louisiana (LA) Health (described above). The State of Louisiana is funding the Louisiana Obese Subjects Study (LOSS), which is a study of the effectiveness of intensive medical management to promote significant weight loss in obese patients. And finally, the U.S. Department of Defense is funding two projects on weight control for active duty and reserve soldiers in the U.S. Army.

The Division has maintained a healthy output of scientific papers, including about 50 original papers and nearly as many chapters and reviews each year since the Division was formed. As we plan for the future, we look forward to a continuing robust Division of Clinical Obesity and Metabolic Syndrome.

Division of Nutrition and Chronic Diseases



William Cefalu, M.D.
Division Chief, Nutrition
and Chronic Disease

Mission - Chronic diseases such as diabetes, cancer and cardiovascular disease contribute greatly to the increased morbidity and mortality not only observed in this country, but noted worldwide. The Division of Nutrition and Chronic Diseases has diverse interests and programs aimed at investigating the causes and/or assessing interventions to treat these major conditions.

Status Report

The Division currently has major research programs in epidemiology, cancer, cardiovascular disease, women's health, stem cell research and diabetes. In addition, the division continues to work closely with the Functional Foods Division to complete studies as part of the National Institutes of Health (NIH) funded Botanical Research Center, whose mission is to investigate the use of botanical extracts on the pathophysiology of metabolic syndrome, a pre-diabetic condition.

The Division's diabetes effort has as its primary interest, the study of the pathophysiology of type 2 diabetes and its complications. Particularly, division researchers are evaluating cellular mechanisms contributing to the development of insulin resistance and the mechanisms by which complications, such as neuropathy, develop. Further, the diabetes program is active in investigating nutritional interventions on a clinical level by which these specific mechanisms can be altered in subjects with type 2 diabetes.

The study of cancer in the Division continues to receive national attention, as during recent years, investigators have developed a number of compounds consisting of lytic peptide-gonadotropin conjugates that have been shown to effectively target and destroy human breast, prostate, ovarian, and testicular cancer xenografts and their metastases in rodent models. In addition, new compounds have been developed and rights to market these compounds were acquired by a newly created company (Esperance Inc.). Meanwhile, the laboratory was designated the William Hansel Cancer Prevention Laboratory, start-up funds were raised and additional faculty investigators recruited. The goal of the Cancer Prevention Laboratory is to develop

treatments that will prevent recurrent cancer after surgery or treatment, and improve the quality and longevity of life in cancer patients. The specific objective of the laboratory is to test, *in vivo* drugs, plant extracts or dietary supplements previously shown to kill cancer cells at low concentrations in *in vitro* experiments.

The DNA Damage and Repair Laboratory continued its studies on the S3 protein that appears to interfere in the removal of highly mutagenic sites in DNA known to be involved in the onset of cancer. Human S3 was originally identified as a component of the small subunit of the ribosome and hence a cytoplasmic protein. Using a variety of experimental and computational approaches, investigators of this laboratory have determined and characterized roles above and beyond protein synthesis and posit that hS3 possesses extra-ribosomal activities that influence DNA repair, and perhaps cellular stress response pathways such as apoptosis. Presently, the working hypothesis of the lab is that hS3 acts to both moderate the repair of 8-oxoG, and acts as a sentinel to set apoptosis in motion under cellular conditions of oxidative stress. Thus hS3 may play a vital role in tumorigenesis as well as aging. Investigators are presently testing this possibility in transgenic mice that harbor hS3 and variants.

In recent years, there has been growing public interest in the use of stem cells for the repair and regeneration of failing tissues, and the Division has had significant growth in this area. Currently, the stem cell program in the division consists of five laboratories: Stem Cell Biology Lab; Transgenics Lab; Ubiquitin Biology Laboratory; Regenerative Laboratory; and Nuclear Programming and Epigenetics Laboratory. The major objective of these labs are to address the fundamental questions relating to adult or somatic stem cells isolated from a variety of organs and species and to focus their inter-related expertise on the isolation, characterization and manipulation of adult stem cells. Independent studies are underway to identify novel mechanisms regulating the imprinting of genes in stem cells, the role of stem cells in wound healing, and the potential

application of human adipose-derived stem cells for tissue engineering.

The molecular mechanisms regulating insulin resistance and the relationship between this syndrome and obesity are still largely unknown. The Functional Genomics Laboratory investigates potential mechanisms and novel candidate genes utilizing different murine genetic models and molecular manipulation of cultured cell lines. Small changes in gene expression are measured using state-of-the-art microarray and PCR approaches to provide insights into how protein expression and intracellular localization and trafficking are impacted by dietary and genetic modulation.

Several new initiatives have been part of the Division growth over the last several years and have included the addition of studies in maternal biology, regulation of gene expression and advances in new technology. As such, the Maternal Biology Laboratory has NIH funded studies that are focusing on the role of specific genes and nutritional factors, e.g. folate, on embryonic development. The Laboratory of Gene Regulation is also interested in this area and has NIH supported studies evaluating molecular mechanisms contributing to diabetic embryopathy. Technological advances in the division are result of efforts from the Protein Structural Biology Laboratory. Division investigators have characterized and tested a number of nanoparticulate constructs for use as contrast agents for Magnetic Resonance Imaging, for treatment of cancers and metastases and for monitoring treatment response. The research focused on superparamagnetic ironoxide nanoparticles that consisted of membrane disrupting peptides (Hecate) and a gonadotropin moiety (LHRH) as targeting agent. These conjugates (LHRH-SPIONs) have been shown to effectively target and accumulate in human breast and prostate cancer xenografts and their metastases. Moreover, the contrast agent specifically labeled tumor cells and metastases and increased the sensitivity of an MR image. In the Protein Structural Biology Laboratory, investigators are studying protein expression and protein structure related to disease biology. Specifically, they are

developing and applying hydrogen/deuterium (H/D) exchange and electrospray ionization-mass spectrometry (ESI-MS) methods for characterizing non-covalent interactions in misfolded proteins associated with amyloid diseases. In addition, they are using MS based proteomic approaches to evaluate the mechanism by which botanical and nutritional interventions improve insulin sensitivity.

Finally, in an effort to enhance new ideas and to support young investigators, the Division continues to provide intramural funding to promising projects. It is anticipated that support of these projects will provide the necessary pilot data for young investigators to submit larger grants required to sustain the growing research activities of the Division of Nutrition and Chronic Diseases.

Division of Health & Performance Enhancement (HaPE)



Eric Ravussin, Ph.D.
Division Chief, Health and
Performance Enhancement

Mission - The overall goal of the Division of Health & Performance Enhancement is to integrate coordinated programs across basic and clinical aspects of the interaction between diet, physical activity and health. The mission of the Division is "to conduct innovative research designed to improve health and performance throughout the life cycle."

Status Report

The Division provides a vehicle for interactions between four areas of research:

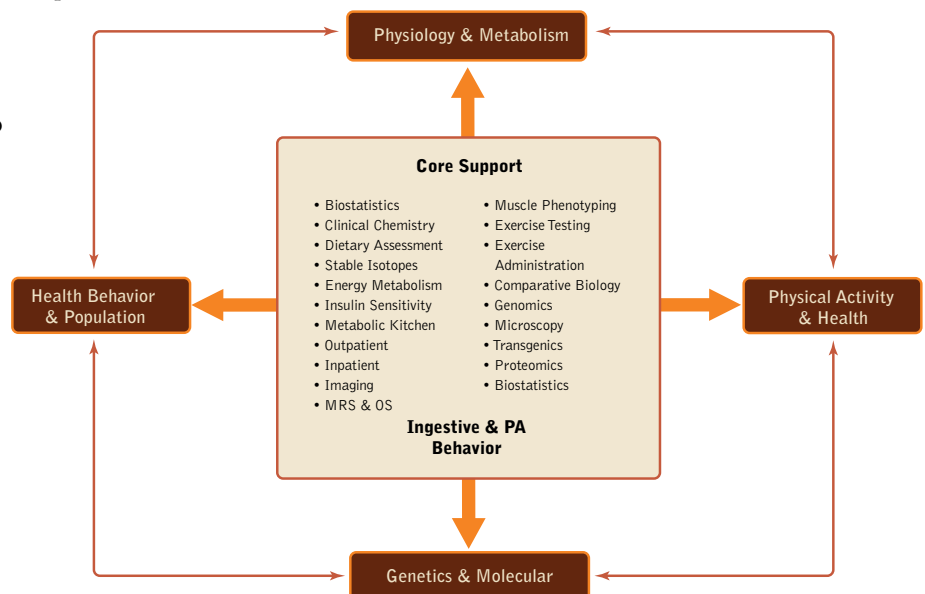
- Physiology and Metabolism
- Behavior and Population
- Physical Activity and Health
- Genetics and Molecular

Importantly and as shown in our organizational graph (LOCATION), the Division receives strong support from many of the core services available to all the Faculty and post-docs at the Pennington Biomedical Research Center. The following core services are particularly relevant to the research goals of our Division: biostatistics, clinical chemistry, dietary assessment, ingestive behavior and physical activity behavior, stable isotopes, energy metabolism, research kitchen, outpatient unit, inpatient unit, imaging, comparative biology, genomics, microscopy, transgenics and proteomics. Our division is furthermore holding weekly HaPE afternoon sessions which allows us to exchange ideas and develop projects in an innovative and creative environment.

Rich faculty interaction within the Division has produced numerous productive projects, including the development and funding of a grant to look at the safety and biology of long term caloric restriction in lean individuals. We are presently enrolling more than 80 healthy participants in a 2-year study on the effect of 25% caloric restriction on biomarkers of aging. A second example is our successful effort to secure a Clinical

Nutrition Research Unit (CNRU) from the National Institutes of Health - NIDDK. During the past two years, we have also encouraged the development of our junior faculty and post-doctoral fellows through pilot and feasibility grants as well as travel awards designed to support attendance at meetings focused on a theme of interest to the mission of the Division.

Some of the ongoing research includes the investigation of the inter-individual variability in the adaptation to a high fat diet at the whole body level (physiology) as well as at the cellular level (molecular). Similar studies of the biological response to eight-week overfeeding with diets of different compositions are ongoing. Our studies of calorie restriction in lean also involve an interdisciplinary approach among faculty from the division. Studies of the mechanisms of insulin resistance associated with obesity are investigating the interplay between the adipose tissue and the skeletal muscle both at the physiological and molecular level. Finally, intervention studies have been implemented in schools and in active duty and reserve soldiers to cause weight loss and prevent or delay the increasing prevalence of obesity.



Population Science



Peter T. Katzmarzyk, Ph.D.
Associate Executive Director
for Population Science

New Investments: Historically, the main strengths of the Center have been in the basic and clinical sciences. The population research being conducted was largely embedded under the umbrella of clinical science. One of the priorities in the Center's five-year strategic plan, *Vision 2010*, is to expand the population research area. To this end, in August, 2007 I assumed the role of Associate Executive Director for Population Science, with a mandate to build an internationally recognized research program in population health. This mandate has been supported by significant investments by the Center, including the recent addition of a \$5 million, 15,000 square foot population science wing to the Claude B. Pennington Jr. building, underwritten by the Pennington Biomedical Foundation, and a commitment of several new faculty positions over the next three years.


The Population Science Paradigm: By investing in population science, we are extending our sphere of influence. Population health research is concerned with studying health issues at the level of the population, rather than in a laboratory, with the over-arching mission of improving the health of the population. This mission is achieved through research, public education, advocacy, and the development of public health policies that reflect the scientific evidence. We aim to take what we learn in the basic and clinical sciences and determine the uptake and impact of this research on the health of the population. In turn, we hope that what we learn in our population studies will feed back into the work being done in the clinical and basic science areas at the Center. For example, population scientists often identify novel or new risk factors for disease prevention – this information can then be used in the clinic to inform treatment options for patients. In this era of “global health risk,” risk stratification is an important issue for the modern, educated consumer of health care. Work being done in population science also feeds back into basic science. Many basic scientists are currently working to uncover the biological mechanisms behind what has been observed in the population.

Scope: Population scientists use many tools and study

designs to answer important research questions about the health of the population. For example, faculty at the Center are involved in several prospective cohort studies, in which a large group of people are evaluated on putative risk factors of interest, and followed over time for the development of disease. There are also several publicly available national health surveys that are used to quantify inter-relationships among risk factors and to estimate the burden of disease in society. Population scientists at the Center are also involved in translational research, in which the basic clinical trial design is applied to community-based interventions in order to examine the real-world impact of prevention programs. These designs, and others, contribute to our understanding of how best to approach the prevention and treatment of disease.

There are currently four laboratories at the Center under the umbrella of population science: investigating health issues in the fields of nutrition, physical activity, chronic disease and clinical epidemiology. In addition, there are several faculty members across the Center that have a strong interest in population science, and who work at the interface of the clinical and population science areas. For example, the health psychology faculty members are currently conducting several school-based and community-based intervention studies that have a strong population health focus, which involve the translation of clinical findings to real-world settings.

The Future: The population science area of the Center has a bright future. Given concerns in North America over an aging population, coupled with a steeply rising prevalence of obesity and related metabolic disorders, state-of-the-art prevention strategies will form the cornerstone of public health in the future. The population scientists at the Pennington Biomedical Research Center will be uniquely positioned to contribute to the current and next generation of prevention programs being developed here, and will be a valuable link between the laboratory and the population.



**“The Division
intends to continue its
efforts to provide up-to-date
community education programs
... to reach a wider audience in
and around Louisiana.”**

Phillip Brantley, Ph.D.
Division Chief, Education

Division of Education



Phillip Brantley, Ph.D.
Division Chief, Education

Mission - to promote the reputation of excellence of our center as a world-renowned research institution and provide professional and community educational programs to enhance the Center's research capacity and increase knowledge of health and nutrition issues.

Status Report

The Division of Education focuses on the following areas: it serves as the Center's Office of Postdoctoral Studies, established to enhance our postdoctoral research experience; the Division's Scientific Symposia series attracts world-renowned scientists and allows for synthesizing knowledge in a selected area of research; and the professional and community education programs sponsored by the Division engage the public and the local medical community and provide educational outreach.

Institutional Postdoctoral Training Program

The Division coordinates many of the activities mandated by the center's Institutional Postdoctoral Training Grant from the National Institutes of Health entitled "Obesity: From Genes to Man." The program supported by this grant is designed to train postdoctoral fellows to become productive research scientists capable of establishing independent scientific careers in obesity research. In addition to research collaboration with faculty mentors, postdoctoral fellows attend graduate nutrition seminars, participate in workshops on grant proposal writing, enjoy presentations by Center faculty and visiting scientists, and participate in ethics seminars and data presentation sessions.

Scientific Symposia Series

Under the leadership of the Assistant Division Director, Anne Schulte, the Division continues to organize two to three scientific symposia each year on topics of interest to Center scientists. These two-day meetings allow top international scientists to visit Baton Rouge and the Center. As many as 30 visiting scientists join together with Center

scientists at each meeting to present data and develop conclusions and recommendations for future research in a targeted area. Meeting proceedings and conclusions are published on the Center's Web site and in scientific journals. Some of our recent symposia are described below.

The eighth in our series of scientific symposia was held April 30 – May 2, 2006. Given recent evidence that viral infections may play a role in some cases of obesity, Nikhil V. Dhurandhar, Ph.D. (Pennington Biomedical Research Center), together with Philippe E. Scherer, Ph.D. (Albert Einstein College of Medicine), and David B. Allison, Ph.D. (University of Alabama at Birmingham), co-chaired a symposium: "Infection, Inflammation and Obesity."

Potential medical uses for novel plant compounds were explored in a symposium "Botanicals and Cardiometabolic Risk," held October 29-31, 2006 and co-chaired by William Cefalu, M.D., and Michael Lefevre, Ph.D. (Pennington Biomedical Research Center), and Rod K. Dishman, Ph.D. (The University of Georgia).

Mechanisms leading to the development of neuropathy, nephropathy, and retinal disease was the focus of a symposium "Diabetes Complications," January 29-30, 2007, co-chaired by Irina Obrosova, Ph.D. and George Bray, M.D., (Pennington Biomedical Research Center) and George King, M.D. (Joslin Diabetes Center and Harvard Medical School).

"Epigenetics Mechanisms in Obesity: Research and Public Health Implications" updated current scientific knowledge on the role of environmental factors, with an emphasis on nutrition *in utero* and postnatal, and their impact on obesity and related chronic diseases such as type 2 diabetes and hypertension. This symposium was held May 20-23 and co-chaired by Kenneth Eilertsen, Ph.D. (Pennington Biomedical Research Center), David Barker, M.D., Ph.D. (Oregon Health and Science University), and Rob Waterland, Ph.D. (Baylor College of Medicine).

Finally, on December 2-5, 2007, a symposium entitled "Neuro-Immune Signaling and Inflammation" explored the basic cellular and molecular mechanisms of inflammatory

disorders, aging, obesity and cancer. Co-chairs for this event were Joost J. Oppenheim, M.D. (National Cancer Institute), Janko Nikolic-Zugic, Ph.D. (Oregon Health and Science University) and Vishwa Deep Dixit, Ph.D. (Pennington Biomedical Research Center).

Professional Enrichment/Community Education

To foster community education and increasing awareness of health concerns, the Division has sponsored public events, focusing on educational outreach. An example is the Annual Men's Health Conference, held each fall at the Center. We have partnered with Blue Cross Blue Shield of Louisiana to provide Louisiana citizens with a web-based health program entitled "The Louisiana 2 Step," designed to promote healthy eating and physical activity. Recently, under the coordination of Patti Smith, the Center has begun offering *Take 5 for Diabetessm*, a brief course in disease prevention and management for community adults. The course was developed by Center diabetes educators and registered as a brand by the Center.

LSU Agricultural Center

The Division continues to partner 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 information and advice to the people of Louisiana through parish extension agents. Dr. Heli Roy who holds joint appointments at the LSU Agriculture Center and Pennington Biomedical Research Center coordinates this effort. Much of the information collected now comprises the "Pennington Nutrition Series," a collection of health and nutrition materials that can be found on the LSU Agriculture Center and Pennington Biomedical Research Center Web sites.


Women's Nutrition Research Program

Dr. Catherine Champagne is the coordinator of the Women's Nutrition Research Program (WNP), an education and outreach program that specifically targets women's health issues. The WNP offers educational programs, including the annual Irene W. Pennington Wellness Day for Women to address women's unique health concerns. The Wellness Day for Women attracts more than 500 women, and consists of a full day of educational seminars on current issues, health-related exhibits, cooking demonstrations, and other feature presentations. The WNP also co-sponsors a spring fun walk and run along with Club South Runners designed to encourage physical activity in families.

Future Goals

We will expand the current institutional postdoctoral training grant and acquire another postdoctoral training grant in the area of botanicals research. We would like to increase the number of postdoctoral fellows at the Center from the current 40 to 75.

We will continue hold two to three scientific symposia per year. Finding a permanent endowment for our symposium series would help guarantee we could maintain this schedule. The Division intends to continue its efforts to provide up-to-date community education programs, directly with its participation in and sponsorship of health fairs and indirectly by expanding collaborations with other organizations to reach a wider audience in and around Louisiana.



“The long term goal is to translate these discoveries into treatments and products that will in due course lessen the burden of chronic disease and improve the quality of life in our state and nation.”

Thomas Gettys, Ph. D.,
Principal Investigator

Clinical Nutrition Research Unit



Eric Ravussin, Ph. D.,
Principal Investigator

In August 2005, the National Institutes of Health designated the Pennington Biomedical Research Center as a **Clinical Nutrition Research Unit (CNRU)**. This unit, led by Principal Investigator, Dr. Eric Ravussin assisted by Dr. Donna Ryan, facilitates and promotes collaborative and multi-disciplinary interactions in nutrition and obesity research. The goal is to foster new research ideas and enhance the translation of basic nutritional research findings into the clinical arena and ultimately into practical application. The research theme for the CNRU is **“Nutritional Programming: Environmental and Molecular Interactions,”** and focuses interdisciplinary efforts to investigate environmental and molecular interactions in early life that may produce, through epigenetic mechanisms, variable risk levels for obesity and metabolic diseases in adulthood. The CNRU supports enrichment activities, pilot and feasibility studies funding and three research cores. Drs. Steve Smith and Don Williamson lead the **Human Phenotyping Core**, which provides and implements advanced techniques for the measurements of body composition, insulin sensitivity, energy metabolism, in-situ biochemistry (MRS), and skeletal muscle and adipose metabolism, as well as for the management of physical activity and behavioral interventions. Drs. Les Kozak, Jeff Gimble and Tom Gettys lead the **Molecular Mechanisms Core**, which provides genomics with the associated bioinformatics support as well as cell culture and cell imaging technologies. Drs. Andrew Butler and Randy Mynatt lead the **Animal Models and Phenotyping Core**, which provides relevant animal models including conditional transgenic, targeted gene knockout mice and state-of-the-art phenotyping capability.

The *External Advisory Board* is now composed of Drs. Rudy Leibel (Chair), Bradford Lowell, Daniel Kelly and John Miles. This group advises us on issues related to the science and technologies of the CNRU. The External Advisory Board meet on a yearly basis and serves as reviewers for our CNRU sponsored Pilot and Feasibility studies.

One of the major missions of the CNRU is to promote



the emergence of new investigators in the field of nutrition related diseases. The CNRU has been successful in awarding P&F grants to four investigators on the first round (2005-2006), four in the second cycle (2006-2007) and four very recently for 2007-2008. The Administrative Core has overseen the fiscal and regulatory management of the grant. This Core has also taken the lead of generating a Pennington CNRU website (www.CNRU.pbrc.edu), listserv (now with 70 subscribers). Furthermore, the Administrative Core organized a two day CNRU retreat in September 2006 identifying several opportunities for research that capitalize on the CNRU cores. However, one of the highlights of the CNRU sponsored events was the organization of a symposium on *Epigenetic Mechanisms in Obesity: Research & Public Health Implications*, May 20 - 22, 2007. This symposium, chaired by David Barker, M.D., Ph.D., Robert Waterland, Ph.D., and Kenneth Eilertsen, Ph.D., was attended by many PBRC and Louisiana scientists.

The Human Phenotyping Core is divided into physiological measures including adipose and skeletal muscle tissues phenotyping, insulin sensitivity and carbohydrate metabolism, *in-situ* biochemistry including proton and phosphorus spectroscopy, energy expenditure and body composition. On the behavioral side, the Core

is providing services of assessment of exercise and physical activity as well as behavioral measures of food intake.

The Molecular Mechanisms Core is providing genomic services using existing technology, qRT-PCR, microarrays and DNA sequencing. The core has developed microarrays of GpC islands and is now providing support to measure gene methylation with the necessary bioinformatic tools. On the cell biology area, primary cell cultures, cell lines and cell repository, as well as cell sorting by FACs are provided under the guidance of Dr. Jeff Gimble. We now have cell bio-imaging under the leadership of Dr. Gettys.

The Animal Models and Phenotyping Core is providing two kinds of services: a) animal phenotyping including body composition, food intake, macronutrient selection, taste sensitivity, energy expenditure, physical activity, body temperature, blood pressure and behavioral testing; b) development of transgenic or knockout animal models, pronuclear injections, embryonic stem cells, cryopreservation and rederivation of animal lines.

The Clinical Nutrition Research Unit was created and is supported by NIH Center Grant 1P30 DK072476 entitled "Nutritional Programming: Environmental and Molecular Interactions" sponsored by NIDDK.

Center for Botanicals and Metabolic Syndrome



William Cefalu, M.D.,
Principal Investigator

The Botanical Research Center was funded in 2004 with a \$7.9 million grant obtained from the National Institutes of Health. The center is based at the Pennington Biomedical Research Center and is a collaborative effort between the Pennington Biomedical Research Center and the LSU Agriculture Center and Rutgers University. The theme of the Center is “Botanicals and Metabolic Syndrome.” In brief, “Metabolic Syndrome” describes the condition characterized by the presence of a cluster of traditional risk factors for cardiovascular disease (CVD) and diabetes, such as hypertension, dyslipidemia, glucose intolerance, obesity and insulin resistance, in addition to less traditional CVD risk factors such as inflammatory processes and abnormalities of the blood coagulation system. Although the etiology for metabolic syndrome is not specifically known, it is well established that obesity and insulin resistance are generally present. Metabolic syndrome contributes greatly to increased morbidity and mortality in humans on several levels. First, metabolic syndrome can be considered a “pre-diabetic” state as insulin resistance precedes the development of type 2 diabetes by many years. Secondly, metabolic syndrome contributes to increased morbidity and mortality in humans by its association with accelerated cardiovascular disease. As the prevalence is now reaching epidemic proportions worldwide, metabolic syndrome represents one of the most important public health problems facing our society today.

Center Mission and Goals

The scientific goal of the Botanical Research Center is the pursuit of 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 pathophysiologic feature of the metabolic syndrome. Our Botanical Research Center consists of three specific research projects, an Animal Research Core, a Botanical Core and an Administrative Core. Each of the research projects evaluates a specific botanical and assesses the effect on pathogenic mechanisms

leading to the development of insulin resistance. Specifically, the botanicals chosen for initial study are *Artemisia dracuncululus L.* (Russian Tarragon) for Project 1, *Shilianhua* (an herb from Southwest China) for Project 2 and *Grape Anthocyanins* for Project 3. These botanicals were selected based on significant preliminary data suggesting favorable effects on pathogenic mechanisms that lead to the development of insulin resistance. However, the center investigators have extended research into other botanicals, that in pilot studies, have shown effects to modulate insulin action.

The Botanical Research Center encompasses the disciplines of nutrition, plant chemistry/characterization, metabolism, physiology and endocrinology, molecular and cellular biology, and genetics and spans both basic and clinical sciences. Thus, our interdisciplinary approach allows for a comprehensive evaluation of botanicals on pathogenic processes by evaluating multiple cellular mechanisms of action.

In addition to the above, the botanical core has identified botanical leads that will be subjected to further studies through a high through-put screening system. Since these leads affect different mechanisms related to the development of insulin resistance and metabolic syndrome, they are very much central to the theme of our Center. Specifically, we have initiated a program for high-throughput screening for promising botanical compounds. In this regard, we have received funding for the *John S. McIlhenny Laboratory of Botanical Research* to initiate this effort. The focus of this effort is to provide pre-clinical screening for promising extracts from plants that may have a role in treating obesity and adult-onset diabetes. The laboratory utilizes tissue culture systems and integrates wide-ranging, state-of-the-art, multiple-target screening with powerful structural and analytical approaches designed to characterize and develop therapeutic and natural agents produced by plants and fungi. This laboratory serves to provide data on each botanical agent so that seed funding can be obtained to fund additional clinical research on these particular

botanicals in the future.

One of the major objectives of our center is to expand the number of investigators pursuing metabolic and botanical research. In this regard, we have a very active pilot grant award program as part of the Botanical Research Center that not only funds promising junior investigators, but has successfully integrated senior faculty whose interest have turned to the study of botanicals and metabolism. The long range goal of this program is to increase the number of successful grant applications submitted by the faculty for which the research award was given.

It is expected that during the initial five years, the Botanical Research Center will promote a collaborative and interactive research environment to establish an internationally recognized center of excellence in the area of botanicals and mechanisms of metabolic disease; to identify and further study botanicals with potential efficacy in metabolic syndrome to identify their bioactive constituents, standardize and optimize those botanicals, provide necessary preclinical and mechanisms of action data, and translate the foregoing findings into clinical studies in humans; and to

expand the critical mass of investigators addressing botanical research by identifying, recruiting and mentoring promising young investigators at the Pennington Biomedical Research Center.

The Botanical Research Center is uniquely equipped to address multiple components of the research process. In this collaboration, the Pennington Biomedical Research Center's contribution is in the clinical, cellular and physiologic evaluation of botanical effects on the components of the metabolic syndrome; The Rutgers University contribution is in the discovery of promising botanical agents and the identification of the active components in those botanicals. Thus, by combining the unique strengths and the unquestioned commitment by our participating institutions, the Botanical Research Center is ideally qualified to make significant discoveries in the botanical research arena.

The Botanical Research Center was created and is supported by Grant #P50AT002776-01 entitled "Botanicals and Metabolic Syndrome" from the National Institutes of Health.

COBRE—Center of Biomedical Research Excellence



Thomas Gettys, Ph. D.,
Principal Investigator


The Center of Biomedical Research Excellence at PBRC is leading an effort to enhance research in Louisiana on obesity and adult-onset diabetes by recruiting, mentoring, and retaining promising young scientists. Our COBRE is devoted to advancing understanding of the cell biology of obesity and diabetes. As such it is focused on discovering fundamental cellular mechanisms that become dysregulated during the development of these diseases. Obesity and diabetes affect a large segment of the national population but Louisiana is disproportionately affected because of higher incidences of both maladies in our state. The impact of these diseases on our economy and quality of life is enormous. Thus the impetus to translate fundamental knowledge into effective treatment strategies, new drugs, and products is both strong and timely.

The NIH recently developed a comprehensive long term plan for enhancing the translation of medical discoveries into improvements in people's health. The NIH Roadmap outlines several strategies for accomplishing this goal, including an emphasis on mentoring and developing our young scientists to power the discovery process. We need to

build our collective understanding of the precise molecular events that lead to disease states, and develop a better understanding of the networks of molecules that function in an integrated manner in our cells and tissues.

We also need to enhance multidisciplinary approaches involving research teams with complementary expertise to better tackle the complexity of the questions being asked and the problems being addressed. In a nutshell, that is precisely how our COBRE is structured, with a complementary emphasis on enhancing the research infrastructure while simultaneously training our young scientists to make fundamental discoveries of the underlying mechanisms of obesity and diabetes. The long term goal is to translate these discoveries into treatments and products that will in due course lessen the burden of chronic disease and improve the quality of life in our state and nation.

The Center of Biomedical Research Excellence was created and is supported by NIH Grant P20 RR-021945 from the National Center for Research Resources.



“2008 will bring our Center to a true milestone: two decades of ‘improving the health of future generations’ through research on nutrition and preventive medicine.”

Dr. Claude Bouchard
Executive Director,
Pennington Biomedical
Research Center

Basic Research Laboratory Reports

Basic Research at the Center is organized within eight areas, each of which has multiple investigators and laboratories.

Cancer Laboratory

DNA Damage and Repair

W. Deutsch, V. Hedge

The William Hansel Cancer Prevention Laboratory

W. Hansel, C. Leuschner, S. Aggarwal

Diabetes

Antioxidant and Gene Regulation

J. Ye, Z. Gao

John S. McIlhenny Botanical Research Laboratory

W. Cefalu, Z. Wang

Mechanisms of Diabetes Complications

I. Obrosova

Experimental Obesity

Gene-Nutrient Interactions

R. Mynatt

Dietary Obesity

G. Bray, D. Braymer, M. Barnes, S. Primeaux

Functional Genomics

A. Zuberi

Infection and Obesity

N. Dhurandhar

Neuroendocrine Immunology

V. Dixit

Human Genomics

Energy Balance

G. Argyropoulos

Human Genomics

C. Bouchard, T. Rankinen, M. Teran-Garcia

Molecular Genetics

Molecular Genetics and Thermogenesis

L. Kozak, R. Koza

Neuropeptides

A. Butler, G. Sutton

Regulation of Gene Expression

M. Saulbaum

Taste Genetics

B. Richards

Neuroscience

Autonomic Neuroscience

R. Rogers, G. Hermann

Blood Brain Barrier Laboratory I

W. Pan

Blood Brain Barrier Laboratory II

A. Kastin, H. Tu

Neurobehavior

R. Martin, J. Zhou

Neurobiology and Nutrition Laboratory-1

H. Berthoud, H. Zheng

Neurobiology and Nutrition Laboratory-2

A. Travagli, K. Browning, Z. Zheng

Neurosignaling Laboratory

C. Morrison

Neurotrauma and Nutrition

G. Holmes

Nutritional Neuroscience and Aging

D. Ingram, T. Utsuki, P. Pistell

Nutrient Sensing

Adipocyte Signaling

T. Gettys

Endocrinology

S. Smith

John S. McIlhenny Skeletal Muscle Physiology Laboratory

A. Civitarese, E. Ravussin

Nuclear Receptor Biology

T. Burris

Protein Structural Biology

I. Kheterpal

Stem Cell Biology

Maternal Biology

C. Kappen, C. Kruger

Epigenetics and Nuclear Reprogramming

K. Eilertsen

Regenerative Biology

B. Kozak

Stem Cell Biology

J. Gimble

Ubiquitin Biology

B. Floyd

DNA Damage and Repair Laboratory



Walter A. Deutsch, Ph.D.,
Professor



Vijay Hegde, Ph.D.,
Instructor

FACULTY:

Walter A. Deutsch, Ph.D.

Vijay Hegde, Ph.D.

RESEARCH TEAM:

Sridevi Yadavilli, Ph.D.

Focus — to understand the relationship between DNA damage and the onset of cancer.

Human S3 was originally identified as a component of the small subunit of the ribosome that resides in the cytoplasm. Using a variety of experimental and computational approaches, we have determined and characterized roles above and beyond protein synthesis and posit that hS3 possesses extra-ribosomal activities that influence DNA repair, and perhaps cellular stress response pathways such as apoptosis. We have shown, using surface plasmon resonance (SPR) analysis, that the *in vitro* binding affinity of hS3 for the mutagenic DNA lesion 8-oxoG exceeds that of any other known DNA binding protein and hypothesized that this high affinity binding could create an obstacle to the efficient repair of an 8-oxoG DNA lesion.

The involvement of hS3 in Base Excision Repair (BER) would seem to be improbable considering that it is associated with the ribosome and appears to be directly involved in mRNA-aminoacyl tRNA interactions during protein synthesis. Therefore, for hS3 to act in BER and also be involved in protein synthesis would require its displacement from cytoplasmic ribosomes, and its subsequent translocation to the nucleus where it could be poised to interact with DNA. We have shown that roughly 40% of cytoplasmic hS3 is indeed translocated to the nucleus under oxidative stress that involves the activation of ERK1/2, which in turn phosphorylates hS3 as part of the translocation process.

We have further traced the DNA damage-induced nuclear translocation of hS3 to the subcellular matrix. Significantly, immunofluorescent microscopy revealed hS3 could be further localized to nuclear 8-oxoG foci. Overall, our results raise the possibility that hS3 influences/moderates the repair of the highly mutagenic lesion 8-oxoG. This is most likely caused by hS3 creating a blockade to enzymes normally involved in 8-oxoG repair, which clearly could have important biological consequences. In agreement with this hypothesis is the finding that knockdowns of hS3 expression in cells harboring siRNAs specific for hS3 are much

more resistant to challenges with a variety of mutagens, suggesting that nuclear hS3 expression can have deleterious consequences on cell survival.

Several sites that could be involved in the high affinity of hS3 for 8-oxoG have been identified using a combination of a hidden markov modeling system and known databases for non-synonymous, coding single nucleotide polymorphisms (cSNPs). Based upon this technology, one SNP mutant produced in our laboratory completely abrogated hS3 binding to 8-oxoG.

We also have compelling evidence that hS3 is involved in apoptosis. Experiments are underway using a tandem affinity peptide (TAP) vector to learn whether the hS3 protein interactions so far identified with proteins involved in apoptosis can be trapped *in vivo*.

Presently, we hypothesize that hS3 acts to moderate the repair of 8-oxoG and acts as a sentinel to set apoptosis in motion under cellular conditions of oxidative stress. Thus, hS3 may play a vital role in tumorigenesis as well as aging. We are presently testing this possibility in transgenic mice that harbor hS3 and variants.

Research in this laboratory is supported by grants from the National Institutes of Health [NCI109798], a NCI Supplement, and the Division of Nutrition and Chronic Diseases.

The William Hansel Cancer Prevention Laboratory



William Hansel, Ph.D.
Professor



Carola Leuschner, Ph.D.,
Assistant Professor



Sita Aggarwal, Ph.D.,
Instructor

FACULTY:

William Hansel, Ph.D., Carola Leuschner, Ph.D., Sita Aggarwal, Ph.D.

RESEARCH TEAM:

Fred Enright, Ph.D. (Adjunct), Janice Keener,
Martha Juban, B.S., M.S.

Focus — The goal of this lab is to develop treatments that will prevent recurrent cancer after surgery or treatment, and improve the quality and longevity of cancer patients.

Drs. Hansel and Leuschner in cooperation with Dr. Fred Enright, Chairman of the Veterinary Science Dept. at LSU, have developed a number of compounds consisting of lytic peptide-gonadotropin conjugates that effectively target and destroy human breast, prostate, ovarian, and testicular cancer xenografts and their metastases. During the past year, new compounds have been developed and Esperance Pharmaceuticals, Inc. has acquired the rights to market these compounds. As part of the research agreement, with Dr. Leuschner as PI, Esperance was given access to our laboratory space. Meanwhile, the laboratory was designated the William Hansel Cancer Prevention Laboratory; start-up funds were raised, and Dr. Aggarwal from the M.D. Anderson Cancer Center joined the lab.

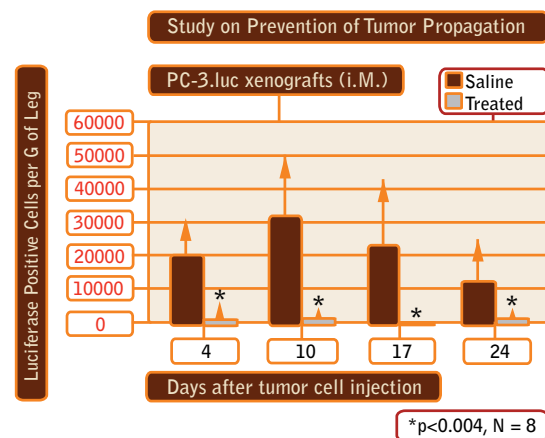
This laboratory tests, *in vivo*, drugs, plant extracts or dietary supplements previously shown to kill cancer cells at low concentrations *in vitro*. Drugs are evaluated by:

- Screening compounds, particularly compounds provided by the Botanical Research Center, for anti-cancer activity, *in vivo*, using a rapid assay system described below.
- Testing compounds that are effective in the screening test for their ability to regress tumors and reduce metastatic cell numbers in the nude mouse model we have developed in previous experiments.
- Further testing compounds that effectively target and destroy primary tumors and metastatic cells in the nude mouse model to determine their efficacy in preventing cachexia and prolonging life after surgical removal of tumors before initiation of treatment

Current Projects

To develop a rapid method of screening a large number of compounds or extracts for anti-cancer activity, we injected

human prostate cancer cells transfected with luciferase (PC-3 luc) intramuscularly into the hind legs of nude mice, which were then treated intravenously for 3 days with saline or Phor21- β CG(ala) and sacrificed on the 4th day. Luciferase positive cells were then measured in homogenates of entire hind legs. Results (below) showed that daily injections of Phor21- β CG(ala) for only 3 days caused highly significant reductions of luciferase positive cells, even when injections were initiated on the first day after inoculation of the mice with the PC-3 luc cells. These results suggest this technique can be developed into a rapid, inexpensive method for *in vivo* screening of substances for anti-cancer activity.



Compounds showing activity in this screening test are further tested with the nude mouse model, developed in our studies with lytic peptide conjugates. A current experiment, in which the effects of curcumin (from tumeric) alone and conjugated with LHRH (GnRH) and LHRH-Phor21, on tumor weights, numbers of metastatic cells in various organs and a number of other parameters in nude mice bearing human pancreatic cancer cell xenografts, is illustrative of the experiments we plan to carry out with compounds that having anti-cancer activities in *in vitro* experiments.

Start-up funds are provided or pledged by private donors and The Pennington Biomedical Research Foundation. Proposals have been submitted to Esperance Pharmaceuticals, Inc.

Antioxidant and Gene Regulation Laboratory



Jianping Ye, M.D.,
Professor



Zhangou Gao, Ph.D.,
Instructor

FACULTY:

Jianping Ye, M.D., Zhangou Gao, Ph.D.

RESEARCH TEAM:

Jun Yin, M.D., Ph.D., Jin Zhang, Ph.D., Can Pang, M.D., Hanjie Zhang, M.S., Tianyi Tang, M.D., and Yanning Wang, M.D.

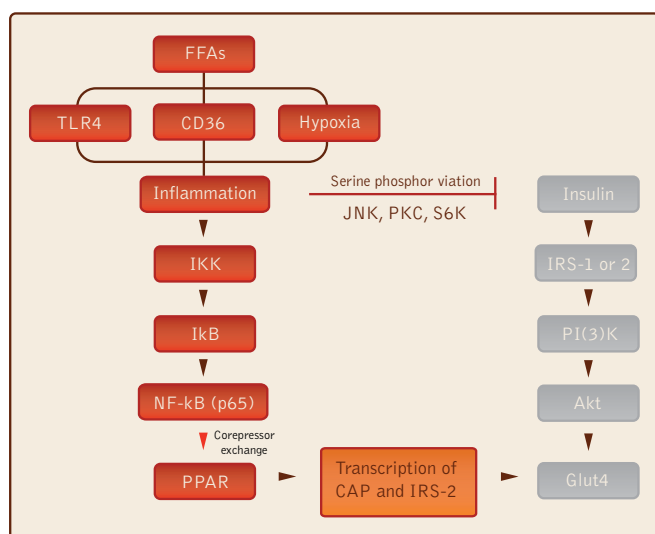
Focus — Insulin resistance links obesity to many diseases including type 2 diabetes, hypertension, and arteriosclerosis. Our research is designed to understand cellular and molecular mechanisms of insulin resistance. We try to address two questions: (1) how insulin signaling pathway is inhibited by inflammation in obese condition; (2) why inflammation occurs in the adipose tissue in obesity.

Our study suggests that in obesity, fatty acids may induce inflammation response in macrophages and adipocytes through activation of cell surface receptors, such as Toll-like receptor 4 (TLR4) (1) and CD36. They may also induce inflammation through a hypoxia response in adipose tissue (2). The inflammation signals lead to inhibition of insulin receptor substrates (IRSs). Two approaches are identified for the suppression of IRSs function by inflammation. The first is serine phosphorylation of IRS-1 by multiple serine kinases such as IKK, JNK, S6K, and PKCs (3-5). The second is inhibition of IRS-2 expression by NF- κ B mediated activation of nuclear corepressor that inhibits PPAR γ function (6). Additionally, inhibition of PPAR γ function by IKK/NF- κ B pathway contributes to insulin resistance directly. These mechanisms are illustrated in the Figure. In

mechanic study, we are also investigating action mechanism of functional foods in the regulation of metabolism of glucose or fatty acids.

In the study, transgenic mice with over-expression and knockout of NF- κ B are used to understand metabolic activities of inflammation. In the phenotype analysis, insulin sensitivity and energy metabolism are examined with clamp and metabolic chamber. The mechanism analysis are conducted with many standard strategies or methods, such as Western blot, immunoprecipitation, immunohistostaining, gel shift assay, chromatin immunoprecipitation assay, reporter assay, transient and permanent transfection, construction of plasmid DNA, adipogenesis, myogenesis, gene-knockdown, retrovirus (Lentivirus) and adenovirus. Many cell lines including 3T3-L1, C2C12, L6, HepG2, HII4E, RAW, 293, MEFs and primary cells (macrophage, adipocytes, muscle cells) are used.

Research in this laboratory is supported by the National Institutes of Health (RO1 grants) and the American Diabetes Association.



John S. McIlhenny Botanical Research Laboratory



William T. Cefalu, M.D.
Douglas L. Manship
Professorship in Diabetes



Zhong Wang, M.D.
Instructor

FACULTY:

William T. Cefalu, M.D., Zhong Wang, M.D.

RESEARCH TEAM:

Leslie Son, Ph.D., April Stull, Ph.D., Yongmei Yu, Ph.D., Ann Coulter, Ph.D., Jianhua Qin, M.Ap. Stat., Xian Zhang, B.S., Xin Ye, B.S., Justin Bordelon, Ilya Raskin, Ph.D., (Adjunct), David Ribnicky, Ph.D., (Adjunct)

Focus - The primary mission of our laboratory is to study the cellular mechanisms contributing to the development of insulin resistance in humans. In addition, our goal is to evaluate the clinical response and mechanism of action by which clinical interventions, i.e. nutritional and/or botanical, modulate insulin resistance.

Current Projects

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 represent a very attractive approach to the treatment of type 2 diabetes.

Our lab has been evaluating dietary supplementation with chromium. We have demonstrated that higher levels of chromium in animal diets may modulate intracellular pathways of glucose metabolism and improve comorbidities associated with insulin resistance. However, chromium benefits appear to be limited by phenotype. Results show that chromium supplementation in lean, insulin sensitive animals does not lead to increased insulin sensitivity, yet obese animals with insulin resistance respond well. This clinical effect correlates to specific biochemical signals in the tissues and together suggests a specific phenotype, i.e. obesity, may be responsible for an abnormality in the intra-cellular insulin signaling cascade that appears to be overcome with chromium supplementation.

We are also undertaking clinical trials to investigate the mechanism by which insulin resistance and/or obesity modulates chromium metabolism and/or excretion. Our hypothesis is that, in subjects with type 2 diabetes, Cr supplementation will improve whole-body insulin-mediated glucose disposal (e.g. insulin sensitivity) by enhancing cellular signaling through the insulin receptor.

Evidence obtained in subjects with type 2 diabetes and on sulfonylureas for control of blood glucose suggest that chromium supplementation may improve insulin resistance,

decrease glucose levels and attenuate weight gain noted from traditional therapies. In particular, we had noted that individuals with type 2 diabetes with poorer glucose control whose diets were supplemented with higher doses of chromium had less weight gain, less increase in percent body fat, and less accumulation of visceral fat in the abdominal area. If confirmed, our data would suggest that chromium may alter some aspect of the energy balance equation for either dietary intake or caloric expenditure.

Our laboratory, as part of PBRC's NIH funded Botanical Research Center, is also active in the investigation of botanical supplements on insulin resistance and other aspects of metabolic syndrome. We have provided several lines of evidence in both *in vitro* and *in vivo* models to suggest that botanicals may modulate intracellular pathways of glucose metabolism. Specifically, we provide evidence that an alcoholic extract of Russian Tarragon (*Artemisia dracuncululus* L) referred to as PMI-5011, may increase insulin action *in vivo* and have identified several novel intracellular pathways that may explain the effect. The overall objective of this project is to examine the role of a specific botanical, PMI-5011, on insulin action *in vivo* and to elucidate potential cellular mechanism(s) of action. To accomplish our goal, we are conducting both *in vitro* and *in vivo* experiments with PMI-5011 and its bioactive components that are designed to assess insulin sensitivity and pathways of glucose metabolism with whole-body, cellular, and molecular approaches. We hypothesize that in both animal models and in subjects with the metabolic syndrome, dietary supplementation with PMI-5011 will improve whole-body insulin-mediated glucose uptake (i.e. insulin sensitivity) by increasing non-oxidative glucose disposal. This increase in whole body glucose disposal will be due to enhanced cellular signaling through the insulin receptor and modulation of genes regulating glucose and lipid metabolism in skeletal muscle.

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

Mechanisms of Diabetes Complications Laboratory



Irina G. Obrosova, Ph.D.
Associate Professor

FACULTY:

Irina G. Obrosova, Ph.D.

RESEARCH TEAM:

Viktor R. Drel, Ph.D.

Sun-Ok Fernandez-Kim, M.S.

Focus – to understand the pathogenesis of diabetes complications, especially neuropathy.

Current Projects

Oxidative-nitrosative stress and its downstream effectors play a role in the pathogenesis of diabetes complications, primarily diabetic neuropathy. Our new data revealed the important role for peroxynitrite in peripheral nerve dysfunction and degeneration in animal models of type 1 and type 2 diabetes.

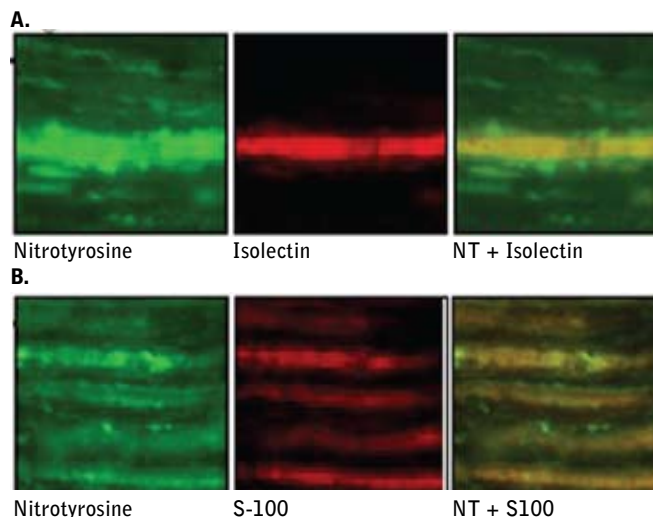
We have shown that peroxynitrite-induced injury manifested by nitrotyrosine accumulation is present in the peripheral nervous system of streptozotocin-diabetic rats and mice (models of type 1 diabetes), leptin-deficient *ob/ob* mice (a model of type 2 diabetes) as well as high-fat diet fed mice (a model of prediabetes and alimentary obesity).

Double immunostaining for nitrotyrosine and specific cell markers has shown that diabetes-associated peroxynitrite injury affects all cell types in PNS. The latter is not surprising because, in contrast to short-lived free radicals, the potent oxidant peroxynitrite is relatively stable and can cross cytoplasmic membrane and move from one cell type to another. Note, that oxidant potency of peroxynitrite is ~2000-fold greater than of hydroxygen peroxide, and even modest overproduction of peroxynitrite is associated with clearly manifest protein nitration and nitrosylation and other changes in metabolic and signal transduction pathways.

Using isolectin, a marker of endothelial cells, and S-100, a marker of Schwann cells, we localized nitrosative stress in the two cell types of diabetic peripheral nerve (rats with 12-week duration of STZ-diabetes, see figure).

Green nitrotyrosine fluorescence is clearly manifest in DRG neurons of STZ-diabetic rats. Using glutamine synthetase as a marker, we have shown that nitrotyrosine is also localized in satellite cells.

We have also shown that under diabetic conditions, peroxynitrite affects neurons, oligodendrocytes, and astrocytes of the spinal cord.



Immunofluorescent staining of diabetic rat sciatic nerve for nitrotyrosine (top left); isolectin (top center), nitrotyrosine and isolectin (top right) (A), and nitrotyrosine (bottom left); S-100 (bottom center), nitrotyrosine and S-100 (bottom right) (B). Magnification x 125.

Using a pharmacological approach with new class of compounds, peroxynitrite decomposition catalysts, as well as inducible nitric oxide synthase-deficient mice, we have demonstrated a major contribution of peroxynitrite to motor and sensory nerve conduction deficits, sensory disorders such as thermal and mechanical hypoalgesia and tactile allodynia, and small sensory nerve fiber degeneration in animal models of type 1 and type 2 diabetes.

Our work on peroxynitrite resulted in six publications including two papers in *Diabetes*, one in *Exp. Neurology*, one in *Eur J Pharmacol*, one in *Int J Mol Med*, and one in *Am J Physiol End Metab*.

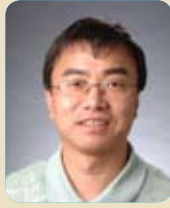
My laboratory is also evaluating: 1) role for PARP in diabetic neuropathic pain; 2) role for PARP in diabetic nephropathy; and 3) role for 12/15-lipoxygenase in diabetic neuropathy.

Research in this laboratory is supported by grants from the Juvenile Diabetes Research Foundation, American Diabetes Association, and National Institutes of Health.

Gene-Nutrient Interactions Laboratory



Randall Mynatt, Ph.D.
Associate Professor



Jingying Zhang, Ph.D.
Instructor

FACULTY:

Randall Mynatt, Ph.D., Jingying Zhang, Ph.D.

RESEARCH TEAM:

Steven Bond, B.S., James E. Baugh, B.S., Dieyun Ding, B.S., Annelie Crook, B.S., Amy Guidry

Focus — Our Lab utilizes an integrative approach combining genetic engineering techniques in mice, clinical studies, cellular physiology and nutrition in the study of obesity and T2D.

Current Projects

It is well established that T2D is a progressive disease and the hallmark of pre-diabetes 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 the lipid accumulation in skeletal muscle and liver represent 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-CoA's (LC-CoA) and acetyl-CoA, which are potent inhibitors of glucose utilization. Our pre-clinical studies suggest robust effects of carnitine supplementation on parameters contributing to insulin action. Carnitine supplementation completely restores insulin sensitivity in genetically obese/diabetic mice and prevents the development of insulin resistance in mice fed a high fat diet. Indirect calorimetry was used in mice to determine the effects of carnitine supplementation on substrate utilization and energy expenditure. Basal and insulin-stimulated carbohydrate oxidation was higher in the carnitine-supplemented group.

These initial “proof-of-concept” experiments clearly demonstrate that dietary carnitine is very effective in improving insulin-stimulated glucose utilization in mice and reversing abnormalities of fuel metabolism. If these findings can be shown to be operative in human subjects, this would offer a very effective adjunctive therapy for T2D. Plans are to submit both a clinical and basic mechanistic grants in February.

Our other area of research interest is the *agouti* gene. It is well recognized that the agouti/melanocortin system is a critical component of body weight homeostasis. The focus

of ongoing studies in my laboratory is to understand the function of agouti/melanocortin signaling in adipose tissue and evaluate its contribution to obesity and diabetes. The primary reason for this focus is that agouti and melanocortin receptors are present and regulated in human adipose tissue. Through work in my lab and some excellent collaboration with Steven Smith and Jackie Stephens have been able to demonstrate that agouti/melanocortin signaling is a key regulator of adipogenesis. Perhaps the most clinically relevant findings are the data examining agouti expression in human adipose tissue. Since transgenic mice that express agouti in adipose tissue become obese, agouti mRNA was quantitated in the subcutaneous fat from humans with a broad range of BMI. There was no correlation between agouti expression levels and BMI, but there were significantly higher levels of agouti expression in the diabetic subjects compared to non-diabetic individuals.

We were also able to show that glucorticoids are potent activators of agouti gene expression. We are continuing to investigate the cell type responsible for agouti expression in adipose tissue and to determine the signaling pathways activated by agouti.

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

Dietary Obesity Laboratory



George A. Bray
Boyd Professor



H. Douglas Braymer, Ph.D.
Professor



Maria Barnes, Ph.D.
Instructor



Stefany Primeaux, Ph.D.
Instructor

FACULTY:

George Bray, M.D., H. Douglas Braymer, Ph.D.,
Maria Barnes, Ph.D., Stefany Primeaux, Ph.D.

RESEARCH TEAM:

Christine Blackmon

Focus – to investigate the differences in response to a high fat diet between animals that become obese eating this diet and those that do not.

During the decade of this MERIT Award, we have noted considerable differences between the SENSITIVE - OM rat and the RESISTANT S5B rat as models of response to high fat diets.

We set out to determine if the serotonergic system mediating fat preference involves pathways from the dorsal raphe nucleus to the PVN and a descending pathway from the PVN to the NTS. Since, we have shown that injections of serotonin directly into the PVN reduce food intake, primarily as fat. Blocking serotonin release in the PVN by activating a receptor in the dorsal raphe increases food intake. In parallel studies we showed that galanin, an alternative pathway that may be involved in regulation of fat intake, was not the controller of the differences between the two strains. Using drugs that activate the serotonin 2C receptor, we demonstrated that food intake was suppressed more in animals that become obese while eating a high fat diet.

Opioid receptors provide one mechanism by which the hypothalamic neuronal system might communicate with the hedonic components of food intake and the hind-brain controls. We have demonstrated the density and mRNA expression of mu opioid receptors are significantly increased in the hypothalamus of Osborne-Mendel rat when compared to the S5B/PI rats. We believe the change in the expression of this receptor system could be contributing to these animals' (Osborne-Mendel) susceptibility to diet-induced obesity by making them hyperphagic and increasing their preference for a high fat diet.

Location of the neurons that express mu opioid receptors in the hypothalamus and hindbrain of Osborne Mendel and S5B/PI rats when they are eating a high fat diet.

When animals have ad libitum access to a high fat diet for six weeks, the gene expression (mRNA) of mu opioid receptors is significantly increased compared to animals with access to a low fat diet. Activation of mu opioid receptors increases total food intake and increases preference for a high fat diet. That this receptor population is increased in leptin resistant animals suggests they could be involved in hyperphagia observed in these animals. We used Immunohistochemical techniques to locate mu opioid receptors in relationship to neurons that contain orexigenic peptides. With confocal microscopy we demonstrated that mu opioid receptors are on NPY/AgRP neurons in the arcuate nucleus.

The location of the mu-opioid receptors on neurons in the arcuate nucleus includes the neurons that jointly express NPY and AgRP. Since the mu-opioid receptor is generally an inhibitory receptor, this may mean that it increases preference for a high fat diet by serving as an inhibitor of an inhibitory system. We are using immunohistochemical and in situ hybridization techniques to determine if mu opioid receptors are co-localized on neurons that contain GABA. If so, we will try to determine the effect of blocking/activating GABA receptors on mu opioid receptors' ability to increase food intake and fat preference.

We also hypothesize the increased response of S5B (RESISTANT) rats to fats in the GI tract compared to OM (SENSITIVE) rats is mediated through a vagal afferent system which utilizes peripheral CCK, glutamate in the NTS and serotonin in the PVN.

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

Functional Genomics Laboratory



Aamir R. Zuberi, Ph.D.,
Assistant Professor

FACULTY:

Aamir R. Zuberi, Ph.D.

RESEARCH TEAM:

Yongjun Wang, Ph.D., Bhavani Krishnan, M.S., Jacalyn MacGowan,
Kylie Durand, Rachel Cooley and Carmel Fargason

Focus – to identify polymorphic genes that regulate resistance to dietary induced obesity and to investigate whether botanical extracts can modify the overall susceptibility to Obesity and type 2 diabetes.

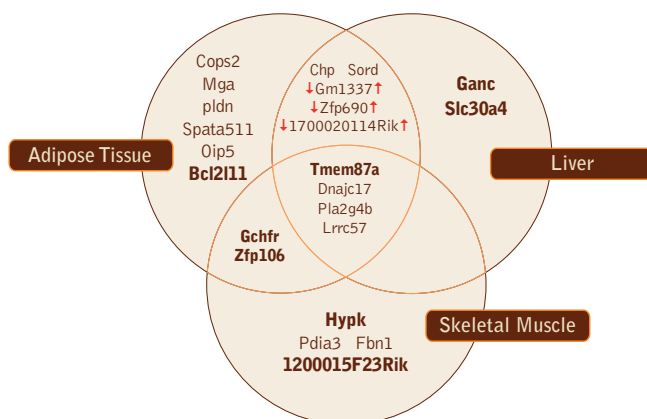
Current Projects

We are investigating 1), the characterization of a small 8.6 Mbp region of mouse Chromosome 2 that contains one or more genes important for the development of dietary obesity, and 2) the physiological effects of botanical extracts on the development and regulation of obesity, insulin resistance and type 2 diabetes.

We have determined that an important dietary obesity gene lies in a small region of 158 genes. 34 of these genes are regulated differently when we compare an obesity susceptible and an obesity resistant mouse strain that only differ in the genetic origin of this region. Interestingly, 23 of these genes differ in expression even before exposure of the two mouse strains to a high fat diet. Some of these gene expression differences occur in skeletal muscle, adipose tissue and liver, whereas others only differ in expression in a more limited number of tissues (below).

Phenotyping of several derived mouse sublines reveal that more than one gene is regulating the susceptibility to dietary obesity in this region. We are focusing on one region that contains only 13 known genes. The only gene mapping to this region that differs in expression between the obesity susceptible and resistant mouse strains encodes Fibrillin 1, a protein that is an important component of the extracellular matrix that provides a structural framework for many organs and regulates tissue elasticity. The expression difference for *Fbn1* is only seen in skeletal muscle tissue and not in adipose tissue. Whereas the *Fbn1* gene has been causally linked to a human disease called Marfan syndrome, Fibrillin 1 expression in skeletal muscle may also play a role in the regulation of fat accumulation and obesity.

Our second research focus is to evaluate the role of botanical extracts in regulating Metabolic Syndrome. This research is in collaboration with several faculty associated with the Botanical Center located at Pennington, the LSU Ag Center and Rutgers University. Our results reveal that not all health claims made by botanical extract distributors can be supported in independent studies. However, we have confirmed a strong insulin sensitizing effect of extracts of Russian tarragon in mouse strains that may be useful in the control of type 2 diabetes. We are currently examining the genetic and molecular basis for this difference and evaluating this finding with respect to the effectiveness of this extract in clinical studies.



Venn Diagram of 23 genes mapping to the 9.6 Mb dietary obesity region of mouse Chromosome 2 that differ in expression in one of three tissues (adipose tissue, skeletal muscle and liver) in mice that have not been exposed to a high fat diet. Genes are positioned so as to indicate the tissue of origin of the expression difference(s). Bold font indicates that the gene has higher expression in the dietary obesity resistant mouse strain. A Normal font indicates that expression is greater in the obesity susceptible strain. Arrows adjacent to three of the genes identify genes that differ in expression profile in adipose tissue (left) and liver (right). Up arrow indicates higher expression in the dietary obesity resistant strain. Down arrow indicates lower expression in the same strain.

Research in this laboratory is supported by grants from the NIDDK and NCCAM institutes of the National Institutes of Health

Infection and Obesity Laboratory



Nikhil V. Dhurandhar, Ph.D.
Associate Professor

FACULTY:

Nikhil V. Dhurandhar, Ph.D. (PI) and Ronald Luftig, Ph.D. (adjunct)

RESEARCH TEAM:

Olga Dubuisson, Ph.D., Scott Loiler, Ph.D., Magdalena Pasarica, M.D., Ph.D., Miloni Rathod, Ph.D., Nazar Mashtalir, M.S., Emily J. McAllister, B.S., Robert Oubre, Pamela Rogers, M.S.

Focus – to understand the role of infections as a cause of obesity.

In the last two decades, 10 obesity-promoting pathogens have been reported, including our reports of the first human virus, adenovirus type 36 (Ad-36). We showed that Ad-36 causes obesity in experimentally infected chickens, mice, rats and non-human primates and reduces serum cholesterol and triglycerides. In humans, natural Ad-36 infection is associated with obesity and relative hypolipidemia.

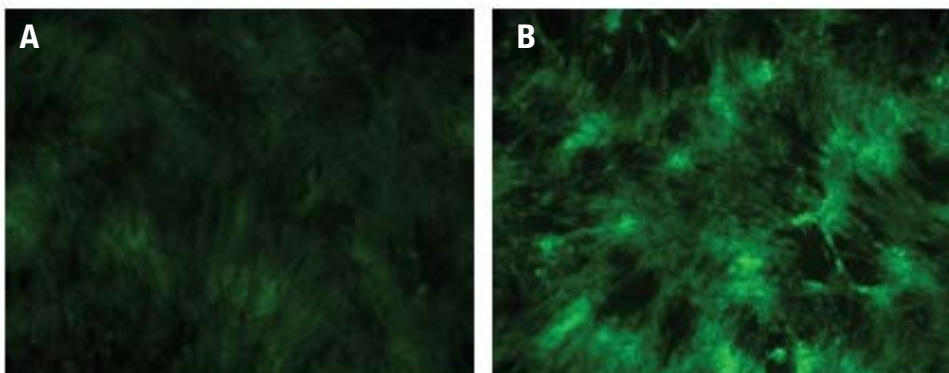
As a requisite to determining the role of Ad-36 in human obesity, our current focus is to understand the genetic and molecular mechanisms of Ad-36 induced obesity. We showed that Ad-36 induces replication, differentiation, and lipid accumulation, in 3T3-L1 cells and human primary preadipocytes (Figure 1). Recently, we identified that the E4 orf-1 gene of Ad-36 is necessary and sufficient to induce an adipogenic effect *in-vitro* and requires its PDZ domain-binding motif for the effect.

In addition to the effect on adiposity, we discovered a remarkable and potentially important effect of

Ad-36 infection. Ad-36 **enhances insulin sensitivity in experimentally infected rats**, an effect that is robust and reminiscent of anti-diabetic agents thiozolidinediones (TZD). Ad-36 increases *in-vitro* glucose uptake by human adipose tissue or primary skeletal muscle cells in a Ras mediated and phosphatidylinositol-3-OH kinase (PI3K) dependent manner. We are currently testing the hypothesis that Ad-36 induced adipogenesis contributes to the insulin sensitizing effect of the virus.

Treatment and/or prevention of Ad-36-induced adiposity is our long-term goal. Developing a vaccine to prevent Ad-36 induced obesity is one of the objectives. Moreover, determining the role of other infectious agents in the etiology of obesity is an important area of investigation.

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



Compared to the uninfected hASC (A), Ad-36 infected cells (B) show greater lipid accumulation indicated by BODIPY staining, a lipid specific green fluorescent dye. Ad-36 induced this lipogenesis even in the absence of differentiation inducing agents.

Neuroendocrine Immunology Laboratory



Vishwa Deep Dixit, DVM, Ph.D.
Assistant Professor

Focus — to understand the interactions between immune and metabolic systems during aging and obesity.

Advancing age and obesity are associated with increased risk of severe infections and cancers due to an underlying immuno-deficient state. The human body's ability to detect and fight pathogens and cancer cells is controlled in large part by the thymus. A healthy thymus generates cancer- and infection- fighting naïve T cells, yet production of these T cells declines as the individual ages due to a process called thymic involution. The main feature of thymic involution is adipocyte accumulation in the thymic space. These thymic adipocytes replace the lymphoid and stromal cell compartment with fat tissue; by the fifth decade of life only 20% of active thymus cells remain.

Various attempts have been made to regenerate the aging thymus through approaches targeting lymphoid stem cells, growth factors and thymic stromal cells. Our laboratory is focused on unraveling the underlying mechanisms that lead to accumulation of fat cells in the thymic environment so that we can forestall thymic involution. Our hypothesis is that the inhibition of ectopic adipocyte development in thymus will prevent deterioration of immune responses typically seen during aging and obesity. The identification of these specific pathways holds promise for developing novel drugs to induce thymic regeneration or prevent thymic decay.

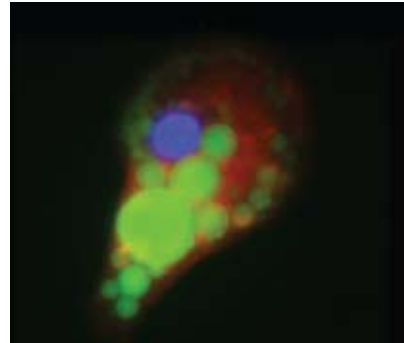
We have recently demonstrated that ghrelin, a stomach-derived hormone that stimulates appetite and induces growth hormone release, can increase thymic function while transgenic animals with targeted disruption of ghrelin and its receptor have accelerated thymic involution. In our most current work we have determined the origin of adipocytes in the thymus and specific pathways that lead to their sustained accumulation within the thymic microenvironment. We have also developed an *in vitro* model with which we can directly determine how fat cell development retards lymphoid stem cells from becoming competent T cells. Using this novel model our laboratory is dissecting the specific mechanisms responsible for thymoadipogenesis and

FACULTY:

Vishwa Deep Dixit, DVM, Ph.D., Assistant Professor.

RESEARCH TEAM:

Hyunwon Yang, Ph.D, Yun-Hee Youm, Ph.D., Rachel Ohlmeyer



Abnormal Thymic Stromal Cell: Immunofluorescent image of stromal cell derived from old thymus during differentiation into a thymic adipocyte. The lipid droplets are stained green, cell is positive for stromal marker called ERTR7 (in red) and nucleus appears blue.

also screening candidate drug targets for promoting immune function.

As the continued deposition of adipocytes in the immune microenvironment is detrimental, similarly, the increase in immune cells in adipose tissue depots also disturbs the normal tissue and organ homeostasis. Working on the interface of immunobiology, aging and obesity the Laboratory of Neuroendocrine-Immunology at PBRC, has found that immune cells are intimately linked to adipocyte biology and may play an important role in various diseases. It is currently believed that the presence of immune cells called macrophages in the adipose tissue is responsible for production of pro-inflammatory cytokines that cause insulin resistance. We have discovered that in addition to macrophages, the adipose tissue in obese animals and humans harbors various activated immune cell subsets that produce excessive amount of cytokines. Our findings have direct implications for understanding the origin of the pro-inflammatory state of obesity, hence providing vital insights into the mechanism of type 2 diabetes and immunodeficiency.

Research in this laboratory is supported by the COYPU Foundation, CNRU and Functional Foods Divisional Awards and the Pennington Medical Foundation.

Energy Balance



George Argyropoulos, Ph.D.
Associate Professor

FACULTY:

George Argyropoulos, Ph.D.

RESEARCH TEAM:

Olha Ilnytska, Ph.D., Rachel Dauterive, Laura Fendick

Focus — My laboratory studies the genetic and molecular mechanisms that regulate food intake and energy balance, employing molecular biology, animal models, and human genetics. Special emphasis is placed on determining the functional properties and the means by which the Agouti-Related Protein (AgRP) gene is regulated. AgRP is a powerful appetite effector that stimulates food intake when it is overexpressed. Conversely, reduction of AgRP in adulthood could reduce appetite and inhibit obesity.

Specific Projects:

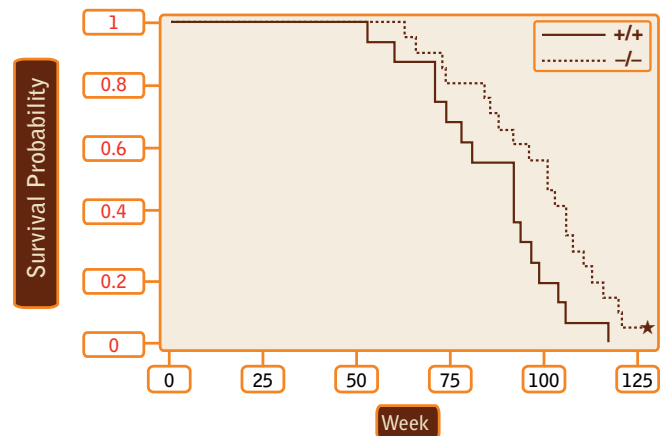
A. Determination of regulatory regions for the human AgRP. This project attempts to identify response elements for modifying hormones and determine binding sites for transcription factors on the promoter of AgRP. Two identified downstream enhancers modulate activity of the minimal AgRP promoter in hypothalamic and periphery-derived cell-types. One of the two enhancers drives expression in several innervated tissues, the spinal cord, testes, muscle, heart, limbs and the tongue. This approach allows the study of gene regulation at the whole organism level.

The CACCC-binding transcription factor Krüppel-like 4 (KLF4) has been identified as a major player in the upregulation of AgRP. *In vitro* studies have shown that KLF4 colocalizes with AgRP in the same hypothalamic neurons. Overexpression of KLF4 in transiently transfected cells leads to a significant increase of AgRP promoter activity and expression levels at the mRNA and protein levels. KLF4 binds to a specific CACCC box in the minimal promoter of AgRP. KLF4 is being viewed as a powerful agent that could be used to increase AgRP expression thus providing a mechanism for ameliorating cancer cachexia.

B. AgRP as an inverse agonist. AgRP is expressed in the hypothalamus as well as the adrenal gland and the testis where it is also upregulated by fasting, a landmark feature of this gene. Intravenously administered AgRP does not cross readily the blood-brain-barrier but rather infiltrates various organs in a fasting-dependent manner. Therefore, AgRP may act as an inverse agonist in peripheral tissues,

perhaps playing a role in energy homeostasis in a fashion analogous to that in the brain. Early data, using a transgenic mouse engineered to overexpress AgRP in the adrenal gland, show that hemizygous mice become moderately obese, suggesting a peripheral role by AgRP in energy balance. We are attempting to determine the mechanism of AgRP's peripheral functions.

C. AgRP-deficiency and longevity. We recently described a line of AgRP knockout (KO) mice developed in our laboratory that is metabolically similar to wild type littermates but lives significantly longer. AgRP KO mice placed on a high fat from the age of 7.7 months outlived their equally obese littermates by 10-percent. The figure below shows the extended lifespan of the AgRP-deficient mice. We are now trying to determine the mechanism by which AgRP plays a role in aging. AgRP may be a factor at the crossroads of energy balance regulation and enhanced aging.



Survival of the AgRP^{-/-} group exceeded that of their wild-type counterparts by 10% (P-value = 0.045).

Research in this laboratory is supported by an RO1 grant (NIH/NIDDK: DK62156).

Human Genomics Laboratory



Claude Bouchard, Ph.D.
George A. Bray Super
Chair in Nutrition



Tuomo Rankinen, Ph.D.
Associate Professor



Margarita Teran-Garcia, M.D., Ph.D.
Associate Scientist

FACULTY:

Claude Bouchard, Ph.D., Tuomo Rankinen, Ph.D., Margarita Teran-Garcia, M.D., Ph.D., Associate Scientist

RESEARCH TEAM:

Ruth Loos, Ph.D., Kathryn Redd, B.S., Christina Riley, B.S., Nadine Spielmann, Ph.D., Adrian Stütz, Ph.D., Brandon Walts, M.S., Jessica Watkins, B.S.

Mission — This laboratory investigates the genetic and molecular basis of 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.

Current Projects

This Laboratory relies on the resources of the *Heritage* Family Study, the *Hygiene* / Dallas Aerobic Center Longitudinal Study (ACLS), and the Swedish Obese Subjects Study. The laboratory is involved in GET-READI, a dietary intervention in African-American families investigating genetic and non-genetic determinants of responses to a heart-healthy diet, and collaborates in the *Cardia* Fitness Study.

Heritage Family Study: We aim to conclude the positional cloning of four QTLs of the response of cardiorespiratory fitness and hemodynamic phenotypes to regular exercise, resolve them in terms of candidate genes and allelic variants, and functionally confirm them. Two strong candidate genes have emerged: titin (TTN; QTL1) and kinesin 5B (KIF5B; QTL2). Fine mapping of QTL3 (Chr 13q11) and QTL4 (Chr 2q33) for training-induced change in submaximal exercise capacity has also been completed. Additionally, we have completed functional studies targeting DNA sequence variation on the KIF5B promoter region, and on KIF5B function in cellular models using gene silencing and overexpression. We will extend these *in vitro* studies to QTL3 and QTL4 candidates.

Following up our observations on skeletal muscle gene expression, we reported that DNA sequence variation in the four-and-half lim domain 1 (FHL1) gene is associated with exercise-training-induced changes in insulin phenotypes as illustrated in figure 1. Note that FHL1 is encoded on chromosome X. Additional candidate gene studies related the PPAR δ gene with cardiorespiratory fitness and plasma lipids, and the CETP gene with plasma HDL cholesterol levels. Figure 2 illustrates the relationship between PPAR δ haplotypes and the mean increase in HDL cholesterol with

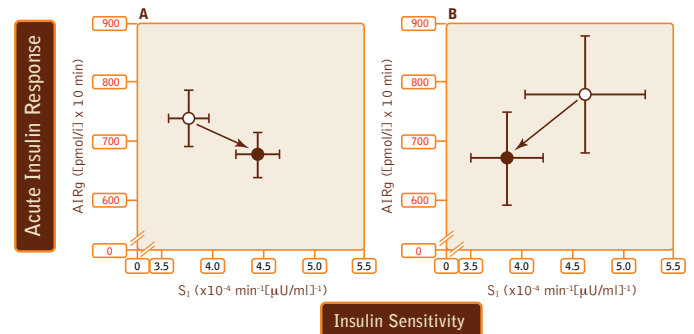


Figure 1. Pre- and post-training effects on S_1 and AIR_g for white men according to the C genotype (n=176) **a** and T genotype (n=40) **b** of the rs2180062 C>T FHL1 SNP. Open circles: mean values pre-training; closed circles: mean values post-training. Error bars denote SE.

the exercise program. Finally, four genome-wide linkage scans for cardiovascular risk factors were published in 2006-2007.

Hygiene: In collaboration with the Cooper Institute in Dallas, TX, we have established a DNA bank of consenting ACLS participants to examine genotype-by-fitness and genotype-by-obesity interaction effects on the risk of chronic diseases. The first project targets hypertension by investigating the contributions of DNA sequence variation in candidate genes, cardiorespiratory fitness and obesity, as well as their interactions, to the incidence of hypertension. We have observed that moderate-to-good cardiorespiratory fitness level is associated with a lower risk of hypertension. DNA sequence variation in the endothelin 1 gene (EDN1) is associated with increased risk of hypertension in individuals with low levels of cardiorespiratory fitness but not in those who have moderate to high fitness levels.

In 2006 and 2007, the laboratory published 46 peer-reviewed original papers and seven book chapters and maintains the Human Gene Map for Performance and Health-Related Fitness Phenotypes, published every two years in *Medicine and Science in Sports and Exercise*.

Research in this laboratory is funded by NIH grants, COYPU Foundation, and by an unrestricted grant from BMS.

Molecular Genetics and Thermogenesis Laboratory



Leslie P. Kozak, Ph.D.
Professor



Robert A. Koza, Ph.D.
Assistant Professor



Jong-Seop Rim, D.V.M., Ph.D.
Instructor

FACULTY:

Leslie P. Kozak, Ph.D., Robert A. Koza, Ph.D., Jong-Seop Rim, D.V.M., Ph.D.

RESEARCH TEAM:

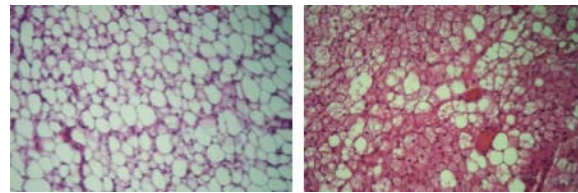
Rea V. P. Anunciado, D.V.M., Ph.D., Pei-Min Chao, Ph.D., visiting scientist (Taiwan), Jessica Hogan, Ph.D., Larissa Nikonova, Ph.D., Tamra Mendoza

Focus — to understand how environmental conditions, such as temperature and nutrition, can modulate the development of organ systems of energy balance to determine the future response of an individual to an obesogenic environment.

Environmental temperature

A healthy body weight results from balancing caloric intake with expenditure of calories by the body's physiological functions. While biologists have identified most of the systems comprising energy metabolism, we want to understand why these systems fail to maintain energy balance for a large number of obese individuals. Our hypothesis is that in the absence of physical activity, no system of energy expenditure can be induced in normal individuals to burn off excess calories. Both humans and mice are similarly affected by a sedentary life style supported with calorically dense foods. Using molecular genetic techniques, we have created mice in which putative biochemical pathways that generate heat have been constitutively changed, and we have examined how these genetic manipulations affect thermogenesis and obesity. By inactivating two thermogenic pathways, the mitochondrial uncoupling pathway and the thyroid hormone sensitive glycerol phosphate shuttle, the mouse becomes less metabolically efficient in maintaining body temperature. Accordingly, more calories are consumed in mutant mice, with the downstream effect being reduced obesity. However, the effectiveness of this increase in thermogenesis in the face of reduced thermogenic mechanisms depends upon a prior condition in which the mice are exposed to a modestly reduced ambient temperature (from 28°C to 20 °C) for a couple of weeks. We have analyzed gene expression in tissues from mutant mice, which are expected to contribute to whole body thermogenesis, to determine how the animal increases its thermogenic capacity. A major transformation occurs in the inguinal fat, located subcutaneously, by its transformation to a brown adipose tissue like organ. Unexpectedly, no changes could be detected in skeletal muscle or liver. Thus, despite the absence of *Ucp1* and the glycerol phosphate shuttle, we proposed that heat is

achieved by a generalized up-regulation of mitochondrial biogenesis with enhanced solute transport by mitochondrial carrier proteins. These studies underscore the impressive capacity of subcutaneous fat to adapt to meet the thermogenic needs of the animal, with secondary, though important, consequences on obesity.



Wild Type
Adiposity Index = 0.76

Gdm.Ucp1^{-/-}
Adiposity Index = 0.31

Histology of the inguinal fat of wild type and **Gdm.Ucp1^{-/-}** mice fed a high fat diet for 20 weeks. **Gdm.Ucp1^{-/-}** mice showed remarkable induction of brown adipocytes in the inguinal fat. Mice were pre-conditioned to 20° ambient temperature for 10 weeks and then reared at 28° C for another 10 weeks. Adiposity index is the ratio between fat mass and fat-free mass.

Nutrition programming

Although it is well documented that allelic variation contributes to obesity in both mice and humans, study of genetically identical mice has shown that an epigenetic mechanism leads to a variation in obesity equivalent to genetic variation. Exploration of this epigenetic phenotype has shown that it depends on a molecular mechanism, centered upon the mesoderm specific transcript (MEST) as a component for uptake of fat from the circulation, for expansion of adipose tissue that is variably induced during a positive energy balance. We found that malnutrition of the suckling mouse affects the expression of MEST in a manner similar to that found in adult mice in an obesogenic environment. We hypothesize that under- or overnutrition in the suckling mouse establishes a lifetime of adipose tissue expansion.

Research in this laboratory is supported by Health Excellent Fund from the State of Louisiana and research grant HD08431 from the NIH.

Neuropeptides Laboratory



Andrew Butler, Ph.D.
Associate Professor



Gregory Sutton, Ph.D.
Instructor

FACULTY:

Andrew Butler, Ph.D., Gregory Sutton, Ph.D., Instructor

RESEARCH TEAM:

Karima Begriche Ph.D., Ganesh Kumar Karunakaran, Ph.D.,
Armand Centanni, Tara Henagan, B.S.

Focus — to investigate mechanisms linking obesity with the development of insulin resistance and liver disease.

This laboratory investigates how obesity increases the risk of developing insulin resistance and type 2 diabetes. In one project, we are investigating how the body “prepares” for a meal. Daily or circadian rhythms of animals are controlled by clock genes that keep track of time. Clocks maintained in neurons in the hypothalamus are critical for maintaining circadian rhythms. Our group is investigating the role of a gene, the melanocortin-3 receptor (Mc3r) that is a component of a system that is regulated by signals of food intake. Another gene in this pathway, the melanocortin-4 receptor, has a critical role in satiety, or meal termination, and humans with mutations in this gene are obese because they over eat.

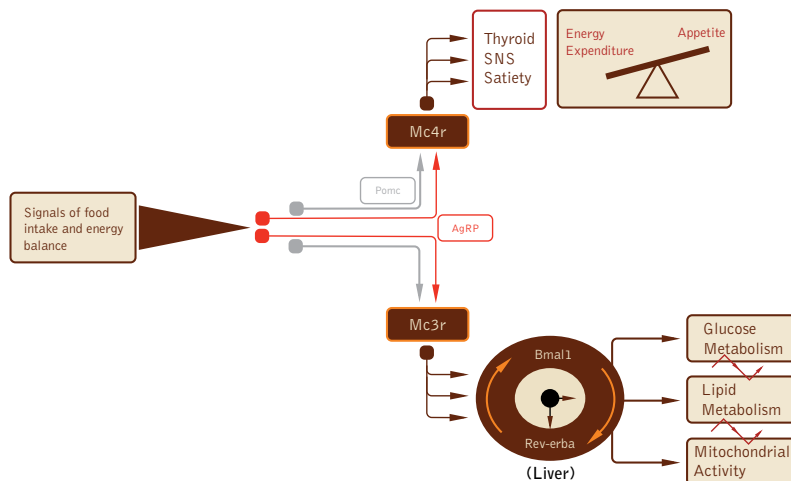
Using mice lacking Mc3r, we are testing the hypothesis that Mc3r expressing neurons coordinate clock cycles with feeding time. We have demonstrated that these mice cannot adapt to scheduled feeding protocols, where food availability is restricted to a specific time of day. Specifically, mice lacking this gene fail to develop an anticipatory behavior and have abnormal clock activity in the brain.

We have also shown that Mc3r in the brain prepare the liver, the first organ in the body that processes nutrients

following the ingestion of a meal. The liver is also responsible for maintaining blood sugars between meals and during a fast, ensuring that the brain has a constant supply of energy. Our data show that the normal circadian rhythms in genes involved in the secretion of glucose, and in the synthesis and secretion of fatty acids by the liver are absent in mice lacking Mc3r.

The second project investigates a new therapeutic target for treating insulin resistance and diabetes. Nonalcoholic fatty liver disease (NAFLD) is the most frequently observed liver disorder in the United States, affecting 15-25% of the general populations and up to 75-90% of over weight individuals. There are no approved drug treatments for this disorder, and patients are only advised to eat less. We have identified a secreted protein whose abundance declines with NAFLD. When we treat obese mice with NAFLD with the protein, we can dramatically improve liver disease. Importantly, the protein also reduces fasting insulin levels, suggesting a reversal of insulin resistance. We are currently exploring the use of the protein as a new treatment for liver diseases and type 2 diabetes.

Research in this laboratory is supported by the National Institute of Diabetes, Digestive and Kidney Diseases, Ipsen Inc., and the Pennington Medical Foundation.



Neurons in the brain receiving signals of food intake regulate satiety, energy expenditure and the circadian clock system. Pomc neurons secrete peptides that activate Mc4r, causing satiety and regulating energy expenditure through the sympathetic nervous system (SNS) and thyroid. Activation of Mc3r sends a “time” signal to clocks in the brain and liver that govern sleep and metabolism. AgRP neurons secrete a peptide that inhibits Mc3r and Mc4r neurons. During a fast, AgRP dominates and increases appetite and reduces energy expenditure.

Regulation of Gene Expression



J. Michael Salbaum, Ph. D.
Associate Professor

FACULTY:

J. Michael Salbaum, Ph. D.

RESEARCH TEAM:

Jacalyn MacGowan

Focus — to understand the relationship between diabetes, birth defects, and gene regulation in the embryo.

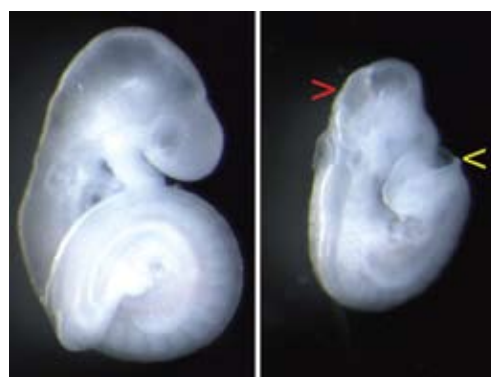
In addition to the detrimental effects on afflicted individuals, diabetes acts as a teratogen. Pregnant women with diabetes face significantly increased risk of birth defects in the infant; such birth defects cause significant morbidity and mortality, and include neural tube defects, cardiovascular malformations, and caudal regression. How diabetes affects embryonic development, and how birth defects are caused under conditions of maternal diabetes, is not well understood.

Our hypothesis is that maternal diabetes during pregnancy de-regulates gene expression in the embryo. Our goal is to identify the key molecular players and define their mechanistic roles for the pathogenesis of neural tube defects in diabetic pregnancies. In mouse models, we have identified 126 genes whose expression is significantly changed in embryos exposed to maternal diabetes. Many of these genes are (i) involved in neural tube defects, (ii) map close to genetic susceptibility loci for adult diabetes and cardiovascular disease, (iii) are expressed in the embryonic central nervous system, and (iv) are essential for embryonic development. We think that members of this group of deregulated genes contribute to the higher incidence of neural tube defects in diabetic pregnancies.

We are now focusing on those de-regulated genes that are expressed in the neural plate and the underlying mesoderm. We will determine (i) which genes are most indicative for exposure to maternal diabetes, (ii) at which stage maternal diabetes has the strongest influence on gene expression, and (iii) which genes can serve as predictive markers for specific abnormalities in neurulation. The outcome will be a set of indicator genes for the interaction of maternal diabetes with nervous system development.

It has been proposed that hypoxia and oxidative stress contribute to diabetic embryopathy. Based on our finding that expression of *Hif1 α* , a key gene controlling the hypoxia response, was decreased by maternal diabetes, and the fact that *Hif1 α* -deficient embryos display neural tube defects, we

hypothesize that the embryo's hypoxia response is critical for central nervous system development. We will test this hypothesis in a genetic model for partial *Hif1 α* -deficiency by exposing *Hif1 α* -heterozygous mutant mice to maternal diabetes, and determine frequency of neural tube defects in embryos. These analyses will reveal how the embryonic hypoxia response in the adaptation to diabetic pregnancy conditions affects morphogenesis of the nervous system.



A healthy mouse embryo at 9.5 days of gestation is shown on the left. The neural tube is properly closed along its entire length except an area at the tip of the tail referred to as posterior neuropore. On the right is a mouse embryo of the same gestational stage from a diabetic mother. The embryo shows diabetes-induced neural tube defects at the hindbrain (red arrowhead) and at the level of the hind limb (yellow arrowhead), which would result in Spina bifida.

We will also conduct functional studies on two genes, *Pdgfra* and *Vinculin*, because both genes show reduced expression in the embryo as consequence of maternal diabetes, null mutants of either gene present with neural tube defects, and both genes are known to interact. Our hypothesis is that the interaction of both genes with maternal diabetes confers susceptibility to neural tube defects. These experiments will determine how a cellular signaling pathway that includes *Pdgfra* and *Vinculin* interacts with maternal diabetes to cause neural tube defects.

Research in this laboratory is supported by the National Institutes of Health (RO1 HD055528).

Taste Genetics Laboratory



Brenda K. (Smith) Richards, Ph. D.
Associate Professor

Focus – to understand the genetic basis for natural variation in the consumption of fat, carbohydrate and total calories.

A quantitative trait locus (QTL) is a region of DNA associated with a physical trait, or phenotype, measured on a quantitative scale. Previously we discovered numerous QTL, in the F2 generation of a B6 x CAST mouse intercross, contributing to nutrient intake traits, including fat, carbohydrate, and total calorie intake. This study was the first to identify genetic linkage for nutrient preference and energy intake in mammals and provides evidence for multiple genetic controls on food intake.

The most significant associations between phenotype and genotype were found on chromosomes 8, 17, and 18. To isolate these QTL, test their effects, and identify the underlying genes, we developed congenic strains in which more than 99% of the genome is B6 with CAST donor DNA in the QTL region of interest. For example, a B6.CAST-17 congenic strain confirmed that the Chr 17 QTL specified two original linked traits: *Mnic1* (macronutrient intake-carbohydrate) and *Kcal2* (kilocalorie intake). Specifically, the congenic mice selected/consumed 27% more carbohydrate and 17% more total calories per body weight, yet similar fat calories, compared with littermate background B6. Moreover, we have found that the Chr 17 QTL also encompasses an activity phenotype, i.e., sub-congenic mice possessing the differential segment have 25% higher spontaneous physical activity levels. Identifying the Chr 17 locus or loci influencing energy intake and physical activity in this model will provide a unique and powerful tool for investigating gene interactions in the control of energy balance.

To identify candidate genes within the Chr 17 QTL, we are comparing gene expression between B6 and B6.CAST-17 congenic mice. In the liver, carbohydrate-preferring B6.CAST-17 congenic mice show decreased expression of several genes associated with fat metabolism and increased expression of genes involved in carbohydrate metabolism, including the glycolytic and glyoxalase (*Glo1*) pathways. Expression of *Glo1* and several ESTs was also increased in

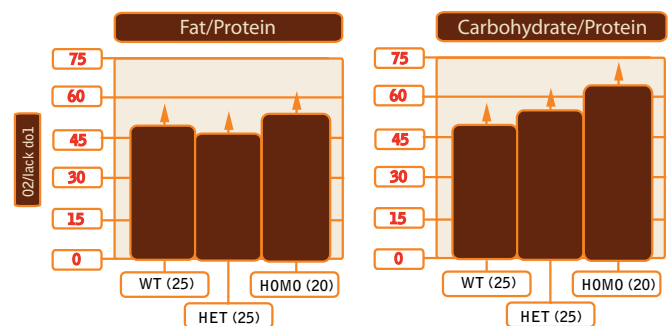
FACULTY:

Brenda K. (Smith) Richards, Ph.D.

RESEARCH TEAM:

K. Ganesh Kumar, Ph.D, Candice Pereira, B.S., Stephannie Marie Ruiz, M.S., Heather Duby, Mary Catherine Kayser

the hypothalamus. These findings suggest this congenic strain has an enhanced ability to utilize carbohydrate and to protect against dietary oxidants.



Cumulative calorie intake over 10 days, adjusted for body weight, is shown for mice selecting their preferred level of fat vs. carbohydrate (protein content was fixed) from a choice between two diets. The B6.CAST-17 homozygous (homo) congenic mice selected/consumed, per body weight, 17% more total calories and 27% more calories from the carbohydrate/protein diet when compared with wild-type (WT) B6 mice. * $P < 0.05$.

Genetic and genomic data indicate at least one molecular component of this QTL may reside in other tissues. The Chr 17 QTL approximates the location of *Glp1r* (glucagon-like peptide 1 receptor), a compelling gene candidate which is expressed in stomach. Elucidating the molecular basis of complex traits involving ingestive behavior will likely require the characterization of gene expression in multiple tissues, the central nervous system notwithstanding. The mechanisms underlying phenotypic differences in nutrient intake could involve genetically determined components in the taste or gastrointestinal systems, intermediate metabolism, or central nervous system. Identifying genes that regulate macronutrient intake in mice will help us understand the contribution of genetic versus environmental factors affecting the regulation of food intake in humans.

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

Autonomic Neuroscience Laboratory



Richard Rogers, Ph.D.
Professor



Gerlinda Hermann, Ph.D.
Associate Professor

FACULTY:

Richard Rogers, Ph.D., Gerlinda Hermann, Ph.D.

RESEARCH TEAM:

Montina J. Van Meter, H.T., Laura Marciante, B.S.

Focus —to understand the relationship between the brain, the immune system, and the digestive tract.

Status Report

Cytokines are protein-like molecules that are released by immune and neural tissues as a consequence of cancer, trauma, or infection. These disease processes are typically associated with severe disruption of feeding behavior and control of digestive functions. Failure of gastrointestinal motility, accompanied by nausea, emesis and anorexia, are also common features of neurodegenerative disease. Our hypothesis is that cytokines, such as Tumor Necrosis Factor [TNF], released as a function of the disease process, directly affect the function of those cells in the brainstem that are responsible for essential control of feeding behavior and digestive function.

In experimental models, if TNF is microinjected directly into these neural circuits in the brainstem of rodents, a profound relaxation of the stomach is evoked that resembles the relaxation seen during bouts of nausea and emesis. In humans, intravenous injection of TNF also causes severe nausea and emesis. Our research at Pennington provides an explanation for how TNF elicits this visceral malaise. Our studies have demonstrated that receptors for TNF are concentrated on the terminal endings of the vagus nerve. The vagus is a mixed visceral sensory and motor nerve that is critical to the autonomic control of the gut. The vagus, in turn, contacts neural circuit elements in the brainstem that integrate information about the status of the gut (as well as information about taste). Normally, these brainstem circuits regulate digestive functions but they also generate the changes in digestive function that are perceived as feelings of nausea and can produce emesis in response to harsh stimulation of the lining of the gut.

We have found that TNF can directly activate the brainstem neural circuitry that controls the gut. But even more impressive is that exposure to TNF results in an “amplification” in the responsiveness of vagal afferent nerve fibers to, otherwise, natural, innocuous stimulation of the

gut as might occur during normal digestion. In this case, the effect of TNF is to greatly sensitize these fibers so that any stimulation is interpreted as harsh, or exaggerated, with the result that nausea is experienced and often emesis produced.

Using an advanced laser confocal microscopy method which allows us to study the effects of TNF on synaptic transmission between vagal fibers and the brainstem gastric control circuitry at the level of the individual vagus nerve terminal, we have recently uncovered the cellular mechanism by which TNF activates vagal afferents. Apparently, TNF amplifies vagal neurotransmission by sensitizing an intracellular stores operated calcium entry into the cytoplasm of the nerve terminal that, in turn, is critical to the regulation of neurotransmission. The end result is that the incoming signal has been amplified and will now be interpreted differently by the brain. We are presently working on pharmacological approaches to interfere with this amplification which may be of therapeutic benefit to a multitude of patients.

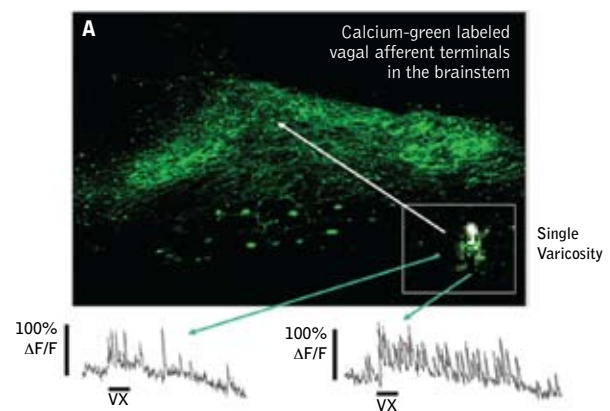
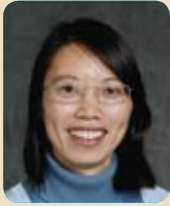


Figure 1. (A.) Confocal image of calcium dye labeled vagal afferents. [Inset is a single nerve terminal from which recordings are made.] (B.) Recording of the results of “normal” stimulation of a vagal afferent terminal with capsaicin. (C.) Same terminal response to capsaicin after exposure to TNF; note amplification of response.

Research in this laboratory is supported by grants from the National Institutes of Health [DK052142, DK056373, HD047643] and the Pennington Medical Foundation.

Blood-Brain Barrier Laboratory – I



Weihong Pan, M.D., Ph.D.
Professor

FACULTY:

Weihong Pan, M.D., Ph.D.

RESEARCH TEAM:

Chuanhui (Jasmine) Yu, Ph.D., Yan Zhang, Ph.D., Xiaojun Wu, Ph.D.

Focus — to determine the role of the blood-brain barrier (BBB) in neuroinflammation and neuroregeneration.

Current Projects

Transport of cytokines in spinal cord injury (SCI): We have shown that in mice after SCI, the transport system for the proinflammatory cytokines tumor necrosis factor alpha (TNF) and leukemia inhibitory factor (LIF) show time- and region-dependent upregulation. We also identified the respective receptors involved in the transport process. These findings lead to further questions: (1) How does transcytosis occur, so that a protein molecule can be directed from the blood side (apical surface of the endothelia of the BBB) to the brain side (basolateral surface), avoiding intracellular degradation so that it can be exocytosed to reach CNS targets? (2) What mechanisms after SCI drive the upregulation of the transport of these molecules? (3) Which are the key steps involved in the upregulation? Thus, we mainly focus on protein trafficking and turnover in the cerebral microvascular endothelial cells composing the BBB.

Functional implications of the upregulated transport:

Cytokines are dynamically involved in neuroinflammation, neuroendocrine changes, and regenerative processes. The specific changes of cytokine transport systems might just reflect an adaptive change of the BBB to CNS insults, or they may serve beneficial roles in promoting functional recovery. Thus, we address the specific consequences of cytokine transport by use of overexpression and knockdown approaches in combination with histological and behavioral parameters.

Signal modification at the BBB: We have shown at the BBB level that one proinflammatory cytokine can affect the signal transduction and transport of another. This indicates that the BBB plays a crucial role in integrating peripheral stimuli and in relaying messages to the CNS after its “interpretation”. We know only very little from studies with LIF receptors, which are subject to modulation by TNF and lipopolysaccharide. Our ongoing studies mainly focus

on the interleukin-15 system and the P-glycoprotein efflux transporter.

Progress in year 2007

We maintained the same level of funding, and showed higher productivity than in previous years. Dr. Yu co-authored five papers and has several more in press. Dr. Zhang and Dr. Wu brought in many new ideas and skills which will help to expand the scope of research in the coming years. The postdoctoral fellows had several poster presentations in international meetings, and did well in the Data Presentations and part of WIP within PBRC. Dr. Zhang has been organizing the journal club for the Division of Neuroscience. Dr. Pan participated in six NIH study section reviews this year, served as a referee for different journals more than once /month, contributed to the BBB consortium reports, was an invited speaker at four international meetings, co-organizing a few of these as well as a Henry Stewart Talk on the BBB, and joined two more editorial boards.

Research in this laboratory is supported by funds from the National Institutes of Health (NIH R01s) from NINDS.

Blood-Brain Barrier Laboratory – II



Abba J. Kastin, M.D.
Professor, United Companies/
Harris J. Chustz Chair



Hong Tu, M.D., Ph.D.
Instructor

FACULTY:

Abba J. Kastin, M.D., Hong Tu, M.D., Ph.D., Instructor

RESEARCH TEAM:

Hung Hsuehou, M.S., and Yi He, Ph.D.

Focus — to determine the role of the blood-brain barrier (BBB) in neuroendocrine control, particularly related to peptides/polypeptides involved in feeding behavior.

Current Projects

Several decades ago we pioneered the concept that peptides in the periphery have CNS effects, and we are still leading in the discovery of the mechanisms involved. Our current interest is how these small proteins cross the blood-brain barrier (BBB) and 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, actively engaged in regulatory functions while protecting the brain from harmful substances.

Adipokines are peptides/protein molecules produced by fat cells (adipocytes) as well as some other cells in the body. The production of individual adipokines changes over the course of obesity and its resulting pathology; as does BBB permeation to adipokines. The communication of adipokines and their CNS targets through the BBB in turn affects the neuroendocrine status. At the cellular level, our goal is to determine the driving force and sorting signals of the intracellular trafficking of adipokines across the cerebral endothelial cells. Peptide and protein ligands were usually thought to be degraded within cells, but the BBB cells may be an exception. We currently investigating protein-protein interactions during transport across the BBB. Our techniques include transport assays in vitro and in vivo involving overexpression, gene knockdown, fluorescent imaging, flow cytometry, fluorescent resonance energy transfer, electron microscopy, immunoprecipitation, gene and protein arrays, and routine quantification of mRNA and protein expression.

In the normal mouse, we continue to characterize transport systems for peptides and proteins. How does the transport of feeding-related peptides change in altered feeding and nutritional states? Do nesfatin and FGF21 enter the brain from the blood? How do different peptides

and polypeptides, such as urocortin and leptin, interact at the BBB level? What isoforms of the leptin receptor are involved in transcytosis and also exocytosis? Are both CRH receptors involved in urocortin transport? What long-term effects do urocortin and leptin exert after injection during the neonatal period? Are there differences in expression of leptin receptors and leptin transport between neonatal and adult mice? Do Avy mice, which develop obesity later in life, transport ingestive peptides differently than their controls? And then, how can we use this information to assist treatment of pathological obesity?

In the last year, we published more than 10 papers on this subject, provided several didactic reviews, and promoted our research and our institution at a variety of international meetings. Dr. Kastin received an honorary professorship from Beijing University (China) this year, and two honors, one in Brazil and one at the University of Florida. Dr. Kastin organized two international meetings and set up two regional branches of the International Neuropeptide Society (INPS) in Asia and South America. These, along with publication of the 215-chapter *Handbook Biologically Active Peptides* by Elsevier and our continued success in editing the journal *Peptides*, reflect our continuous effort to move the field forward.

Our unpublished data point to a more complex interplay of different cellular constituents of the BBB in the transport and CNS actions of leptin. This may be extremely significant in neonatal development and in neuroinflammation, as well as in obesity.

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

Neurobehavior Laboratory



Roy J. Martin, Ph.D.
Gordon Cain Professor



Jun Zhou, Ph.D.
Instructor

FACULTY:

Roy J. Martin, Ph.D., Jun Zhou, Ph.D.

RESEARCH TEAM:

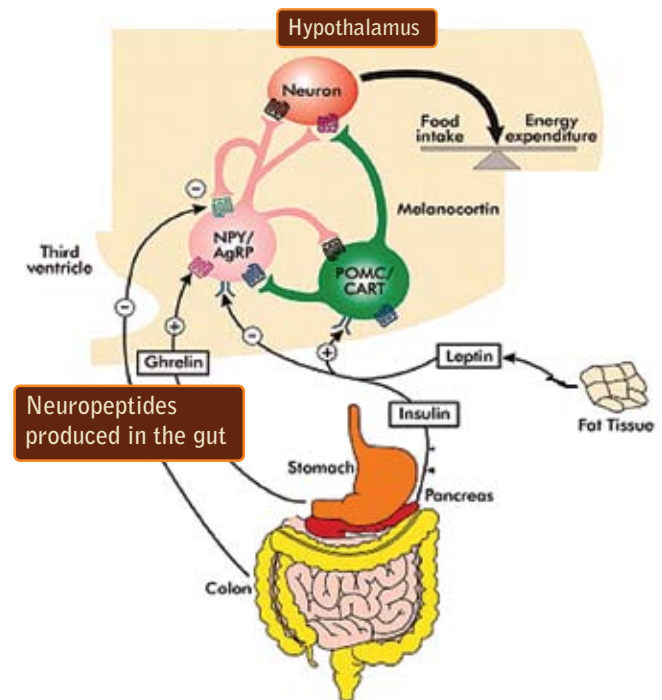
Mike Keenan, Ph.D., associate professor (adjunct), Anne M. Raggio, B.S., Li Shen, M.S.

Focus — nutrient (macronutrient) regulation of neuropeptide expression in the gut and brain.

Neuropeptides expressed in the gut and brain are important in the control of feeding behavior. The gut and brain can “sense” ingested nutrients and regulate the neuropeptides expression accordingly. “Nutrient sensing” plays a key role in dietary control of food intake. Our laboratory has provided critical support for the theory of macronutrient-sensing mechanisms. Our overall goals are to identify unique cellular signaling mechanisms (ChREBP, GPR40-43, AMPK, mTOR) by which carbohydrates, amino acids, short chain and long chain fatty acids are sensed by neurons to regulate neuropeptides involved in feeding behavior. We are testing 1) the ability of monosaccharides to alter AMPK activation determines their effectiveness to modify neuropeptide gene expression in the gut and brain, which in turn modifies food intake, 2) excess fatty acids and ketones decrease food intake by their effect on increasing cellular ATP status, decreasing AMPK activation, stimulating POMC expression and suppressing the expression of NPY and AgRP, 3) consumption of high protein diets, which exceed the amino acid needs for protein synthesis, will result in higher amino acids concentration in the body.

The elevated amino acids will be sensed by the brain, resulting in a cascade of responses to suppress food intake. These studies will lead to diet formulations which target signaling mechanism known to be sensitive to bioactive nutrients. The following is an example of a successful application of knowledge about bioactive nutrient signaling of neuropeptides.

A multidisciplinary team of AgCenter and PBRC Faculty has made significant progress on the use of dietary resistant starch to combat obesity. Resistant starch is a dietary carbohydrate that resists digestion in the small intestine and ferments in the large intestine. Ingesting resistant starch daily for longer than a week produces novel signaling in the gut enteroendocrine cells, which leads to consistently higher plasma levels of total GLP-1 and total PYY at all time points measured over a 2 hour period, decreased body fat



Adapted from Gale et al 2004

accumulation, and improved glucose tolerance.

Understanding of nutrient sensing mechanisms that control feeding behavior may ultimately result in formulating diets or discovering therapeutic agents that prevent over eating and obesity.

This work is supported by grants from the National Institutes of Health (R21 DK073403-01A1), the LSU AgCenter and the Pennington Medical Foundation.

Neurobiology and Nutrition Laboratory I



Hans-Rudolf Berthoud, Ph.D.
George H. Bray Professor



Huiyuan Zheng, Ph.D.
Instructor

FACULTY:

Hans-Rudolf Berthoud, Ph.D., Professor, Huiyuan Zheng, Ph.D., Instructor

RESEARCH TEAM:

Natalie Lenard, Ph.D., Tanja Babic, Ph.D., Laurel M. Patterson, B.S., Robbie Leigh Townsend, B.S., Katherine Stewart and, David Montgomery, Student Workers.

Focus — Our laboratory has a general interest in the neural mechanisms of nutrient detection, control of appetite and regulation of energy balance and how they are involved 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 lifestyle. 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 effects of chronic loss or gain of function of these pathways on the development of diet-induced obesity are currently tested in several transgenic mouse models and local injections of viral vectors. These 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 look at the mechanisms by which longer-term and cognitive signals from the hypothalamus and forebrain are integrated with gut-related signals of satiety. We have shown that hypothalamic neurons expressing the feeding peptides proopiomelanocortin (POMC)/ alpha-melanocyte stimulating hormone (α -MSH) and cocaine and amphetamine-regulated transcript (CART), orexin, and melanin-concentrating hormone (MCH),

all project to the dorsal vagal complex in the medulla oblongata, where they contact neurons receiving vagal afferent inputs signaling nutrient arrival. We have further shown that the MC3/4-receptor agonist MTII decreases and the antagonist SHU9119 increases meal size when injected into the 4th ventricle or directly into the dorsal vagal complex, suggesting that these peptidergic projections from the hypothalamus modulate the level of satiety and meal size. We are currently attempting to molecularly fingerprint and neurochemically characterize the specific brainstem neurons receiving both gut and descending input signals using electrophysiological, calcium imaging, gene expression analysis, and neuroanatomical tracing strategies in the hope to find novel drug targets to fight obesity.

Finally, we are continuing our research on the anatomical and neurochemical organization of vagal and sympathetic output to the gastrointestinal tract, liver, pancreas, and fat tissue. In one project using genetically altered pseudorabies virus for transneuronal retrograde tracing, we have identified neurons in the caudal raphé nuclei and other medullary sites that receive input from hypothalamic peptidergic projections such as α -MSH, orexin, and MCH and project to brown adipose tissue. We are currently investigating the role of leptin-sensitive neurons with regard to their autonomic premotor functions using a transgenic mouse model that expresses green fluorescent protein (GFP) under the control of the long form leptin receptor.

Our projects are funded by the National Institutes of Health Grants DK47348 and DK 071082, and a Grant from the Coypu Foundation.

Neurobiology and Nutrition Laboratory II



R. Alberto Travagli, Ph.D.
Professor



Kirsteen N. Browning, Ph.D.
Assistant Professor

FACULTY:

R. Alberto Travagli, Ph.D., Kirsteen N. Browning, Ph.D.,
Zhongling Zheng, M.D., Ph.D.,

RESEARCH TEAM:

F. Holly Coleman, B.S.

Focus – to understand the cellular mechanisms underlying the central control of gastrointestinal (GI) functions.

Current Projects

We combine *in vitro* with *in vivo* techniques to study and characterize the sensory and motor components of autonomic neural circuits controlling gastrointestinal (GI) functions. Our aim is to elucidate the cellular mechanisms underlying the control that the central nervous system exerts on the physiological functions of the upper GI tract.

One project deals with the organization and plasticity of brainstem vagal circuits controlling GI motility and homeostasis. Sensory information from the GI tract is perceived and modulated by neurons in the nucleus of the tractus solitarius (NTS) before being transmitted to motoneurons of the dorsal motor nucleus of the vagus (DMV); these nuclei are essential for the coordination of vago-vagal reflexes. Although vago-vagal reflex control of the gut is understood at a basic mechanistic level, there are many factors (e.g. the organisms' place in the environment, time of day, taste of food, stress, pain, cytokine production in disease, hormonal background, etc.) that can radically alter feeding behavior or GI function.

Data from our laboratory suggest that the integration of digestive function in relation to the state of the GI tract is dependent on visceral sensory data carried by the afferent vagus nerve. It appears that tonic sensory inputs from the GI 'dampen' the responsiveness of vagal circuits to circulating neurotransmitters and hormones and, by preventing unnecessary responses, keeps the vagal output in an idle state. Subthreshold manipulations of these vagal sensory inputs, however, can unmask responses in otherwise silent neural synapses suggesting that the processing of GI sensory information can be altered drastically by through the ability of neuropeptides and hormones to differentially gate neuronal transduction mechanisms. Our immunohistochemical data support this concept of short-term circuit plasticity since similar manipulations allow the detection of otherwise concealed membrane receptors.

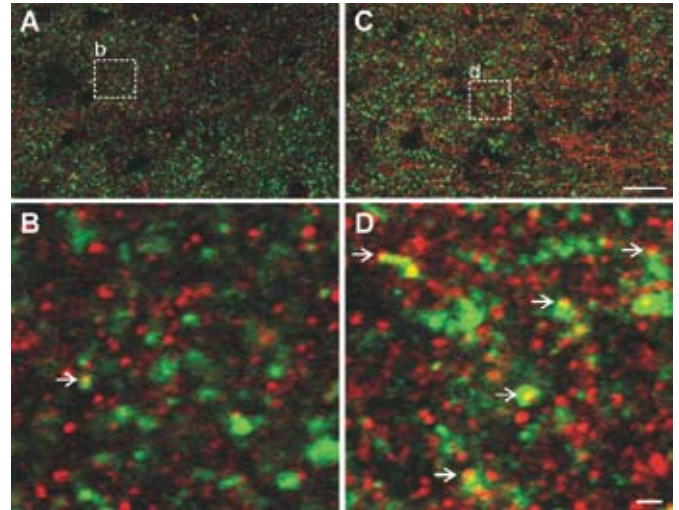


Figure taken from Browning et al., (2006) *J. Physiol.*, 575.3: 761-776. (A) low magnification micrograph illustrating a portion of the dorsal vagal complex from the control (vagally intact) side of the brainstem. μ -opioid receptor-IR = red; GAD-IR = green; co-localized profiles = yellow. (B) high magnification micrograph illustrating the detail (b) of a MOR-IR profile co-localized with GAD-IR (arrow head). (C) low magnification micrograph from the contralateral (deafferented) side of the brainstem as in (A). (D) high magnification micrograph illustrating, in detail (c), that deafferentation increases the number of MOR-IR profiles co-localized with GAD-IR (arrowheads)

Among the various neurotransmitters and hormones that display cyclical variations related to the animals feeding status is cholecystokinin (CCK). Previously, CCK was understood to act on brainstem vagal circuits in an indirect, paracrine manner. We have discovered recently, however, that CCK exerts profound effects on brainstem vagal circuits controlling GI functions due to a *direct* effect on the areas, such as NTS and DMV. Furthermore, CCK is able to unmask these otherwise silent inhibitory circuits hence may act to alter the processing of vagal sensory information by 'gating' central circuits and altering vagal reflex neurotransmission pattern

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

Neurosignaling Laboratory



Christopher Morrison, Ph.D.
Assistant Professor

FACULTY:

Christopher Morrison, Ph.D.

RESEARCH TEAM:

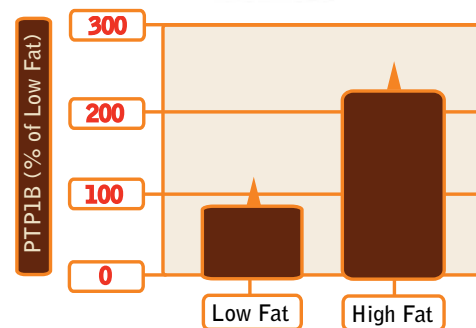
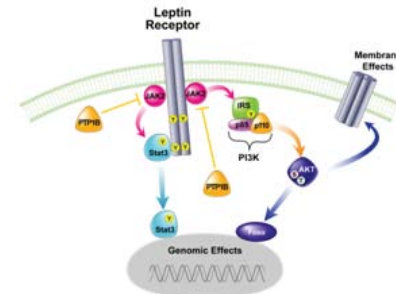
Christy White, D.V.M, Megan Purpera, M.S.

Focus — neural mechanisms that control food intake in response to changes in body weight or dietary macronutrients.

The defective signaling of a variety of brain neuropeptides or receptors alters both food intake and body weight. The Neurosignaling Laboratory focuses on the cellular mechanisms underlying the neural regulation of food intake, with a particular interest in the signaling molecules and neuronal circuits involved in the brain's 'perception' of nutritional state and subsequent regulation of feeding behavior.

One area of focus is the neuronal circuits and signaling molecules utilized by the hormones leptin and insulin. Defects in leptin or insulin signaling, or in the downstream circuits they regulate, lead to obesity and diabetes, indicating that neuronal leptin and insulin action is critical for appropriate body weight and glucose homeostasis. Recent work by our group and others indicates that obesity is associated with an inability of either leptin or insulin to engage key neuronal circuits within the brain. However, the molecular basis for leptin resistance is only beginning to be understood. The enzyme protein tyrosine phosphatase 1B (PTP1B) acts within the cell to inhibit both leptin and insulin signaling. Our data indicate that PTP1B levels are increased within the hypothalamus in multiple models of leptin resistance, and that acute inhibition of PTP1B improves leptin sensitivity. These data suggest that increases in PTP1B may be a key mediator of leptin resistance and obesity. Therefore, we are focusing on the cellular mechanisms that underlie this increase in PTP1B, and our data suggest that dietary fat and hyperleptinemia may independently contribute to this increase.

In addition, we have also recently focused on mechanisms by which changes in dietary protein alter food intake. High protein diets suppress food intake while low protein diets increase food intake, indicating that protein availability significantly influences feeding behavior. Our recent data indicate that acute injection of amino acids into the brain suppresses food intake, suggesting that amino acids may act



Increased hypothalamic PTP1B contributes to leptin resistance. A. Leptin acts locally within the hypothalamus to suppress food intake, but the enzyme PTP1B inhibits the function of the leptin receptor. This inhibition is predicted to predispose to obesity. B. Male rats are placed on a low fat (LF) or high fat (HF) diet for 28 days, and levels of PTP1B protein within the mediobasal hypothalamus are measured via Western Blot. PTP1B levels are significantly increased in response to the HF diet, consistent with the hypothesis that increases in PTP1B contribute to hypothalamic leptin resistance and possibly weight gain in response to a high fat diet.

directly within the hypothalamus to control food intake. We are currently focusing on the intracellular mechanisms by which amino acids might regulate hypothalamic neurons, and our data indicate that the classic fuel sensing molecules mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) may mediate the direct effects of amino acids on hypothalamic neurons.

Research in this laboratory is supported by grants from the National Institutes of Health (NS051570, RR021945), the Clinical Nutrition Research Unit, and by the Pennington Medical Foundation.

Neurotrauma and Nutrition Laboratory



Gregory M. Holmes, Ph.D.
Assistant Professor

Focus — to understand the mechanisms of digestive system dysfunction following central nervous system trauma.

Gastrointestinal (GI) function is diminished in humans after spinal cord injury (SCI). Because the vagal circuit controlling the stomach remains physically intact after human SCI, the paradoxical esophageal and gastric dysfunction following SCI suggests that other circuits within the damaged spinal cord may set the gain of these reflexes. Our hypothesis is that high thoracic SCI interrupts ascending (spinosolitary) circuits regulating vagal parasympathetic control of the stomach leading to gastroparesis.

We have demonstrated a profound gastroparesis in our experimental model of SCI. Gastric motility in both the empty and distended stomach is significantly diminished following injury. We also observe a reduction in gastric relaxation to stimuli mimicking the addition of gastric contents. Vagal motor control over gastric reflexes is the result of a complex interplay between two competing and antagonistic projections. One gastric projection provides tonic excitatory input that is important for regulating the milling of ingested solids and the delivery of reduced particles to the small intestine. A separate, non-adrenergic non-cholinergic (NANC), inhibitory vagal projection to the stomach regulates gastric capacity. Thus, stimuli activating NST neurons that form the vago-vagal control loop can cause inhibition of gastric motility by removing cholinergic excitation and by activating a parallel inhibitory path. The relative degree to which these competing circuits are affected by SCI remains to be determined.

Paralyzed individuals also have difficulty maintaining a neutral energy balance. Some long-term SCI individuals become significantly underweight. Low body weight increases the risk of infection and delays the recovery from traumatic injury. Furthermore, insufficient subcutaneous fat increases the risk of long-term pressure ulcers and subsequent pro-inflammatory cytokine release, which can exacerbate the cachexic state of the patient. We recently demonstrated that SCI animals fed a standard laboratory-

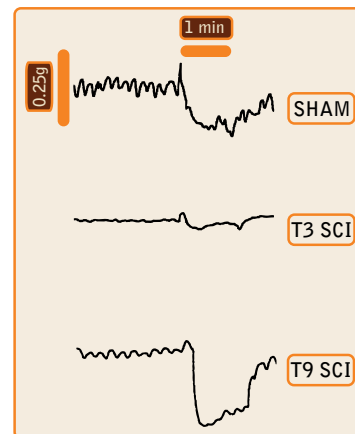
FACULTY:

Gregory M. Holmes, Ph.D.

RESEARCH TEAM:

Stefany D. Primeaux, Ph.D., Instructor, Melissa Tong, B.S.,
Emily Q. Creekmore, M.A.

chow diet were significantly leaner than able bodied cohorts, yet their mean energy intake was 50% greater than controls. We hypothesize that the prolonged post-injury loss of fat mass is not due to hypophagia but possibly to permanent changes in GI transit and absorption as well as whole body homeostatic mechanisms.



Polygraph records from fasted animals 3 days after surgery. Trace includes 2 min of basal gastric motility prior to 1 min of balloon distension of the esophagus (denoted by horizontal bar) followed by 1 min of recovery.

Most of the human SCI population studied in western societies is predisposed to insulin insensitivity, lipid abnormalities, hyperleptinemia and carbohydrate intolerance. While these abnormalities are common to obesity, SCI individuals do not present the excess weight that often defines obesity. The high-fat western diet may be a causative factor; SCI animals fed a high-fat diet accumulate fat faster, suggesting a greater sensitivity to dietary fat. We are exploring the obesity-related disorders that occur after SCI. As medical improvements extend the lifespan of the SCI population, post-injury changes in nutritional requirements suggest the need for dietary guidelines specific for the SCI population.

Research in this laboratory is supported by the National Institute of Neurological Disorders and Stroke, and the Pennington Medical Foundation.

Nutritional Neuroscience and Aging Laboratory



Donald K. Ingram, Ph.D.
Professor



Tadanobu Utsuki, Ph.D.
Instructor



Paul Pistell, Ph.D.
Instructor

FACULTY:

Donald K. Ingram, Ph.D., Tadanobu Utsuki, Ph.D., Paul Pistell, Ph.D.

RESEARCH TEAM:

Sumeet Juriani, M.S.

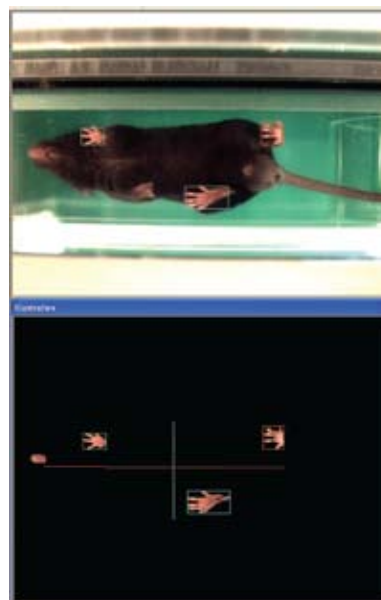
Focus — to discover and develop nutraceutical and pharmacological interventions that retard aging and age-related disease and promote late-life brain and behavioral function.

Aging is regulated through the interaction of genetic and environmental factors, with nutrition playing a major role. Our laboratory is dedicated primarily to investigating the effects of nutritious low calorie diets on aging, longevity, and function, particularly brain and behavioral function. In various rodent models, nutritious diets in which calories are reduced 30-50% below normal levels can markedly increase lifespan, reduce age-related disease and pathology, enhance stress responses, and improve physiological and behavioral function. This caloric restriction (CR) is now being investigated in clinical trials at the PBRC. While studies conducted thus far in humans indicate that CR can potentially provide health benefits similar to those observed in animal studies, such stringent diets may be difficult to maintain long term.

Genetic pathways that regulate the anti-aging effects of CR have been identified. These discoveries have created opportunities for evaluating pharmaceuticals and nutraceuticals that can stimulate specific pathways to invoke protective mechanisms activated by CR. In principle, these “CR mimetics” would provide the benefits of CR without requiring lifelong dieting. We have examined a fake form of glucose, 2-deoxyglucose (2DG), which acts as a glycolytic inhibitor. 2DG provided a wide range of physiological effects observed in animals under CR, including enhanced stress protection, but this compound proved toxic following chronic administration. To expand our search, our laboratory is constructing high throughput screens to discover new CR mimetics. Targets include glucose transporters and hexokinase inhibition. Inhibition of these targets would affect signaling through the glycolytic pathway regulating cellular glucose metabolism. We hypothesize that inhibition of glycolytic processing will trick the cell into activating a CR-like response. As a major component of our search for CR mimetics, we will screen libraries of

compounds derived from natural plant products. Currently we are evaluating several new compounds for the ability to protect mice against the negative health consequences of a high fat diet similar to the beneficial effects of CR. This approach is modeled after previous studies in which we showed that the plant polyphenol found in high concentration in red grapes, resveratrol, could provide such protection.

In addition to our own nutritional studies, we are interested in age-related alterations in locomotion, posture, and balance, variables associated with the increased incidence of falls among the elderly. Very fine analyses of gait in rodents is illustrated below. We are also examining the role of tumor necrosis factor-alpha in neuroinflammation and developing phosphodiesterase inhibitors to treat cognitive dysfunction. Thus, in general, the major goal of our research is to enhance the quality of life for the elderly.



(A). Video image of mouse walking on a transparent treadmill. (B). Enhanced image of mouse paws to which image analyses are applied to provide geometry of gait, e.g., speed of walking, stride length, swing time (paw in the air), foot coupling measures (in-phase or out-of-phase gait patterns of feet).

Research in this laboratory is supported by grants from the Glenn Foundation for Medical Research and the National Center for Complementary and Alternative Medicine.

Adipocyte Signaling Laboratory



Thomas W. Gettys, Ph.D.
Professor

FACULTY:

Thomas W. Gettys, Ph.D.

RESEARCH TEAM:

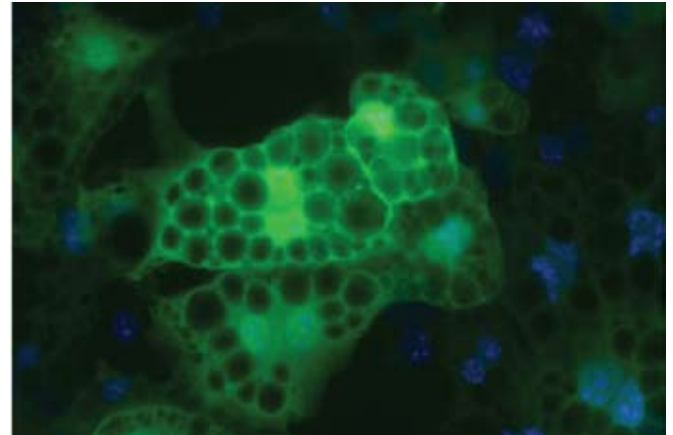
Laura Stewart, Ph.D.; Peter Huypens, Ph.D.; Ji Suk Sul, Ph.D., Jeho Shin, M.S.; Anik Boudreau, B.S.; Haley Echlin, B.S.

Focus – to investigate the underlying mechanisms and signaling systems which translate input from the sympathetic nervous system (SNS) into transcriptional responses that regulate the endocrine and metabolic functions of adipose tissue.

Current Investigations

Regulation of SNS-dependent remodeling of adipose tissue by a novel form of PGC-1 - The SNS integrates the function of metabolic tissues through regulation of transcriptional programs that effect remodeling of the cellular proteome. Evidence has emerged to support the view that PGC-1 is the critical transcriptional co-activator linking β -adrenergic receptors to transcriptional programs which have the common theme of increasing oxidative capacity through coordinated induction of nuclear-encoded mitochondrial genes. We have discovered a novel splice variant of PGC-1 which produces a truncated protein representing the first 267 AAs of the N-terminus of PGC-1 and an additional 3 AAs from the splicing insert. Expression of the N truncated 270 AA protein (NT-PGC1) is dynamically regulated in the context of the physiological signals which regulate full length protein. However, its unique domain structure modifies subcellular localization and protein stability of NT-PGC-1 such that a specific subset of functions shared with the parent protein are significantly enhanced. In particular, we propose that NT-PGC-1 plays an important, previously unappreciated role in mediating SNS-dependent remodeling of adipose tissue. Our goal is to assess the *in vitro* and *in vivo* role of this novel protein with respect to how it functions to complement the transcriptional activity of PGC-1 and influences the translation of sympathetic input into adipose tissue.

Dietary Methionine Restriction Extends Lifespan by Limiting Fat Deposition - Calorie restriction (CR) and dietary methionine restriction (MR) extend lifespan to comparable extents in rodents, but do so through opposite effects on metabolic efficiency. The Rate of Living hypothesis proposes that CR delays all causes of death by reducing oxidative metabolism and the associated formation



Confocal image of brown adipocytes stably transformed with NT-PGC-1. Compared to adipocytes stably transformed with empty vector, the NT-PGC-1 over expressing cells have increased mitochondrial numbers (~2-fold), mitochondrial gene expression, and an enhanced rate of fuel oxidation.

of reactive oxygen species (ROS), thereby slowing the accumulation of oxidative damage. In contrast, MR increases lifespan through a mechanism independent of reduced food consumption that involves a significant increase in fuel oxidation and corresponding reduction in metabolic efficiency. Thus, both dietary regimens have a similar effect on fat deposition; CR through limitation of energy intake and MR through reduction in metabolic efficiency. Our studies show that MR reduces adiposity by producing a significant diurnal increase in O_2 consumption and fatty acid oxidation in white adipose tissue. These complimentary responses indicate that adipose tissue may be a key primary target through which MR limits fat deposition, preserves peripheral insulin sensitivity, and maintains mitochondrial integrity. More importantly, our studies provide an exciting new animal model of longevity that challenges established dogma regarding the underlying mechanisms of aging and increased lifespan.

Research in this lab is supported by grants from NIH and the Orentreich Foundation for the Advancement of Science.

Endocrinology Laboratory



Steven Smith, M.D.
Professor

Focus — to understand the physiological, cellular and molecular connections between diets, particularly those high in fat, and the development of insulin resistance, a precursor to type 2 diabetes.

We are investigating how people differ in ability to burn fat, and in the cellular systems that control fuel selection in muscle (i.e. what nutrient cells prefer to burn). We recently discovered that biopsied muscle cells grown in the lab retain the characteristics of their donors: cells from lean, insulin sensitive people burn fat, and cells from obese, insulin resistant people don't. This suggests the risk for developing obesity and diabetes is due to fundamental differences in fuel metabolism in muscle cells.

We've also discovered that high fat diets change the pattern of genes turned on and off in muscle. Genes required for glucose metabolism are turned off by high fat diets and, quite unexpectedly, genes required for mitochondrial biogenesis and energy metabolism were downregulated. This observation was recapitulated in a mouse model of diabetes and suggests a model for how dietary fat causes defects in energy and fat metabolism that are precursors of diabetes.

Recent work suggests that the key to improving fat metabolism and reducing diabetes risk may lie in the energy producing organelles called mitochondria. Our lab members developed a chemical 'cocktail' that mimics the effects of exercise in muscle cells grown in the lab. Stimulating muscle cells for just one hour a day nearly doubled fat metabolism and made the muscle cells more responsive to insulin. At the same time, there was an increase in the number of mitochondria.

There may be a connection between defects in the production of mitochondria and insulin sensitivity. For example, the muscle tissue of patients with type 2 diabetes have damaged mitochondria, and muscle tissue in young persons with a family history of type 2 diabetes have reduced numbers of mitochondria. One theory is that insulin resistance comes first - leading to defects in the production of mitochondria. However, we wanted to know

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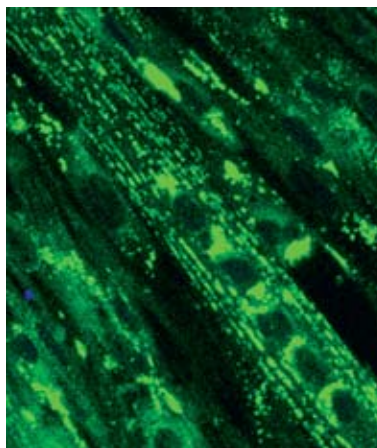
Steven R. Smith, M.D.

RESEARCH TEAM:

Hui Xie, M.Ap.Stat., Magdalena Pasarica, Ph.D., Olga Sereda, M.D., Cedric Moro, Ph.D., Sudip Bajpeyi, Ph.D., Shantele Thomas, B.S., Ivan Pavlov, B.S.

if turning on the formation of mitochondria first might lead to improved insulin action.

We treated cells from healthy young donors with a cocktail of chemicals that turned on signaling molecules in the cells - signals that are known to be activated during exercise.



Cells stained with Bodipy 488; lipid droplets inside the muscle cells are green. Endocrinology lab researchers developed a cocktail that works like exercise to turn on the formation of mitochondria in these cells. The cocktail also re-organized the lipid droplets into a "pearls-on-a-string" pattern, and the cells were able to burn fat more effectively. Mitochondria are the powerhouses of cells and known to be defective in diabetes. These cells also became more insulin sensitive.

This exercise-like cocktail increased the ability of the cells to burn both fat and glucose. We also found a significant positive correlation: cells with more mitochondria burned more fat and were more insulin sensitive. This gives obesity researchers a new model system to study fat metabolism in muscle tissue and test new drugs to turn on mitochondrial biogenesis and fat oxidation. The exercise mimetic cocktail will help us dissect the pathways linking low mitochondrial content to insulin resistance in type 2 diabetes.

Research in this lab is supported by grants from the U.S. Department of Agriculture, the National Institutes of Health, the Department of Defense, Takeda Pharmaceuticals, Novartis, and Orexigen.

John S. McIlhenny Skeletal Muscle Physiology Laboratory



Anthony E Civitarese, Ph. D.
Instructor

FACULTY:

Anthony E Civitarese, Ph.D. and Eric Ravussin, Ph.D.

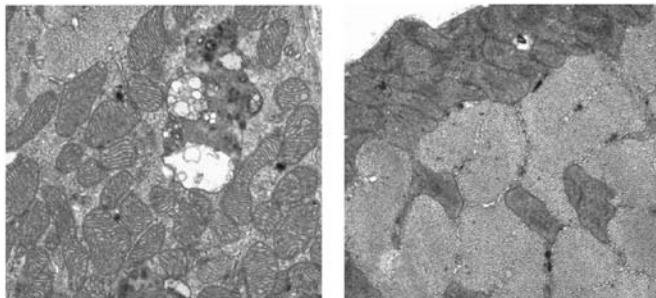
RESEARCH TEAM:

Jeremy Ravussin, B.S., and Lauren Brown, B.S.

Focus – 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 (T2DM), and some muscle defects that occur with aging (sarcopenia and oxidative stress).

Central to these investigations are:

1. The inner mitochondrial rhomboid protease named PARL. PARL is a mediator of mitochondrial dynamics and cellular apoptosis. In addition, the PARL gene is down regulated in insulin resistance states including T2DM and aging. A down regulation in PARL protein in skeletal muscle results in lower mitochondrial energetic and impaired mitochondrial morphology (see figure below) and lower glucose metabolism.
2. The adiponectin/AdipoR axis. The adiponectin



mCK-CAR-PARL (ADV+)

mCK-CAR-PARL (-)

Electron micrograph (x20,000) of alter inner mitochondrial cristae morphology in mck-CAR-PARL(-) transgenic mice.

signaling system is known to be a potent regulator of lipid and glucose metabolism with both adiponectin and its receptors (AdipoR1 and AdipoR2) being down regulated in insulin resistant states. Work from the Civitarese/Ravussin laboratory has investigated the relationship between adiponectin signaling and mitochondrial function in 3 complementary settings: in muscle from humans who are predisposed to develop T2D; in muscle from insulin resistant adiponectin *KO* mice and in primary cultures of human myocytes. We have shown that the adiponectin axis (ligand and receptors) exerts potent anti-diabetic effects

by inducing AMPKK/AMPK phosphorylation, increasing mitochondrial number and oxidative metabolism and reducing the generation of reactive oxygen species (ROS). This work was published in the July 2006 issue of *Cell Metabolism*. Currently, the lab is investigating the role of Osmotin, an “adiponectin-like” plant protein which displays AdipoRs agonist properties.

3. The effects of calorie restriction (CR) on mitochondrial energetics in humans. CR delays the rate of aging and prolongs average and maximum lifespan in many species. The mechanisms underlying aging retardation by CR are poorly understood. However, it has been suggested that they may involve a decrease in cellular oxygen consumption and ROS production. Improved metabolic efficiency may play an important role in the response to CR. The Civitarese/Ravussin laboratory has described for the first time the effects of CR on mitochondrial energetics in the skeletal muscle of healthy non-obese humans. It shows that CR lowers whole body energy expenditure (metabolic adaptation), in parallel to a surprising induction in mitochondrial biogenesis with a concomitant up-regulation of the transcription of PGC1 α , SIRT1, eNOS and the PARL genes and a decrease in DNA damage. Since the increased mitochondrial mass was not accompanied by an increase in mitochondrial enzyme activity, we propose that CR induces biogenesis of “efficient” mitochondria as an adaptive mechanism which in turns lower oxidative stress. This work was published in the March 2007 issue of *PLOS Medicine*.

Research in this lab is supported by grants from NIH (R01 AG20478, DK0724760) and various pharmaceutical corporations.

Nuclear Receptor Biology Laboratory



Thomas P. Burris, Ph.D.
Professor

FACULTY:

Thomas P. Burris, Ph.D., Professor

RESEARCH TEAM:

Yongjun Wang, Ph.D., M Rogers, M..S, Ying Ling, M.S.

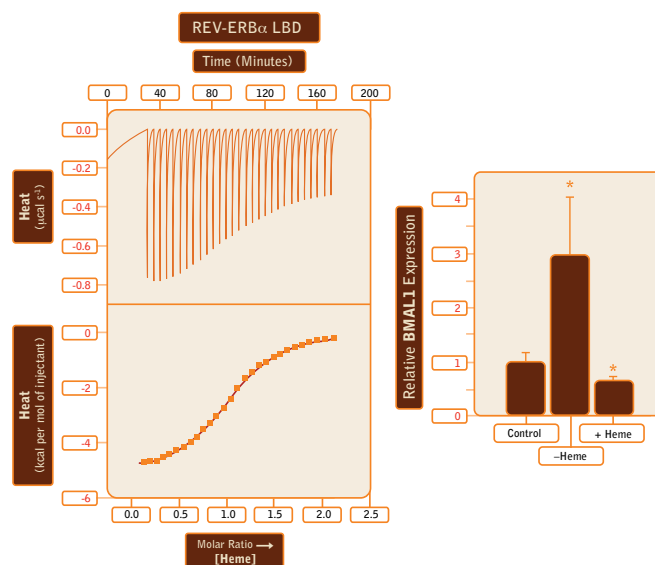
Focus — to delineate the biochemical regulatory pathways utilizing nuclear hormone receptors as sensors of metabolic intermediates.

Members of the nuclear receptor (NR) superfamily regulate a wide range of physiological functions including growth and development, reproduction, inflammation and metabolism. These receptors typically respond to hydrophobic signaling molecules such as steroid hormones, lipophilic vitamin derivatives, and lipophilic dietary metabolites and directly regulate the expression of target genes. Our laboratory is particularly interested in how the NRs that respond to dietary metabolites regulate metabolic function and how these NRs may be targets for drugs used to treat and prevent metabolic disorders such as diabetes and obesity.

Previously, we discovered that the receptors for oxidized cholesterol derivatives (LXR α and LXR β) and bile acids (FXR) regulate carbohydrate metabolism and activation of these receptors by synthetic agonists resulted in improvement of diabetic symptoms. Our most recent work on LXRs has focused on characterization of novel pathways for LXR to regulate gene expression. Using chromatin immunoprecipitation followed by microarray technology (ChIP/chip) we have identified numerous LXR target genes including a unique negative LXR response element. This has led to the discovery that LXR directly regulates cholesterol biosynthesis in a negative feedback loop mechanism. Our data suggest that one may be able to reduce cholesterol biosynthesis with drugs that target LXR.

Approximately one-half of the NR superfamily are orphan receptors that have no identified ligand. We continue to look for the physiological ligands for receptors that have a known role in metabolic regulation. Several of these include REV-ERB α , REV-ERB β , ROR α , ROR β , and ROR γ all of which are known to regulate lipid metabolism as well as the mammalian circadian rhythm. Recently we identified heme as the physiological ligands for the REV-ERBs. Heme binds directly to the ligand binding domain of these two receptors and regulates their ability

to interact with transcriptional corepressors such as NCoR. Modulation of heme levels affects the ability of REV-ERB α to repress its target genes such as *Bmal1* and *Elovl3*. *Bmal1* is a crucial component of the mammalian clock and thus our discovery that heme modulates the ability of REV-ERB α to regulate this gene suggests that we may be able to design synthetic ligands that alter the normal circadian rhythm in humans. This may lead to improved treatments for metabolic disorders as well as for depression, sleep disorders, and cancer.



Discovery of the physiological ligand for the orphan nuclear hormone receptor, REV-ERB. Isothermal titration calorimetry demonstrates the direct binding of heme to the ligand binding domain of REV-ERB. Cell-based experiments demonstrate that heme regulates the REV-ERB-dependent regulation of the target gene **BMAL1**, a critical gene involved in regulation of metabolism and the circadian rhythm.

Research in this laboratory is supported by grants from the National Institutes of Health, PheneX Pharmaceuticals AG, Eli Lilly and Company and Invitrogen, Inc.

Protein Structural Biology



Indu Kheterpal Ph.D.
Assistant Professor

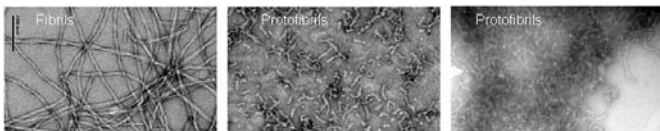
Focus — to study protein expression and protein structure related to disease biology.

Structure of proteins, misfolded proteins and protein complexes.

Protein aggregation and abnormal tissue deposition of normally soluble proteins are common features of >25 amyloid-associated diseases (e.g. Alzheimer's disease (AD), Parkinson's disease, diabetes). Many non-pathogenic proteins can also be induced to form the amyloid structure *in vitro*. Despite the dissimilarities in primary, secondary and tertiary structure of these polypeptides, all amyloid fibrils contain an extensive β -sheet network and are 6-10 nm in diameter and several μ m in length. These common characteristics of amyloid structure make it very interesting in the perspective of human disease and concerning fundamental aspects of protein folding/misfolding.

We are developing and applying hydrogen/deuterium (H/D) exchange and electrospray ionization-mass spectrometry (ESI-MS) methods to identify and characterize molecules aimed at slowing, preventing or reversing A β amyloid formation in AD. We are also applying H/D exchange methods to probe the secondary structure of islet amyloid polypeptide (IAPP) fibrils associated with Type 2 diabetes.

Protein aggregates are heterogeneous, large and non crystalline, and therefore, not amenable to conventional methods of high-resolution structure determination (X-ray crystallography and solution NMR). Thus, the



Electron micrograph of negatively stained images of fibrils and two different protofibril fractions. Protofibrils are transient structures observed during *in vitro* formation of mature amyloid fibrils and have been implicated as the toxic species responsible for cell dysfunction and neuronal loss in Alzheimer's disease (AD) and other protein aggregation diseases.

FACULTY:

Indu Kheterpal, Ph.D.,

RESEARCH TEAM:

Madhavi Minnamreddy, M.S.; Ginger Ku, M.S.; Liana Coleman, B.S.; Jordan McGee

H/D exchange methods provide very valuable structural information. We have developed H/D exchange-MS methods to study the structure of amyloid fibrils and protofibrils and have used them extensively to investigate the structure of amyloid fibrils associated with AD. This methodology has provided insight into the structures of monomers, protofibrils, and fibrils and into the structural relationships among these states.

Proteomics: tools and applications

Understanding the role and mechanism of botanical and nutritional treatment in modulating insulin sensitivity

We are using quantitative proteomic and phosphoproteomic approaches to evaluate the mechanism by which botanical and nutritional interventions improve insulin sensitivity. A variety of botanical and nutritional treatments are postulated to modulate insulin action; however, the exact mechanism by which these extracts modify glucose and insulin levels is not clear. In collaboration with Dr. Cefalu of PBRC, we are using two dimensional (2D)-gel-based and 2D-liquid chromatography-based technologies in conjunction with MS to map modifications in protein expression and phosphorylation levels due to the botanical and nutritional treatments in skeletal muscle cells in culture. These studies will provide essential data to understand the mechanism of action of botanical extracts and nutritional treatments in improving insulin sensitivity at the molecular level and will lead to a better understanding of the insulin signaling cascade.

MS based proteomics is a very powerful tool and allows detection of 100's to 1000's of proteins and site-specific post-translational modifications. These methods do not require any prior knowledge of proteins and provide molecular level information.

Research in this laboratory is supported by grants from the American Federation of Aging Research, the Louisiana State University Board of Regents and the Pennington Medical Foundation.

Maternal Biology



Claudia T. Kappen, Ph.D.
Professor, Peggy M. Pennington Cole Chair in
Maternal Biology & Risk of Obesity



Claudia Kruger, Ph.D.
Instructor

FACULTY:

Claudia T. Kappen, Ph.D., Claudia Kruger, Ph.D.

RESEARCH TEAM:

Jacie MacGowan

Focus — to understand the impact of maternal nutrition on gene function in embryonic development and the consequences for disease.

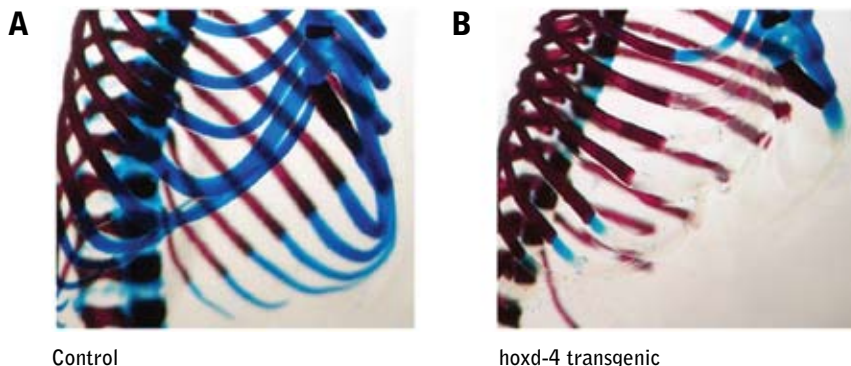
The development of the embryo is governed by a set of genes that control how and where organs, tissues and cells form. These genes are key regulators in embryonic development and any perturbation has the potential to result in birth defects. The risk for birth defects is elevated in the case of mutations in these genes or in the presence of maternal malnutrition or metabolic disease. Our overarching goal is to understand the interaction of genetic and environmental factors in embryonic development, and to prevent birth defects through optimal maternal nutrition during pregnancy. Adverse exposures in utero may also predispose to adult disease, such as obesity, diabetes and cardiovascular disease, and these long-term consequences are a second focus of our research program.

We have created several mouse models for birth defects in the skeleton. In the *Hoxb6* knockout mouse, the development of vertebra and bones in the neck-chest transition zone are altered in that several vertebrae have abnormal shape and the first pair of ribs is absent. These defects are visible at birth and are dependent in severity on the strain of mouse used, indicating that there is a genetic interaction between *Hoxb6* and other genes in the genome. By using whole-genome scans and genetic backcrossing, we are attempting to identify such interacting genes.

In a second model of defective skeletal development, *Hoxd4* transgenic mice, the ribs do not develop properly, due to a defect in cell differentiation and cartilage formation (see Figure). We have shown that supplementation of the mother's diet with folic acid during the pregnancy is able to prevent these defects. The underlying molecular mechanisms are unclear at present; our research suggests that there are potential interactions with extracellular matrix-degrading enzymes (e.g. Mmps) and signaling molecules (e.g. Wnts).

Maternal diabetes during pregnancy predisposes to several types of birth defects, including skeletal defects, heart defects and neural tube closure defects, which are also preventable by folic acid supplementation. We have identified over 100 genes that are altered in mouse embryos enduring diabetic conditions, and we are using genetic methods to define the interaction of maternal metabolism with function of these genes. A second focus of this project is on the role of the placenta in nutrient supply under conditions of maternal diabetes. With prevalence of diabetes in women of child-bearing age increasing in the US, it is important to not only provide a more refined set of diagnostic criteria for birth defects risk, but also to develop strategies for prevention of complications of an increasing number of pregnancies affected by diabetes.

Research in this laboratory is supported by grants from the National Institutes of Health [HD037804, AR052731] and the Pennington Medical Foundation.



Control

hoxd-4 transgenic

A: Rib cage from a normal newborn mouse stained with Alcian Blue (cartilage) and Alizarin Red (bone); **B:** Rib cage from a *Hoxd4* transgenic mouse with incomplete differentiation of cartilage (notice absence of Alcian Blue). This defect is preventable with dietary folate supplementation during critical stages of pregnancy.

Epigenetics and Nuclear Reprogramming Laboratory



Kenneth J. Eilertsen, Ph. D.
Associate Professor

FACULTY:

Kenneth J. Eilertsen, Ph.D.

RESEARCH TEAM :

Heather Kirk-Ballard, M.S., Rachel Power, Ph.D., Jong-Seop Rim, Ph.D., Christian Barnes, B.S., Lettie Harkins, B.S.

Focus — 1) to understand how the epigenome is established in early development. 2) to understand how perturbations to the developing epigenome may contribute to disease. 3) to learn how to modify the epigenome to enable the development of technologies such as somatic cell nuclear transfer (or cloning) and/or generating autologous sources of therapeutic stem cells.

Epigenetics refers to features of chromatin (DNA and associated proteins) that are heritable over rounds of cell divisions. This heritability however, is not associated with an organism's DNA sequence. Epigenetic features play significant roles in cellular differentiation, allowing cells to maintain unique functional characteristics despite sharing the same DNA sequence. For most mammals, establishing epigenetic features that will serve as the basis to distinguish cell types begins immediately after fertilization. As examples, after fertilization, mice, cattle and humans undergo a wave of DNA demethylation (removal of a methyl group from specific DNA nucleotides) followed by a wave of remethylation (addition of a methyl group to specific DNA nucleotides). These waves of demethylation and remethylation are thought to be required for normal embryonic and tissue development. Perturbations to these highly coordinated processes may be detrimental to development, differentiation and long-term health of an organism. The biological pathways that regulate these processes, however, are poorly understood.

My lab attempts to identify pathways that regulate these events. We use somatic cell nuclear transfer (or cloning) and embryo culture using cattle and mice as model organisms. Our data indicate the majority of cattle clones fail to proceed beyond early stages of development. Those that survive to birth are typically abnormal, often characterized by large body and organ sizes. We have learned that cattle clones are characterized by aberrant waves of demethylation and re-methylation which result in alterations of methylated DNA. The molecular basis for altered DNA methylation is unclear, but we have learned that several genes that control methylation reactions of all biological molecules within cells are mis-expressed in cattle clones when compared

to normal embryos. Similarly, mouse embryos produced by fertilization but transferred to culture aberrantly express the same or closely related genes. These findings are significant because humans conceived using assisted reproductive technologies (ART) such as in vitro fertilization (IVF) are routinely exposed to culture and have unusually high incidences of epigenetic-based diseases. Examples include Beckwith-Weidemann and Angelman syndromes, and suboptimal culture environments may play a role in increasing the incidences of these diseases.

I am also interested in commercializing scientific discoveries and contributing to the economic development of Baton Rouge and Louisiana. To that end I have started a biotechnology company called NuPotential, Inc. The company's mission focuses on modifying the epigenome of fully differentiated cells to restore differentiation potential. In theory, it is possible to harvest skin cells from a donor and 'reprogram' them to differentiate into multiple tissue types. To accomplish this reprogramming, epigenetic features that define the skin cell must be erased. NuPotential accomplishes reprogramming by treating differentiated cells with combinations of small molecules, proteins, interfering RNA and specialized culture media.

Research in this laboratory has been supported by the Pennington Medical Foundation, the Clinical Nutrition Research Unit and the Botanical Research Center.

Regenerative Biology Laboratory



Barbara Kozak, Ph. D.
Assistant Professor

FACULTY:

Barbara Kozak, Ph.D.

RESEARCH TEAM:

Jaroslawn Staszkiwicz, D.V.M., Ph.D., Jessica A. Manuel, B.S.

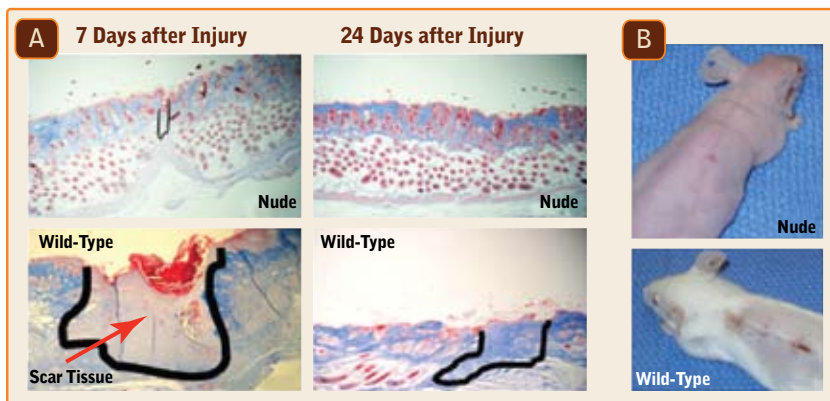
Focus — (1) to understand how tissues and organs can be rebuilt after injury or damage. (2) to investigate commitment of adult stem cells into the adipocyte lineage.

Scar tissues pose a problem of great medical importance, since their excessive formation hinders the functionality of the post-injured tissue following burns, myocardial infarcts and nerve damage. Thus, prevention or reduction of scarring remains one of the major goals of medical research. Regeneration, unlike wound repair, comprises the replacement and restoration of damaged adult organs with tissues of normal architecture and function, and without scar formation. Scarless repair of wounds has been observed during healing of amputations of limbs in amphibians, wounds of mammalian fetuses and, as we have recently shown, in skin wounds inflicted to FOXN1-deficient nude mice. Nude mice are the only adult mammals known to exhibit a skin wound healing process with regenerative features similar to those displayed by amphibians and mammalian fetuses. Extensive studies on regenerative processes in amphibians have revealed that matrix metalloproteinases (MMPs) are indispensable for regeneration. We have found that MMP13 and MMP9 show a bimodal pattern of activity, which takes place in early

and late stages of scarless skin repair in FOXN1-deficient nude mice, strongly resembles the pattern of expression of these proteins occurring during regeneration in amphibians. However, the mechanism by which inactivation of the transcription factor FOXN1 allows a process of scarless repair in nude mice is unknown. We propose to use this unique mouse as a model system to identify the mechanisms of scar formation during wound healing. Our hypothesis is that FOXN1 represses *Mmp13* and *Mmp9* expression during normal scar formation; however, its absence in nude mice leads to up-regulation of *Mmp13* and *Mmp9* with concomitant scarless repair of skin.

Weight gain associated with obesity is characterized by an increase in adipose mass that is achieved by two processes: hypertrophy of existing fat cells and hyperplasia throughout generation of new adipocytes. Since mature adipocytes cannot proliferate, their numbers in adipose tissues increase through recruitment of adipocyte cells precursors (preadipocytes) and/or preadipocyte precursors (progenitor cells and stem cells). However, molecular markers to identify the origin of these precursor cells for the adipolineage remain to be elucidated. Our laboratory has shown that the outer ears of mice contain a population of mesenchymal stem cells (ear mesenchymal stem cells - EMSC).

The EMSC possess the ability to differentiate into adipocytes, osteoblasts, chondrocytes and myocytes in both primary cultures and clonally expanded cell lines. Our recent in vitro studies revealed that a stem cell antigen (Sca-1) enriched population of primary ear cells have a greater capacity to differentiate into adipolineage than Sca-1 depleted. Our present effort is focused on determining whether cell surface protein stem cell antigen-1 (Sca-1) plays a role in differentiation and recruitment of stem cells into the adipolineage.



(A) Histological comparison of wounds from Nude and C57BL/6-wild type mice, 7 and 24 Days after injury. The wounded region is encircled in black. (B) Macroscopic appearance of post-injured animals on Day 7.

Research in this lab is supported by grants from the Pennington Medical Foundation, Health Excellence Fund from the State of Louisiana and National Institutes of Health.

Stem Cell Biology Laboratory



Jeff Gimble, M.D., Ph.D.
Professor

FACULTY:

Jeff Gimble, M.D., Ph.D.

LABORATORY STAFF:

Gang Yu, M.S., Xiyong Wu, M.D., Martin Vidal, D.V.M., Sreedhar Thirumala, M.S., Teddi Hebert, Brian Goh.

Focus — to further the characterization and understanding of adipose tissue, adult stem cells and especially the formation and development of adult stem cells.

The investigators of this lab pursue the following inter-related areas:

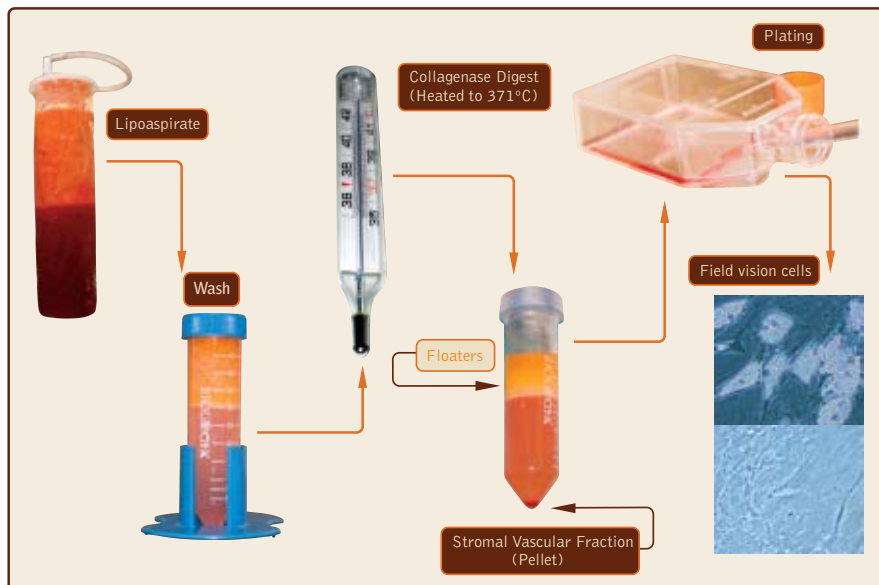
(a) The expansion and characterization of adult stem cells isolated from adipose tissue and bone marrow obtained from both human subjects and experimental animal models. These cells have potential to serve as building blocks for the emerging field of regenerative medicine. Collaborations with Drs. Barry Robert, Ken Eilertsen, Rick Rogers, and other investigators at the Pennington Biomedical Research Center as well as the LSU School of Veterinary Medicine and the Department of Mechanical Engineering are underway.

(b) The circadian biology of adipose tissue, bone, and other metabolically active peripheral tissues. Recent studies have demonstrated that the transcriptional machinery responsible for maintaining circadian rhythms in the brain

exists within bone and fat. The studies are being conducted with in collaboration with investigators at Duke University, LSUHSC-Shreveport, and Hebrew University.

(c) Carcinogenesis. Lipomas and liposarcomas are among the most frequent benign and malignant soft tissue tumors clinically in the U.S. These fatty tumors derive from cells resembling the adipose derived stem cells. Dr. Eilertsen, in collaboration with Dr. Gimble, is using the novel tools he has developed for epigenetic imprinting studies and applying them to the analysis of soft tissue tumors. Investigators at Memorial Sloan Kettering Cancer Center collaborate on this project.

Research in this laboratory is supported by funding from the Clinical Nutrition Research Unit, the Pennington Medical Foundation, and an STTR Phase I Grant from the NIAAMS.



Procedural steps in isolating and expanding adipose derived human stem cells

Ubiquitin Biology Laboratory



Beth Floyd, Ph.D.
Assistant Professor

FACULTY:

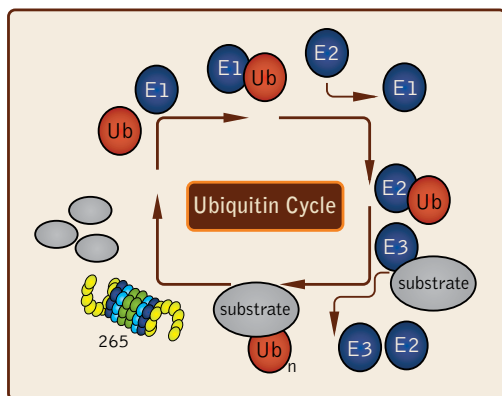
Beth Floyd, Ph.D.

RESEARCH TEAM:

Gail Kilroy, B.S., Harold Boutté, Meredith Soniat

Focus — to understand how adipocyte formation and function is influenced by ubiquitin-proteasome regulation of protein stability and activity.

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



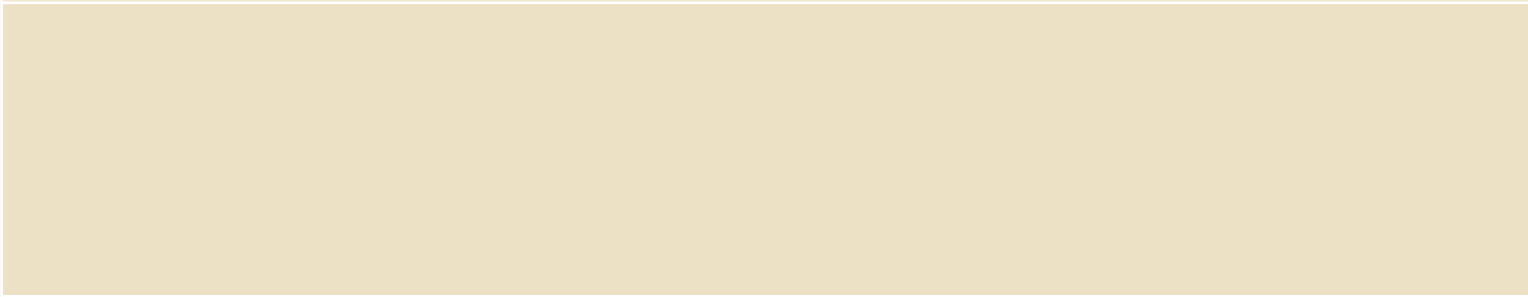
The stability of most intracellular proteins, such as PPAR γ , is determined by the ubiquitin-proteasome system. The ubiquitin-proteasome system is a highly conserved pathway that is responsible for the carefully timed degradation of proteins, making this pathway central to cellular functions. Interaction with this system involves attachment of ubiquitin to the targeted protein via a

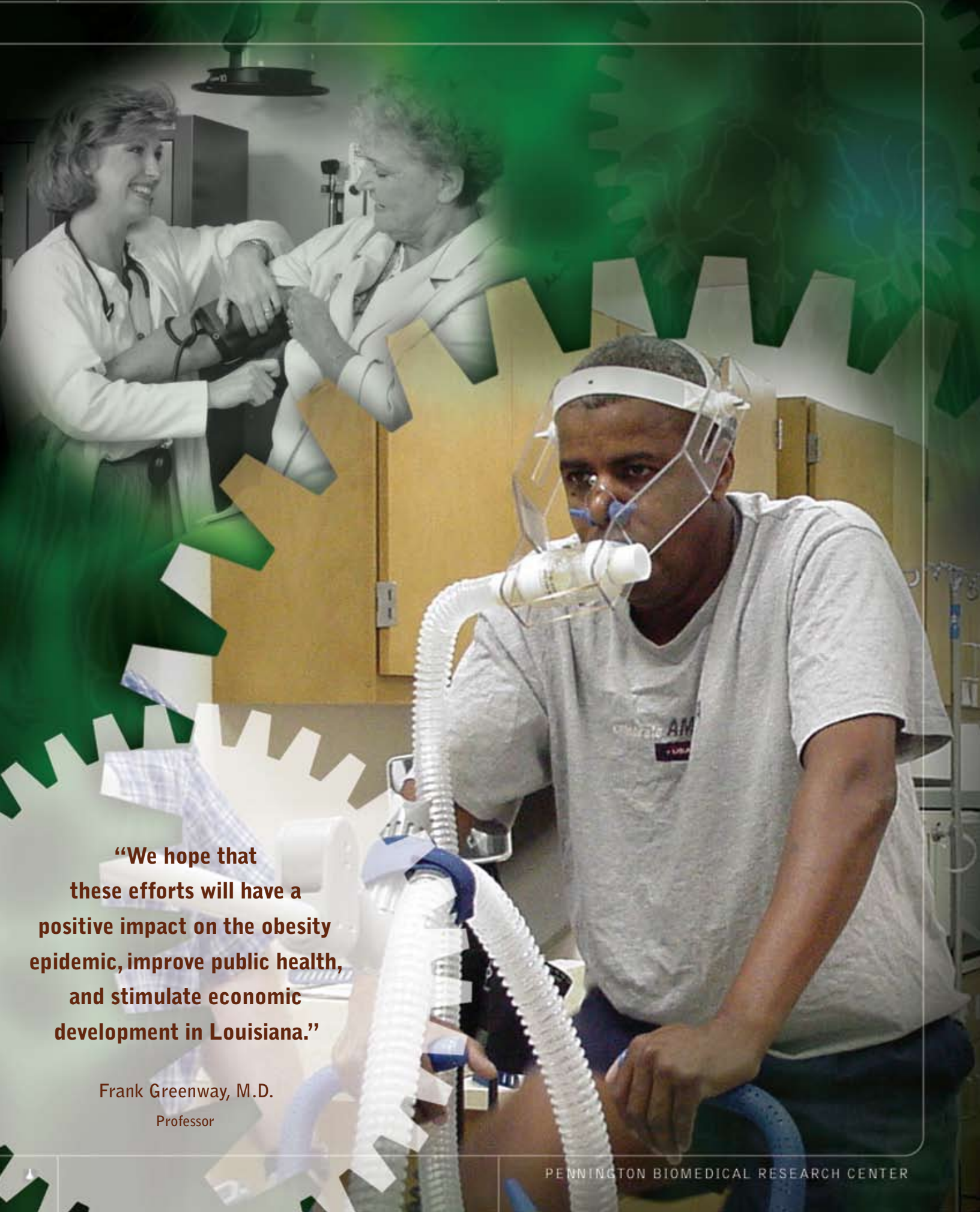
multienzyme cascade, leading to delivery of the protein to the 26S proteasome for destruction. In association with Dr. Jacqueline Stephens, we previously learned that inhibiting the proteasome-dependent degradation of PPAR γ increases PPAR γ activity, indicating disposal of PPAR γ by the ubiquitin-proteasome system regulates PPAR γ activity. To understand the connection between PPAR γ activity and degradation, we are using cellular and molecular approaches to dissect how PPAR γ is recognized by components of the ubiquitin-proteasome pathway.

We have learned that the region of PPAR γ responsible for binding TZDs contains a signal for binding to ubiquitin. This signal can be localized to a small number of amino acids that are known to be required for PPAR γ activity, thus linking activation of PPAR γ to its ultimate degradation. In addition, we found other regions of PPAR γ that are capable of destabilizing an otherwise stable and unrelated protein, suggesting regulation of PPAR γ stability involves complex interactions not limited to the TZD binding region. In collaboration with Drs. William Cefalu and Zhong Wang, we also demonstrated that PPAR γ activity and stability in adipocytes is influenced by resveratrol, a small molecule found in grapes and berries. In addition, resveratrol alters the effect of insulin in adipocytes, raising the possibility that naturally occurring bioactive molecules can affect adipocyte biology via regulation of PPAR γ stability and activity. Finally, in collaboration with Dr. Jeffrey Gimble, we are beginning to use adipose-derived stem cells to develop a human model system to investigate the role of the ubiquitin-proteasome system in regulating PPAR γ and other proteins essential for the development of adipocytes.

As evidence accumulates that modulation of PPAR γ levels, rather than a simple “on-off” model, can profoundly affect PPAR γ activity, these studies may offer insight into future therapeutic targets for the treatment of a range of obesity-related disorders.

Research in this laboratory is supported by grants from the National Institute on Aging and the National Institutes of Health-supported COBRE and Botanical Research Center.





“We hope that these efforts will have a positive impact on the obesity epidemic, improve public health, and stimulate economic development in Louisiana.”

Frank Greenway, M.D.
Professor

Clinical Research Unit Reports

Clinical research at the Center is organized within three areas, each of which has multiple investigators and laboratories.

Behavioral Approaches for the Prevention and Treatment of Obesity

Behavioral Medicine

P. Brantley, V. Myers, H. Roy

Health Psychology

D. Williamson, R. Newton, Jr., T. Stewart

Women's Health, Eating Behavior, and Smoking Cessation Program

P. Geiselman

Ingestive Behavior

C. Martin

Clinical Physiology

Exercise Biology

C. Earnest, T. Church, T. Rankinen

Human Physiology

E. Ravussin, Y. Tchoukalova

Preventive Medicine

T. Church, C. Earnest

Clinical Trials

Diet, Physical Activity, and Behavior Modification Trials

G. Bray, D. Ryan, F. Greenway, S. Smith, A. Gupta

Pharmacology-Based Clinical Trials

F. Greenway, A. Gupta

Behavioral Medicine Laboratory



Phillip J. Brantley, Ph.D.
Professor



Valerie H. Myers, Ph.D.
Instructor



Heli Roy, Ph.D.
Adjunct Associate Professor

FACULTY:

Phillip J. Brantley, Ph.D., Valerie H. Myers, Ph.D., Heli Roy, Ph.D.

RESEARCH TEAM:

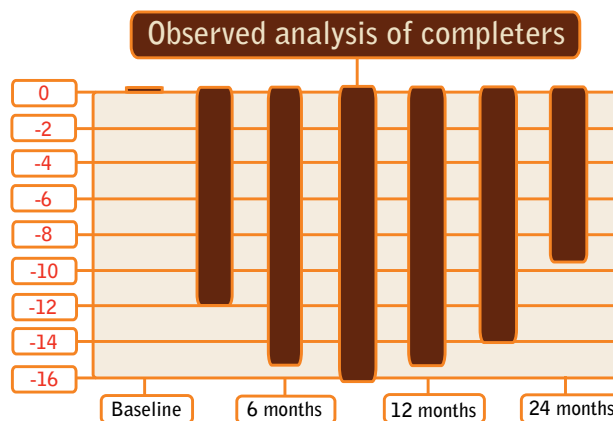
Brooke Barbera, Patti Smith, Dorothy Whitehead Pekmezi

Focus — to understand interactions between biological, behavioral and psychosocial factors that relate to health promotion, risk factor reduction, disease management and adaptation to medical conditions associated with metabolic syndrome, including diabetes and cardiovascular disease.

Weight Loss Maintenance (WLM) is a multicenter, randomized trial comparing strategies for maintaining long-term weight loss in participants who lost at least 4 kg during an initial six-month program (Phase I). We are one of four participating clinical sites (Duke University Medical Center, Johns Hopkins Medical Center and Kaiser Permanente Center for Health Research in Portland, Oregon). Eligibility criteria were overweight/obese and on medications for hypertension and/or dyslipidemia. During Phase I, 1,685 participants entered a behavior-change program of weekly group sessions promoting calorie reduction, increased physical activity, and DASH dietary plan. Individuals who lost ≥ 4 kg were randomly assigned to one of three conditions: 1) PC-Personal Contact intervention (monthly contacts primarily via telephone); 2) IT - Interactive Technology intervention (frequent contacts through a state-of-the-art, interactive Web-based program); 3) a Self-Directed/Usual Care control group. The primary outcome is weight change from the end of the initial weight loss program to the end of the 30-month weight maintenance intervention period (Phase II). We've previously cited results from Phase I. In Phase II, 63% of participants (n=1032) were randomized. Mean weight loss in Phase I was 8.4 kg. At one year post-randomization, 90% of PC participants completed monthly contacts with no apparent gender-race subgroup differences. Eighty percent of IT participants completed monthly log-ins to the website with slightly lower rates among AA females (70%). At 6 months, 96% of outcome data had been collected, and 94% at one year. Analyses of Phase II data are complete along with a competitive continuation submission to continue the trial into a third phase. Successful data collection rates and results were instrumental in securing an administrative supplement grant to begin Phase III. To date, 916

participants have been randomized into Phase III.

The Louisiana Obese Subjects Study (LOSS) is a five-year pragmatic clinical trial comparing obese members of the Louisiana state employees' health insurance program (PI, Donna H Ryan, M.D.). The study will randomize 480 individuals into either intensive medical treatment (n=240) or usual care (n=240) to be delivered in seven primary care clinics across Louisiana. To date, 414 participants have been randomized. The intensive medical intervention comprises three phases: Phase 1: 12 week liquid diet. Phase 2: 4 months of pharmacotherapy, structured diet, and group behavioral counseling. Phase 3: 33 months of weight loss maintenance strategies, including a toolbox approach and group behavioral counseling. Mean weight loss at 12 months is 14.5%. Data collection at year 2 is on-going (see figure).



Mean % Weight Loss in the Intensive Intervention Group

Weight loss for those individuals who have completed at least 1 year of intervention (n=105) is as follows: 81.9% achieved $>5\%$, 70% achieved $>10\%$, 44.8% achieved $>15\%$ and 29.5% achieved $>20\%$. Interim analyses revealed primary care clinics with no prior experience in weight loss could achieve acceptable weight loss results.

Research in this laboratory is supported by grants from the National Heart Lung Blood Institute (U01 HL068955) and the Louisiana Office of Group Benefits.

Health Psychology Laboratory



Donald Williamson, Ph.D.
Professor



Robert Newton Jr., Ph.D.
Assistant Professor



Tiffany Stewart, Ph.D.
Instructor

FACULTY:

Donald Williamson, Ph.D., Robert Newton Jr., Ph.D., Tiffany Stewart, Ph.D.

RESEARCH TEAM:

Robin Barnes, Sandra Coulon, B.S., Allison Davis, M.A., Megan Franklin, Helen Guay, M.A., RD, Hongmei Han, M.Ap.Stat., Alicia Hymel, B.S., John Lambert, A.S., Laura LiBassi, Sandra May, M.S., LDN, RD, Matt McGucken, B.A., Gina Pennington, RD, Shelly Prince, M.S., LDN, RD, Kristi Rau, Alicia Sample, RD, Michael Sclafini, Nakisha Singleton, MPH, Melanie Spinks, B.A., Heather Walden, M.S., Jeff Wiggins

Focus — The Health Behavior Research Group conducts research on behavioral approaches for the prevention and treatment of obesity and related metabolic disorders. This research involves testing the efficacy of community-based, internet-based, and clinic-based interventions for changes in health behaviors.

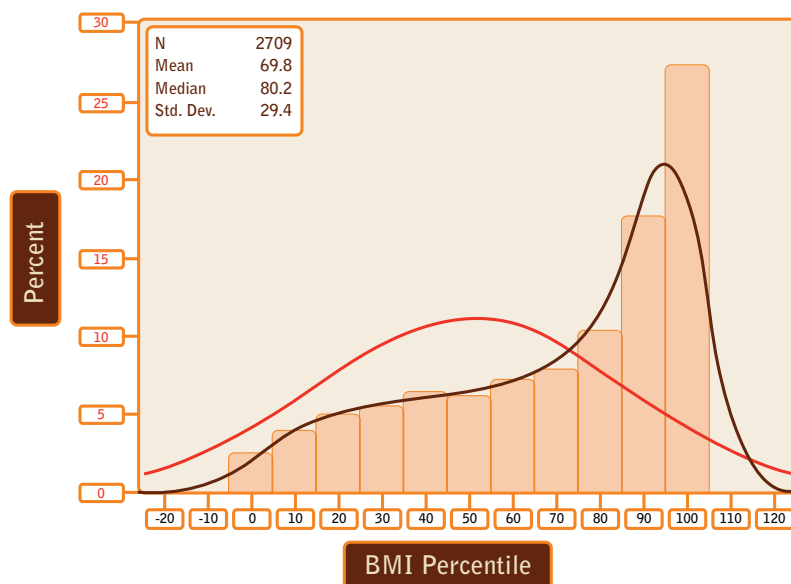
LA Health: This study is a collaboration between the Louisiana Public School System, the Louisiana Board of Regents, and the Pennington Biomedical Research Center to address the childhood obesity problem. This cluster randomized controlled trial tests the efficacy of two school-based prevention programs (combination of primary and secondary prevention and primary prevention alone) that are designed to prevent weight gain in children initially enrolled in grades 4 to 6 over a three-year period. The LA Health project is the first statewide obesity prevention program for children developed by PBRC. The baseline (fall 2006) findings pertaining to the extent of obesity in a sample of 2,709 students from rural communities in Louisiana is shown in Figure 1.

Military Health Behaviors: Promotion of Healthy Weight

and Fitness in Career Personnel: Initiated in May 2003, this study has two primary aims: (1) development of an environmental/internet-based intervention to promote healthy weight and physical fitness, and (2) tests of efficacy for weight management and consumer satisfaction with the environmental/internet-based intervention in a single population, i.e., soldiers at Fort Bragg, N.C. During Phase 1 of this study, the architectural design of the internet-based intervention was developed. In July 2006 we initiated Phase 2, during which the evaluation of the intervention will be completed.

Weight Measurements and Standards for Soldiers: This study is conducted with U.S. Army Reservists of the 94th Regional Readiness Command in New England. The focus of this three-year study is to test the efficacy of an environmental/internet-based intervention to increase health risk communication and promote healthy body weight /fatness and physical performance.

Research in this unit is funded by the National Institutes of Health, Department of Defense, and United States Department of Agriculture.



This graph shows the distribution of BMI of the Louisiana sample (in terms of percentile scores) in black and the expected sample norms from Centers for Disease Control in red. The BMIs for children from Louisiana are highly skewed toward extreme obesity. In fact, using standard definitions for childhood obesity, 18 % of the sample is classified as obese and an additional 27 % are classified as overweight. Thus, 45% of the LA Health sample is significantly overweight and needs to lose weight (one of the objectives of the LA Health study).

Women's Health, Eating Behavior and Smoking Cessation Program



Paula J. Geiselman, Ph.D.
Associate Professor

FACULTY:

Paula J. Geiselman, Ph.D.

RESEARCH TEAM:

Megan Apperson, M.A., Amanda Manning, M.A., Michael Businelle, Ph.D., Kelly Keeton, B.S., Megan Lipe, B.S., Y'annika Edwards, Netosha MacDonald, B.S., and Amy Tedder.

Focus — The objective of this laboratory is to study the robust role of fat and other macronutrient intake and fat preferences in the control of appetite and body weight, especially in pre- and post-menopausal women following smoking cessation..

We developed the Geiselman Macronutrient Self-selection Paradigm © (MSSP) and the Geiselman Food Preference Questionnaire © (FPQ) for the accurate assessment of fat and other specific macronutrient intake and fat preference. These novel instruments are designed to vary fat content significantly and systematically with sugar, complex carbohydrate, and protein content in a battery of foods in which fat is commonly consumed in the United States. The MSSP and the FPQ have strong test-retest reliability and have been validated against long-term macronutrient intake. These instruments were developed to include food stimuli that are appropriate for lean, obese, and post-obese males and females and individuals with eating disorders. Foods included on the MSSP and the FPQ are among the top sources of fat for Caucasian and minority men and women. These instruments are being used in a number of projects at the PBRC. The FPQ is also being used at other institutions.

Although significantly increased food intake has been implicated as the principal factor in postcessation weight gain, the literature on the effects of smoking cessation on specific macronutrient selection following smoking cessation has been highly equivocal. Increases in specific macronutrients, to the exclusion of other macronutrients, have been reported for total carbohydrate consumption, sugar consumption, fat consumption, and protein consumption. Other studies have reported that no macronutrient specificity is associated with postcessation hyperphagia. However, previous investigations of macronutrient specific changes in food intake following smoking cessation have had significant methodological problems. Until now, no studies have assessed postcessation changes in specific macronutrient intake in a validated and reliable macronutrient self-selection paradigm. Women were tested with our MSSP and FPQ while still

smoking and then were enrolled in a two-week smoking cessation program. At one-month postcessation tests were repeated. Both pre- and post-menopausal women showed a postcessation increase in total caloric intake due to an increase in high-fat/high-sugar foods. Foods that are high in both fat and sugar content are most likely to be associated with hyperphagia and weight gain and, therefore, may contribute to the postcessation weight gain that is observed in many women. These results have generated testable hypotheses of pharmacologic interventions that may be effective in the control of the above-reported postcessation increase in appetite for high-fat/high-sugar foods.

The following studies at PBRC are using or have recently used the MSSP and the FPQ: Differences in macronutrient self-selection in lean, obese, and post-obese women (Geiselman, PI); Substrate oxidation and post-exercise food selection in lean and obese women and men (Geiselman, PI); Food intake in perimenopause and menopause in African-American and Caucasian women (Geiselman, PI); Effects of consuming mycoprotein, tofu or chicken upon subsequent eating behavior, hunger, and satiety (Williamson, PI); Primary care office management of obesity (P. Martin, PI); Effects of chromium picolinate on food intake and satiety (Anton/Williamson, PI); Effects of stevia on food intake, satiety, and eating attitudes in lean and overweight adults (Anton/C. Martin, PI); and Effects of chromium picolinate on food intake, satiety, and eating attitudes in overweight women with food cravings (Williamson, PI).

Research in this unit is supported by a grant from the Bristol-Myers Squibb Foundation, Inc.

Ingestive Behavior Laboratory



Corby K. Martin, Ph.D.
Assistant Professor

Focus — to investigate behavioral, physiological, psychological, and environmental factors that regulate the food intake of humans.

The Ingestive Behavior Laboratory conducts research to understand how food intake is regulated and to identify and test the efficacy of novel interventions to reduce food intake and promote weight loss. An additional aim of the Ingestive Behavior Laboratory is to develop and validate novel technology and methods to measure food intake in laboratory and free-living conditions.

The Ingestive Behavior Laboratory includes three rooms equipped with Universal Eating Monitors that continuously and covertly record food intake during food intake tests. During these tests, subjective ratings of appetite are collected using a computer application that prompts participants to rate appetite using Visual Analogue Scales. These data are used to examine the effect of interventions on subjective levels of satiety and food intake. A recent study conducted in the Ingestive Behavior Laboratory demonstrated that a widely accepted behavioral intervention for reducing food intake (i.e., slowing eating rate during meals) only reduced the food intake of men, but not women (graph at right). This study also demonstrated that slowing eating rate during the last half of the meal, rather than slowing eating rate during the entire meal, resulted in increased ratings of satiety, even after correcting satiety ratings for the amount of food consumed. These findings have direct implications for delivering more effective behavioral weight loss interventions. The Ingestive Behavior Laboratory also tests medical treatments for reducing food intake, including pharmacological and herbal compounds, and medical devices. For example, we recently demonstrated that an intragastric balloon effectively reduced food intake and decreased body weight.

Novel and technologically advanced methods are being developed in the Ingestive Behavior Laboratory to measure the food intake of free-living people. We developed and tested the ability of the Remote Food Photography Method (RFPM) to accurately estimate food intake in free-living

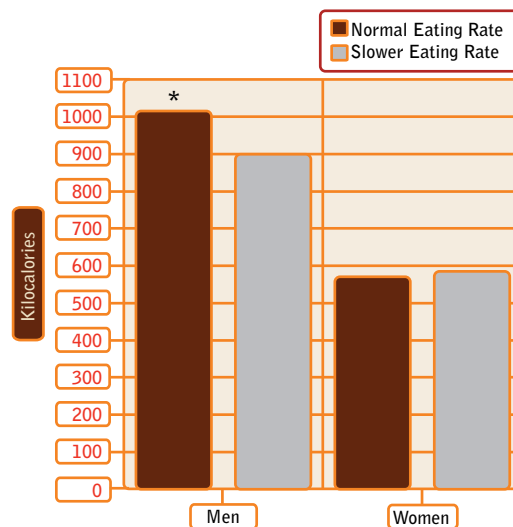
FACULTY:

Corby K. Martin, Ph.D

RESEARCH TEAM:

Sandra Coulon, B.S., Michael Sclafini, B.S.

conditions. The RFPM consists of a camera-enabled cell phone that participants use to take photographs of their food selection and plate waste. These photographs are sent to the researchers via a wireless network and energy (kilocalorie) and macronutrient intake is estimated by trained Registered Dietitians who utilize a customized computer application. Initial tests of the accuracy of this method indicate that it underestimates food intake by approximately 5% and this error variance does not differ across food intake levels. Compared to existing methods, the RFPM provides marked improvement in accurately measuring food intake in free-living conditions and providing people with near “real-time” feedback about their dietary intake. Ongoing research aims to improve the RFPM by developing and testing a semi-automated computer application that estimates food intake using advanced computer imaging algorithms. Additionally, our research includes the use of accelerometry to collect data on participants’ energy expenditure, which allows us to investigate both sides of the energy balance equation.



Research in this Laboratory is supported by the National Institutes of Health and the Clinical Nutrition Research Unit of Pennington Biomedical Research Center.

Exercise Biology Laboratory



Conrad Earnest, Ph.D.
Assistant Professor

FACULTY:

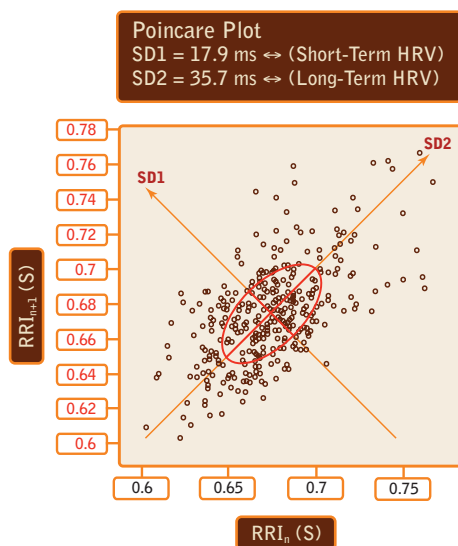
Conrad Earnest, Ph.D., Tim Church, M.D., MPH, Ph.D.;
Tuomo Rankinen, Ph.D.

Focus — to understand the metabolic effects of exercise and nutrition on metabolism, obesity, and fatigue is it relates to and performance and recovery.

Exercise clearly improves health and attenuates the effects of many diseases including obesity, diabetes, cardiovascular disease, cancer and depression. The underlying fact is that exercise positively affects a constellation of mechanisms within the body, and is one of the few interventions that can improve multiple cellular, circulatory, musculoskeletal and genetic physiological systems simultaneously. Our goals are to explore the mechanisms that explain the benefits associated with exercise training.

We are currently examining the relationship between cardiovascular exercise and autonomic function system. Autonomic function – or the balance between the sympathetic and parasympathetic nervous system – is strongly linked to mortality, diabetes and insulin resistance, where the root mechanisms for dysfunction are heavily influenced by obesity and physical inactivity. Our published data supports the hypothesis that exercise improves autonomic function in sedentary, over-weight, postmenopausal women who undertake an exercise program. In this same population, we also observed that when autonomic

function improves so to does insulin. These are important findings for women in menopause or who are postmenopausal as autonomic function is, in part, modulated by estrogen. Estrogen may be



one of the reasons for the low prevalence of cardiovascular disease protection in women prior to menopause. Thus, exercise positively affects autonomic balance after menopause at a time when risk factors for disease are increasing in sedentary women.

We are also examining the influence of varied doses of exercise (intensity and duration) in populations with pre-diabetes and type 2 diabetes. Evolving exercise research shows that short bouts of “interval exercise” produce greater changes in exercise capacity, mitochondrial biogenesis, enzymatic markers associated with glucose regulation, levels of peroxisome proliferator activator protein- γ co-activator1 α (PGC-1 α), fat oxidation, body composition and quality of life than traditional “aerobic” training. Also, a recent report demonstrated that interval training, though typically an exercise technique for athletes, was more effective than traditional aerobic training in 75-year-old patients with stable heart disease.

We are also exploring the role of oxidative stress as it relates to exercise. Oxidative stress in response to unaccustomed exercise may significantly alter mitochondrial function, specifically oxidative metabolism. ^{31}P NMR is an established method to non-invasively quantify oxidative metabolism via phosphocreatine (PCr) recovery kinetics. The aim of our exploratory experiments is to develop a model system for the non-invasive measurement of mitochondrial function in exercise-trained individuals using ^{31}P NMR. Our long-term goal of this project is to implement this model as a tool to evaluate interventions designed to preserve optimal mitochondrial function during periods of exercise training. The aims of our current project are to (1) establish a model of unaccustomed exercise with pre- and post-testing time points for PCr recovery kinetics and then (2) establish an in-magnet exercise protocol for exercise trained individuals that will induce a drop in PCr to allow for a valid modeling of PCr recovery kinetics.

Research in this laboratory is partially supported by grants from the NIH, Edward G. Schlieder Foundation and Gatorade Sports Science Institute.

Human Physiology Laboratory



Eric Ravussin, Ph.D.
Professor



Yourka Tchoukalova, M.D., Ph.D.
Instructor



Leanne M. Redman, Ph.D.
Instructor

FACULTY:

Eric Ravussin, Ph.D., Yourka Tchoukalova, M.D., Ph.D., Leanne M. Redman, Ph.D., Anthony Civitarese, Ph.D.

RESEARCH TEAM:

Jose Galgani, Ph.D., Darcy Johannsen, Ph.D., RD, Lan Chi Luu, Ph.D., Xiaobing Fang, M.A., Stacy Carling, B.S., Jeremy Ravussin, B.S., Christina Rowley, M.S., Mandy Shipp, B.S., RD, Crystal Traylor, WHNP, Sarah Masters, B.S., Jennifer Xhang, B.S.

Focus — to understand the relationships between preadipocyte physiology, adipocyte size and number, adipose tissue expansion in obesity, and metabolic abnormalities. To perform research in aging designed to assess the impact of caloric restriction in non obese humans on biomarkers of longevity. To conduct a population based study of healthy aging called the Louisiana Healthy Aging Study.

An increase in both adipocyte size (hypertrophy) and number (hyperplasty) contributes 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.

We study preadipocyte proliferation, differentiation, and apoptosis in people with normal weight or obesity, with and without type 2 diabetes using primary stromovascular cultures from subcutaneous abdominal adipose tissue obtained by biopsy. We have recently completed a weight loss study in more than 60 individuals with type 2 diabetes mellitus (part of the **LookAHEAD** randomized controlled study) and found that the improvement in insulin sensitivity was associated with a shrinking of adipocyte size.

We are now embarking on an important prospective study led by Dr. Eric Ravussin on the effect of 8-week overfeeding in overweight fat-matched individuals with hypertrophic or hyperplastic adipocytes. The proposed studies have been designed to investigate the respective roles of the adipose and skeletal muscle tissues in the development of ectopic fat depots (muscle and adipose) and insulin resistance. We hypothesize that individuals with both a poor potential for adipose tissue expansion and an impaired function of

muscle mitochondria will have the most deterioration of insulin sensitivity after 8 weeks of overfeeding.

After a first phase of Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (**CALERIE**) designed to assess the feasibility and safety of caloric restriction in non obese humans, we are now conducting a new study of caloric restriction in collaboration with Washington University and Tufts. The study is a multi-center, parallel-group, randomized, controlled trial (RCT). A sample of 250 participants are enrolled, and 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 will be followed over a period of 24 months. A comprehensive set of evaluations are performed prior to initiating the intervention, with follow-up evaluations at Months 1, 3, 6, 9, 12, 18 and 24 after randomization.

The overarching hypothesis of the **Louisiana Healthy Aging Study** is that characteristics of an individual's energy metabolism predispose to long life (or not so long life) and retention of physical and cognitive capacity, promoting the sense of well-being associated with healthy aging.

An exciting development of the Human Physiology Lab is the establishment of a new group led by Dr. Redman focused on **Obesity, Insulin Resistance and Reproductive Function**. The overall focus of the laboratory will be to conduct clinical and basic studies to further the understanding of the interactions between obesity, insulin resistance and reproductive function in women. This is also an important and almost untouched area of research in both women and men.

Research in this lab is supported by grants from the National Institutes of Health (R01DK060412; R01AG029914; U01AG020478; P30DK072476) and a grant from the Coypu Foundation Trust for the John S. McIlbenny Laboratory of Skeletal Muscle Physiology.

Preventive Medicine Laboratory



Tim Church, M.D., M.P.H., Ph.D.
Professor, John S. McIlhenny
Chair of Health Wisdom



Conrad Earnest, Ph.D.
Assistant Professor

FACULTY:

Tim Church, M.D., Ph.D., Conrad Earnest, Ph.D.

RESEARCH TEAM:

Angela Thompson, M.S.P.H., Stephanie Anaya, M.S., Stephanie Pope, B.A., Lauren Sparks, Ph.D., Neil Johannsen, Ph.D., Shannon Cocheam, B.S., Sheletta Donato, M.S., R.D., Ruben Rodarte, M.S.

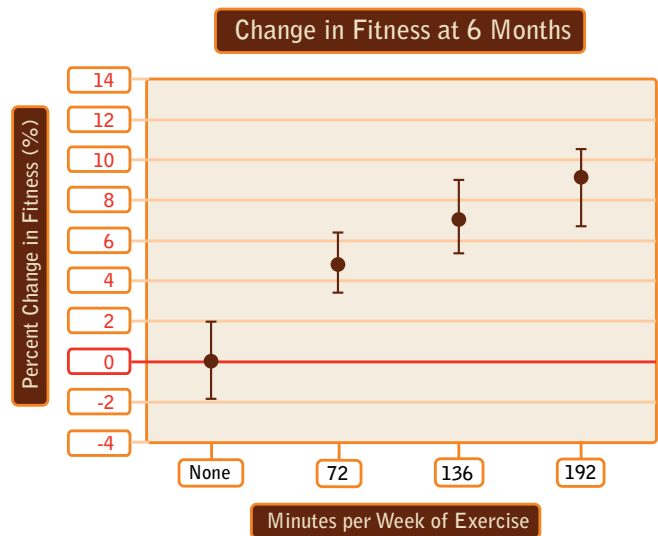
Focus — to understand the role of physical activity in the prevention and treatment of chronic diseases such as diabetes, cancer and depression as well explore strategies to promote healthy aging.

During the time of this report, we established The Exercise Testing Core, refurbished the fitness center into a state-of-the art exercise training facility and have hired an outstanding staff for both facilities. We have also secured a large NIH funded clinical trial entitled *HART-D*. The goal of the Health Benefits of Aerobic and Resistance Training in individuals with type 2 Diabetes study is to compare the effect of weight training alone, and weight training in combination with aerobic training to aerobic training alone on hemoglobin A_{1c} in initially sedentary women and men with type 2 diabetes. Although it is generally accepted that regular exercise provides substantial health benefits to individuals with diabetes, the exact exercise prescription in terms of type (aerobic versus weight training versus both) still remains largely unexplored, particularly as it pertains to weekly blood sugar control assessed by HbA_{1c}. The goal of *HART-D* is to assess HbA_{1c} before and after 9 months of intervention along with a variety of other outcomes.

The Preventive Medicine Group recently had the findings from the Dose Response to Exercise in postmenopausal Women study (DREW) published in the *Journal of the American Medical Association*. DREW is the largest exercise trial ever conducted at one site in women and represents over six years of work. The aim of DREW was to examine the role of different doses of exercise in improving heart disease risk factors in women. A graph depicting the primary results is presented at right. To summarize we found that though more exercise results in greater benefit even the lowest amount of exercise (72 minutes a week) had benefits. We are currently working on manuscripts from the study focused on weight, quality of life and other interesting outcomes. We also recently completed the intervention component of the Inflammation and Exercise trial (INFLAME), which examines the effect of exercise on the inflammatory marker C-reactive protein (CRP). Although

there is no medication currently approved to reduce CRP, there continues to be increased significance placed on CRP as a risk factor for heart disease. Thus INFLAME will provide valuable insight into the therapeutic role of exercise in improving CRP.

Plans for future work include examining the role of exercise in the treatment of fatty liver disease, weight loss for prevention of cancer recurrence in breast cancer survivors and behavior based strategies that promote of healthy aging.



Results from DREW study demonstrating that more weekly exercise is associated with more benefit but even a minimal amount of exercise (72 minutes per week) has benefit

Research in this laboratory is supported by grants from the National Institutes of Health [DK068298, HL075442, HL069870, & AG027529], Coypu Foundation, Edward G. Schlieder Foundation and the Pennington Medical Foundation.

Diet, Physical Activity and Behavior Modification Trials



George A. Bray, M.D.
Boyd Professor

FACULTY:

George A. Bray, M.D., Boyd Professor, Donna H. Ryan, M.D., professor, Frank L. Greenway, M.D., professor, Steven R. Smith, M.D., professor, Alok Gupta, M.D., assistant professor

RESEARCH TEAM:

Nursing, Dietary and Clinic Staff (see page 106)

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 endpoints.

Current Projects

Diabetes Prevention Program (DPP) - Look AHEAD Trial - POUNDS Lost Trial

A. Diabetes Prevention Program

The study compared an Intensive Lifestyle Program versus Metformin or placebo. The Intensive Lifestyle Program produced 7% weight loss and reduced the risk of diabetes by 58%, and responses were similar among men and women of several ethnic groups. Metformin slowed the conversion rate to diabetes by 31%, and produced a small but significant 2.5% weight loss. Among those without metabolic syndrome at baseline, the incidence of the metabolic syndrome at three years was reduced by 41% in the ILS group and 17% in the metformin group. Success in the lifestyle program was higher in individuals with higher initial body weight, lower levels of physical activity and higher self-confidence in their ability to lose weight. Lifestyle intervention reduced risk factors, including hypertension, low HDL and small dense LDL.

B. Look AHEAD (Action of Health in Diabetes) Trial

Look AHEAD is a 16-center randomized clinical trial in overweight and obese patients with type 2 diabetes designed to evaluate the long-term effects of an intensive weight loss intervention on the time to incidence for major cardiovascular events.

An Intensive Lifestyle Intervention (ILI) involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity was compared to a Diabetes Support and Education (DSE) condition.

Participants assigned to ILI lost an average 8.6% of their initial weight versus 0.7% in DSE group ($p < 0.001$). 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 HbA_{1c} dropped from 7.3% to 6.6% in ILI ($p < 0.001$) versus from 7.3% to 7.2% in DSE. Systolic and diastolic pressure, triglycerides, HDL-cholesterol, and urine albumin/creatinine improved significantly more in ILI than DSE participants (all $p < 0.01$).

At 1 year, ILI resulted in clinically significant weight loss in persons with type 2 diabetes. This was associated with improved diabetes control and CVD risk factors and reduced medicine use in ILI versus DSE.

C. Prevention of Obesity Using Novel Dietary Strategies (POUNDS LOST) study.

POUNDS Lost is a trial conducted at the Center and at Harvard School of Public. It is a clinical study of the relative effectiveness of diets varying in fat, protein and carbohydrate for weight loss and long-term maintenance in free-living, overweight men and women who receive a standardized behavior and exercise program. The study compares four diets, differing in fat, carbohydrate and protein composition, on weight-loss and its long-term maintenance. *POUNDS Lost* has randomized 800 overweight or obese people among four diets: (1) low-fat, average protein; (2) low-fat, high protein; (3) moderate fat, average protein; (4) moderate fat, high protein. A low-fat, average protein diet will be the reference diet.

This study enables investigators to test a number of hypotheses about optimal dietary macronutrient strategies in weight loss. Long-term adherence may be related to enhanced diet satisfaction, which may be improved by preserving moderate fat content. Diets higher in protein may be more effective for sustained weight loss, regardless of fat content, because of effects on satiety or metabolic rate.

Research in this unit is supported by multiple grants from National Institutes of Health.

Pharmacology-Based Clinical Trials



Frank Greenway, M.D.
Professor

FACULTY:

Frank Greenway, M.D., Alok Gupta, M.D.,

ADJUNCT FACULTY:

David Baker, DVM, Drake Bellanger, M.D., William Cassidy, M.D., Lisa Colvin, Ph.D., FACSM, Karen Elkind-Hirsch, Ph.D., Vivian Fonseca, Ph.D., MBBS, Stewart Gordon, M.D., Jimmy Guidry, M.D., Michael Jazwinski, M.D., Jolene Johnson, M.D., Zhijun Liu, Ph.D., Jennifer Lovejoy, Ph.D., Pamela Martin, Ph.D., John Paige, M.D., William Raum, M.D., Ph.D., Lars Sjoström, M.D., Ph.D., Melinda Sothorn, Ph.D., Brooke Whisenhut, Ph.D., Marney White, Ph.D., Eugene Woltering, M.D.

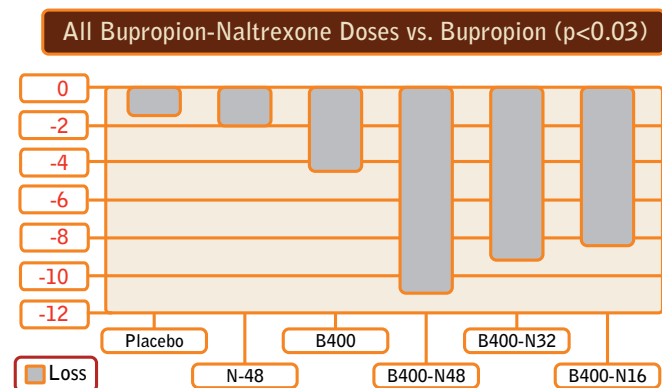
RESEARCH TEAM:

Yolanda Robertson, N.P., Anne Chatellier, R.N., Allison Strate, R.N., Aimee Yoches, B.S., LPN, Amber Torres, R.D., Angela Eldridge, B.S., Aubrey Windham, B.S., Carolyn Johnson, LPN, Chrystal Duncan, LPN, Cindy Puckett, R.D., Dawn Rachal, B.S., Diane Crow, LPN, Heidi Millet, B.S., Jana Ihrig, R.N., Jennifer Arceneaux, R.N., Karen Jones, R.N., Marisa Smith, B.S., Melody McNichol, B.S., Nancy Rajapho, M.S., Natalie Currier, R.D., Patricia Pinsonat, R.N., Stacie LaPrarie, R.N., Susan Mancuso, R.N., Jennifer Perrault, Elizabeth Tucker, B.S., Mary Beth Burnett, Melissa Lingle, B.S., Janet Fahr, B.S., Annette Hutchison, B.S., Charles Sides, RPh., Claire Hazlett, RPh., Lura Reed, Linda Guy

Focus — The outpatient clinical trials program focuses on obesity in areas of pharmaceutical development, dietary herbal supplements, foods and medical devices.

Examples of Current Projects

Our pharmaceutical trials range from early proof-of-concepts trials to trials determining the proper dose of a drug (phase II trials) to large drug approval trials (phase III trials). One proof of concept trial tested two drugs approved for other purposes in combination for weight loss. Using drugs already approved expedites the time-consuming and expensive drug approval process. The drug combination was discovered in the laboratory, tested in animals and is now being tested in obese people in hopes it will become a new combination drug for obesity treatment (see figure).



48 Week Percent Weight Loss: Placebo, Naltrexone 48 mg and Bupropion 400 mg with 0, 16, 32 and 48 mg Naltrexone.

Dietary herbal supplements are regulated as foods, and studies demonstrating their efficacy are required to support advertising claims. Eucommia is an herb that was processed at LSU by Dr. Liu for animal and human use. The safety was confirmed in rats at the LSU Vet School by Dr. Baker, and eucommia reduced blood pressure in rats with high blood pressure. Eucommia capsules are being tested in humans with blood pressure elevations between 120/80


(the healthiest blood pressure) and 140/90 (blood pressure requiring drug treatment). If the trial is successful, it will set the stage for development of a dietary herbal supplement to optimize blood pressure. Since the eucommia was developed at LSU, its success may spawn new cropping opportunities, a new processing industry and new product sales, promoting economic development in Louisiana.

It is well recognized that high blood pressure is associated with strokes, heart attacks and death. We now know, through the use of monitors that measure blood pressure for up to a week, that abnormal fluctuations in blood pressure are a greater risk factor for these diseases than high blood pressure itself. In a study using blood pressure monitoring for a week, we found that blood pressure fluctuations are more common in pre-diabetes and may explain part of the increased risk for heart attacks in this condition. This knowledge opens the door for developing better blood pressure treatments for these people in the future.

Lipolysis, the release of fat from fat cells, is accelerated to a greater extent by the combination of two approved medications, than by the sum of the effect of both medications separately. This medication combination is now being injected into lipomas to see if they will shrink and disappear. Lipomas are non-cancerous tumors composed of fat cells, and the present treatment for lipomas is surgery.

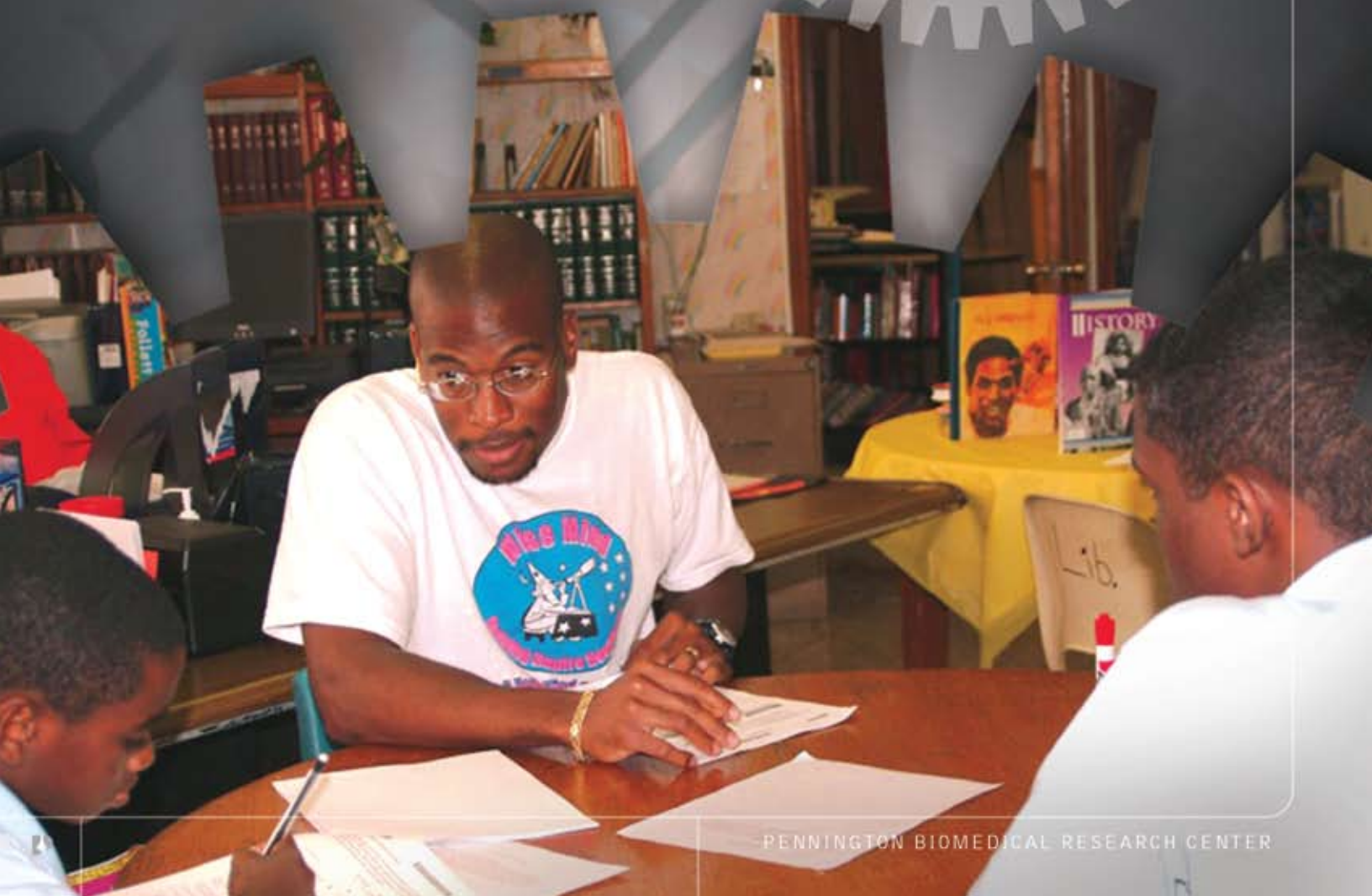
Thus, the outpatient clinical research program focuses on the treatment of obesity and the medical conditions complicating obesity. Obesity is a serious medical problem that is growing in prevalence and presently has no good medical treatment. The Center's outpatient clinic is addressing this unmet need 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.



“Our future directions include determining the public health burden of physical inactivity and obesity in the United States population and their impact on life expectancy.”

Peter T. Katzmarzyk, Ph.D.,
Professor, LPFA Chair in Nutrition



Population Science Laboratory Reports

Population Science research takes place within the following units.

Chronic Disease Epidemiology and Health Delivery

D. Harsha

Clinical Epidemiology

R. Horswell

Nutritional Epidemiology

C. Champagne, D. Harsha, B. Kennedy

Physical Activity Epidemiology

P. Katzmarzyk

Chronic Disease Epidemiology and Health Delivery



David W. Harsha, Ph.D.
Associate Professor

FACULTY:

David W. Harsha, Ph.D.

Focus — The translation of methods proven to be effective in behavioral interventions for cardiovascular disease, overweight, and metabolic syndrome, and the evidence driven study of effectiveness of such behavioral strategies in real world populations. In addition the evaluation of the environmental, economic, and social contexts of these studies is examined for the degree to which they shed light on effectively implementing interventions in demographic and ethnic populations of interest.

Current Projects

Research goals include focus on delivery of meaningful health interventions in real world populations. This flows from prior research demonstrating the efficacy of behavioral interventions for cardiovascular disease, overweight, and metabolic syndrome in well controlled settings. Emphasis is placed on dietary, physical activity, and other lifestyle factors related to risk for these conditions. The development of behavioral techniques for addressing these conditions in a fashion tailored to specific populations would advance the public health impact and benefits derived from them.

From the demonstrated utility of controlled studies, practical and well targeted strategies must be developed to address these public health issues in the real world. In particular is the need to introduce such interventions in

low-income, substantially minority, small town and rural populations regionally and ultimately nationally as well as intervene on populations suffering from the deficits of natural disasters such as hurricanes Katrina and Rita. Attention must be paid to the fashion in which risk develops in childhood and becomes established in adulthood.

Future Directions

Future directions are targeted at collaborating with community and local government health outreach programs to deliver effective health interventions to needy populations in Louisiana.

Research in this unit is supported by grants from the National Institutes of Health, the US Department of Agriculture, and the Department of Defense.

Clinical Epidemiology



Ron Horswell, Ph.D.
Associate Professor

FACULTY:

Ronald Horswell, PhD

RESEARCH TEAM:

Shannon McNabb, M.A., Jay Besse, B.S.

Focus — The broad goal of the clinical epidemiology unit is to identify modifiable factors related to variation in clinical outcomes within patient populations and to quantify the importance of those factors with regard to their effects on outcomes. Secondly, for identified high-importance factors amenable to clinical or public health interventions, we ultimately hope to develop and evaluate programs designed to modify the factors and thereby improve outcomes.

Current Projects

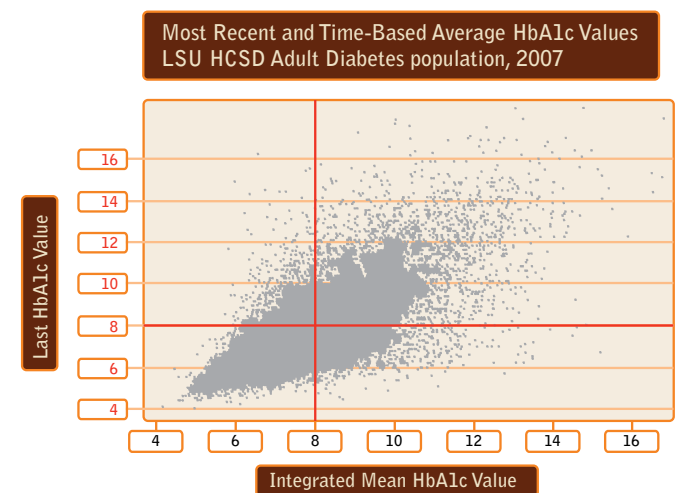
The Clinical Epidemiology Group seeks to identify modifiable factors related to variation in clinical outcomes, with current work focusing on outcomes in diabetes, congestive heart failure, and breast cancer patient populations. The Group works closely with the LSU Health Care Services Division (LSU HCSD) and coordinates a number of studies conducted within the LSU HCSD patient population.

One such upcoming project (to begin in late 2007 or early 2008) will use a controlled trial to test the ability of an information technology-based patient-centered intervention to improve health outcomes. In the treatment arm of the study, patient-specific data pertaining to health status, risk factors, and needed tests, will be summarized in the form of a short, easy-to-read report (the “Patient Health Sheet”) and given to the patient at the beginning of the clinic visit. This report will flag items that the patient should discuss with his/her physician and encourage that discussion. The study will be conducted at 20 LSU HCSD primary care clinics located at the seven main HCSD sites.

The Clinical Epidemiology Group also conducts retrospective analytical projects on a number of topics. A general goal of these retrospective projects is to develop methods for identifying subgroups of patients who are having difficulty controlling their chronic diseases and determine what characterizes these subgroups; i.e., determine what distinguishes them from patients with better controlled chronic disease. The figure (to right), for example, shows the distribution of most recent HbA1c levels and long-term (calculated over time) HbA1c levels for adult diabetes

patients in the LSU HCSD patient population. Analysis has found that about 23% of LSU HCSD adult diabetes patients have most both recent and time-based mean HbA1c levels > 8%. In the coming year, the Clinical Epidemiology Group will emphasize further identification and characterization of patient subgroups with particular health maintenance problems, as well as investigation of root causes for those problems.

Related to these research efforts, the Clinical Epidemiology Group also coordinates the calculation of measures of quality of care and access to care used by the LSU HCSD disease management programs. Currently, approximately 100 measures assessing access to care, care processes, and patient health status are calculated quarterly. These measures cover a broad range of disease management and evidence-based medicine programs, including adult diabetes, congestive heart failure, asthma, HIV, cancer screening, smoking cessation, and chronic kidney disease.



Research in this group is partially supported by contracts with the Louisiana Tobacco Control Program and with the LSU Health Care Services Division.

Nutritional Epidemiology



Catherine M. Champagne, Ph.D.
Professor



David W. Harsha, Ph.D.
Associate Professor



Betty M. Kennedy, Ph.D.
Instructor

FACULTY:

Catherine M. Champagne, Ph.D., RD, LDN, FADA, David W. Harsha, Ph.D., Betty M. Kennedy, Ph.D.

RESEARCH TEAM:

H. Raymond Allen, Ph.D., Marlene Afton, B.S., Michelle Begnaud, RD, LDN, CDE, Barbara Cerniauskas, RD, LDN, CDE, Laura Decuir, RD, LDN, Katherine Lastor, RD, LDN, Eric LeBlanc, B.S., Erma Levy, MPH, RD, LDN, Dawn Turner, B.S.

Focus — Nutritional epidemiology includes all studies of the relations between diet and health in human populations. To this end, the goal of this laboratory is to provide nutrition education and/or counseling that improve diet and health.

Current Projects

The Lower Mississippi Delta Nutrition Intervention Research Initiative (Delta NIRI)

The Delta NIRI is an ongoing collaborative, multi-year research effort to design, carry out, and evaluate nutrition interventions directed at improving the nutrition and related health concerns of residents in the impoverished and disadvantaged Lower Delta region of Arkansas, Louisiana, and Mississippi.

Previous findings indicated that Delta residents consumed diets inferior in nutrient content and quality of food servings compared to the US population. In all 3 states, pilot interventions were put into place with the investigators partnering with communities. In Louisiana, Franklin Parish was the designated pilot community. The Franklin NIRI is presently conducting a nutrition intervention called PUSH (People United to Sustain Health) which focuses on achieving and maintaining a healthy weight by improving diet. Incorporating more fruits and vegetables is a key strategy being promoted in this project.

Dietary Counseling Activities

A number of projects at the Pennington Biomedical Research Center involve dietary counseling efforts. The Diabetes Prevention Project Outcomes Study (DPPOS) is following individuals from DPP who have successfully made lifestyle changes; this project will continue until 2008. The Look AHEAD trial focuses on lifestyle changes in a population of diabetic individuals. 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, 30-month period of either personal contact or internet efforts. WLM will hopefully be continued for a phase 3

with successful receipt of new funding. The POUNDS LOST trial utilizes four different diet treatments varying in protein and fat to scientifically test these diets for weight loss effects. Subjects are asked to follow structured meal plans or exchange options in order to adhere to the dietary targets. The research dietitians/interventionists play a key role in working with these participants by conducting both group and individual sessions utilizing nutrition information and behavior change messages. POUNDS LOST will end the intervention phase in December 2007 and write-up of results to follow.

Soldier Nutritional Epidemiology

Since 1996, nine studies have been supported in collaboration with USARIEM. No studies have been conducted since 2002. Due to the war in Iraq, most field trials have been put on hold.

Research in this unit is supported by grants from the U.S. Department of Agriculture, the National Institutes of Health and the U.S. Army.

Physical Activity Epidemiology Laboratory



Peter T. Katzmarzyk, Ph.D.,
Professor, LPFA Chair in Nutrition

Focus — to investigate the effects of physical activity, fitness, and obesity on morbidity and mortality, and to quantify their impact on population health.

The Physical Activity Epidemiology Laboratory is collaborating in three large-scale epidemiological investigations, including the Canadian Physical Activity Longitudinal Study (PALS), the Canadian Heart Health Surveys Follow-up Study, and the CAMBIO Research Network (Canada-Mexico Battling Childhood Obesity). We also collaborate with researchers here at the center and at the University of South Carolina on the Aerobics Center Longitudinal Study (ACLS), and the HERITAGE Family Study.

Physical Activity Longitudinal Study (PALS)

PALS is a cohort study of individuals of 15 years and older who participated in the nationally representative 1981 Canada Fitness Survey and/or the 1988 Campbell's Survey of Well-Being in Canada. Participants received a follow-up, self-administered questionnaire covering a variety of health-related topics between 2002 and 2004. We are currently investigating the role of physical activity and obesity in the prevention of chronic disease in this 20-year cohort.

Canadian Heart Health Surveys Follow-up Study

The Canadian Heart Health Surveys Follow-up Study was initiated in 2004 to determine the impact of individual- and community-level factors on the relationships between obesity, other chronic disease risk factors, and mortality. The original Canadian Heart Health Surveys were conducted in Canada between 1986 and 1992, and comprise a cohort of approximately 28,000 people. This project aims to establish a longitudinal framework from the existing survey data by linking forward to the Canadian Mortality Database.

CAMBIO Research Network (Canada-Mexico Battling Childhood Obesity)

Funding for CAMBIO is provided through a grant from the Canadian International Development Research Center

FACULTY:

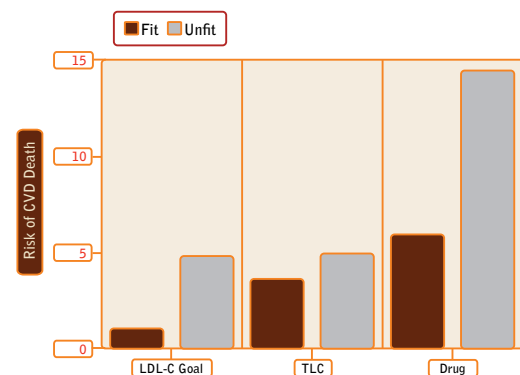
Peter T. Katzmarzyk, Ph.D., FACSM

RESEARCH TEAM:

Susan B. Sisson, Ph.D., Emily Mire, M.S.

on behalf of the Global Health Research Initiative. The overarching goal of CAMBIO is to address the problem of childhood obesity in Mexico, within the context of the nutrition transition. Our long-term aims are to increase research capacity and knowledge transfer, and to promote partnerships and collaborations. To achieve our goals, four key activities are being undertaken: developing and delivering an annual short course on obesity, developing a collaborative program of research, facilitating faculty and student exchanges, and building international partnerships and networking.

Our future directions include determining the public health burden of physical inactivity and obesity in the United States population, and their impact on life expectancy. We also plan to capitalize on existing data here at the Center to establish a cohort of people to follow over time to assess the development of risk factors and chronic disease.



Relative risk of cardiovascular disease mortality in men from the Aerobics Center Longitudinal Study (ACLS) across categories of global cardiovascular risk. In men who met their LDL goal, those that qualified for therapeutic lifestyle changes (TLC), and those that were eligible for drug therapy, men who are physically fit had a lower risk of mortality than those who were unfit.

Research in this unit is currently funded by the Canadian Institutes for Health Research, Heart and Stroke Foundation of Canada, the Canadian International Development Research Center and the Pennington Medical Foundation.



“A major asset to researchers at the Center is having access to a laboratory that is continually developing and implementing new methodologies.”

Professor Jennifer C. Rood, Ph.D.

HEMOGLOBIN
 Red cell
 ratio PCV
 M.C.V.
 M.C.H.
 M.C.H.C.
 ESR
 WHITE CELLS
 Neutrophils
 Lymphocytes
 Monocytes
 Eosinophils
 Basophil
 BLOOD PIC

84
 29.0
 33.3
 2
 6.16
 54
 32
 6
 6
 3

Animal Metabolism and Behavior



Andrew Butler, Ph.D.
Associate Professor

FACULTY:

Andrew Butler, Ph.D.,

STAFF:

Armand Cassani, B.S

Mission — to facilitate the assessment of metabolism and behavior in rodent models of the metabolic syndrome.

Genetic mouse models are an essential tool in the analysis of the function of known and novel genes. Over expression or genetic targeting (“knock out”) provide important information about the specific role of a gene in pathways that regulate metabolic processes and behavior. Indeed, mouse models of obesity have played an essential role in the most important recent discovery in the obesity field, the axis involving leptin secreted from fat cells and the melanocortin system in the brain.

In addition to maintaining existing strains, the Center now has the capability to produce new models to investigate the function of genes identified by Investigators at this Institution. The Institution can now produce transgenic mice over expressing genes. In addition, services have been established for the conditional targeting of genes, where gene activity can be manipulated in an organ-specific manner. The mission of the Animal Metabolism and Behavior Core is to facilitate in the assessment of the phenotype of genetic mouse strains by Investigators. We currently possess systems that measure feeding behavior, energy expenditure, physical activity, and non-invasively measure body composition (fat mass, fat free mass) in mice. We can also measure circadian rhythms of physical activity in normal light:dark and constant dark settings. The Core is planning an expansion of the services available to include more sophisticated measurements of meal size and feeding bout frequency, of fine motor function, and of memory.

Cell Biology and Cell Imaging Core



David H. Burk, Ph.D.
Instructor

FACULTY:

David H. Burk, Ph.D.

STAFF:

Laura Roan, B.S., Courtney Cain, B.S.

Mission — The Cell Biology and Bioimaging Core’s primary purpose is to facilitate access to state of the art imaging and analytical instrumentation, technical expertise, assistance and training for researchers at the Pennington Biomedical Research Center and surrounding research community.

The CBB Core is located centrally in the new Basic Sciences Building and is divided into two workspaces. The imaging and analytical suite located in L4076 houses high end imaging platforms and fluorescent based analytical equipment. Here researchers may make use of several imaging modalities ranging from basic widefield fluorescence to multi-photon confocal microscopy on our Zeiss 510 META. Analytical platforms include a Flexstation fluorometric plate reader and a BD FACSCalibur flow cytometer equipped with two lasers and four fluorescence detectors. The specimen preparation area in L4016 houses several cryostats, a rotary microtome, vibratome and sliding microtomes.

The Core was developed as part of PBRC’s NIH Center of Biomedical Research Excellence (COBRE), which is devoted to advancing understanding of the cell biology of obesity and diabetes. The primary objectives of the CBB Core are to advance the development of the cellular bioimaging component of our research infrastructure, thereby enhancing the training of young scientists to make fundamental discoveries of the underlying mechanisms of obesity and diabetes.

Cell Culture Core



FACULTY:

Margarita Terán-García, M.D., Ph.D.,
Jeff Gimble, M.D., Ph.D.

Margarita Terán-García, M.D., Ph.D.

Comparative Biology Core



FACULTY:

Barry Robert, DVM, Ph.D., DACLAM

STAFF:

Cindy Kloster, B.S., RVT, RLATG, CPM, Cynthia Angelloz, RALAT, Tracy Brown, Josh Borne, Linda Chase, LAT, Lindsey Clemones, B.S., Kyle Daigle, Michelle Dry, Darryl Howard, Frank Hsu, Faye Louviere, ALAT, Deborah Minor, ALAT, Suna Ozoral, Anna Pearson, Monique Simmons, Shannon Sterba, Renarda Williams.

Barry Robert, DVM, Ph.D.
Associate Professor

Mission — to provide the Pennington Biomedical Research Center scientists with a facility to conduct cell and tissue culture experiments in a safe and effective manner.

The cell culture core provides investigators with equipment dedicated to cell and tissue culture needs along with trained personnel and maintenance in a controlled, security access laboratory suite. Cell cultures can be developed from human and animal tissues and employed as disease models relevant to cancer, cardiovascular, diabetes, neurological, obesity, and stem cell research. The facility includes the following shared equipment: biological safety cabinets (4), humidified incubators (3), automated carbon dioxide manifold, microscopes (2), a digital camera system, water baths, balances, pH meter, liquid nitrogen cryotanks for cell storage, and freezer/refrigerators for storage of reagents. The core also includes a dedicated room for viral vectors requiring Biological Safety Level 2 control or radioisotopes.

Mission — to provide superior animal housing space, complete animal husbandry and veterinary care services, training, and technical support for Center scientists using animal models.

The Core is a 38,000-square-foot centralized service facility that includes laboratory animal housing, receiving and quarantine facilities, animal procedural, behavioral testing and surgical laboratories, and a diet preparatory area.

The Core is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. This accreditation represents the “gold standard” for laboratory animal care and use, underscoring the Center’s commitment to the highest quality laboratory animal program. The Core unconditionally endorses and complies with the NIH *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, *The Guide for the Care and Use of Laboratory Animals*, and the USDA *Animal Welfare Act and Regulations*. Furthermore, the Center’s Institutional Animal Care and Use Committee composed of scientists, a veterinarian, and a community member, must review and approve the care and use of all Center laboratory animals.

We provide training opportunities to the research staff and Core personnel, including an animal care and use orientation program for all new research employees using laboratory animals. We also offer specific technical training in laboratory animal biotechnology for scientists and their staff members. Core personnel are continually trained under the American Association of Laboratory Animal Care’s Laboratory Animal Technician series to assure that our staff is following all applicable regulations and providing the highest standards of care to our laboratory animals.

Genomics Core Facility



Robert Koza, Ph.D.
Assistant Professor

FACULTY:

Leslie Kozak, Ph.D., Robert Koza, Ph.D.

STAFF:

Susan Newman, B.S., Jana Smith, B.S.

Mission — to provide DNA sequencing, DNA fragment analysis, qualitative and quantitative analysis of DNA, protein, and RNA samples, quantitative PCR, microarray services, robotics, and bioinformatics services.

The laboratory is equipped with two Applied Biosystems' 3130XL sixteen capillary genetic analyzers for DNA sequencing and fragment analysis. Four Applied Biosystems 7900HT Sequence Detection Systems equipped with 96 well, 384 well, and low density array blocks perform quantitative PCR. An Applied Biosystems 1700 microarray system and an Illumina microarray system are available for researchers who wish to use a commercial microarray system. The microarray facility has the capability to produce custom oligonucleotide or cDNA microarrays. Spotfire software and Bioconductor R Scripts are used for analysis of microarray data. Two pipetting robots, a Becton Dickinson Biomek FX and a Perkin Elmer MultiProbe II, are available for robotic liquid handling. These instruments facilitate high-throughput pipetting of 384 well format plates. They can be programmed for large pipetting projects. Two Agilent 2100 Bioanalyzers are used for protein, DNA, and RNA analysis and quantitation. A NanoDrop Spectrophotometer is used for RNA and DNA quantification. An Odyssey Infrared Imager uses direct infrared fluorescence detection for western blot analysis. For large DNA extraction and purification projects, a Qiagen AutoPure robot is used. Three computer workstations are available for sequence analysis and alignment, PCR primer design, and RT-PCR data analysis.

The Genomics Core Facility provides training and consultation for sequence analysis, real-time PCR, and microarray analysis.

Proteomics



Indu Kheterpal, Ph.D.
Assistant Professor

FACULTY:

Indu Kheterpal, Ph.D.

STAFF:

Liana Coleman, B.S., Ginger Ku, M.S., Madhavi Minnamreddy, M.S., Jordan McGee

Mission — to provide scientific and technical knowledge and resources for state-of-the-art proteomics to foster new research as well as support ongoing research at the Center.

The proteomics core provides identification and measurement of the relative abundance of proteins within a cell, tissue or biological fluids, determination of the subcellular localization of proteins, examination of protein modification, identification of secreted proteins, characterization of protein complexes and protein structure determination.

Sensitive imaging techniques coupled with sophisticated imaging and analysis software provide capabilities for spot matching and quantification between multiple gels. 2D difference gel electrophoresis using fluorescent dyes allows for multiplexing up to three samples on the same gel for direct quantitative comparison. Automated spot excision from preparative 2D-gels and automated in-gel protein digestion and peptide extraction facilitate sample preparation for protein identification.

Nano electrospray ionization quadrupole time-of-flight mass spectrometer (nESI-Q-TOF-MS) and MALDI-TOF MS facilitate high throughput identification of peptides and proteins. Protein identifications are made by comparing MS data to sequence information from genomic, protein and EST databases. The 2D-LC technology for differential expression analysis includes protein labeling, digestion and separation of peptides using strong cation exchange chromatography and reverse phase LC prior to MS analysis.

Recent projects include: identification of changes in secretome of adipose-derived adult stem cells following adipogenesis; comparison of proteomic profiles of bone marrow stem cells and adipose derived stem cells; identification of changes in proteomic profiles of 3T3-L1 cells after transfection with zfp106; identification of changes in proteomic profile of skeletal muscle cells after botanical treatments; and identification of MEST interaction partners.

Transgenic Core



Randall Mynatt, Ph.D.
Associate Professor

FACULTY:

Randall Mynatt Ph.D., Jingying Zhang, Ph.D.

STAFF:

Steven Bond, B.S., Dieyun Ding, B.S.

Biostatistics and Data Management Core



William D. Johnson, Ph.D.
Professor

FACULTY:

William D. Johnson, Ph.D., Ronald Horswell, Ph.D.

STAFF:

Connie Murla, B.S., Jessica Arnold, M.S.,
Richard Heap, B.S., John Ruth, B.S.

Mission — to provide controlled manipulation of gene expression and to facilitate investigators in understanding gene function. The transgenic core currently produces mice for Center faculty and investigators at other institutions. The transgenic core uses pronuclear microinjection and embryonic stem cell technologies to control gene expression in mice.

Services Provided

A. Transgene Preparation: Two services available. 1) The investigator can supply a plasmid, and we will excise and purify the transgene 2) We will work with the investigator and design, construct and purify the transgene

B. Pronuclear Microinjection of Transgenes and Bacterial Artificial Chromosomes (BAC): Approximately 200 one-cell eggs from FVB/N or C57BL/6J are injected with the transgene. Creation of transgenic mice on additional backgrounds can be done after testing the suitability of the strain for microinjection.

C. Gene targeting: We have initiated the time saving, recombining strategy for introducing lox P sites in genes for tissue specific knockout mice on the C57BL/6J background. This is a “turn key” service for generating mice with floxed alleles. The core will make the knock out vector construct, electroporate and screen the ES cells for recombination

C. Injection of Embryonic Stem Cells: Targeted embryonic stem cells are injected into C57BL/6J blastocyst. Chimeric mice are delivered at approximately 5 weeks of age

D. Cryopreservation: Approximately 10 males and 30 females are provided by user. Fertilized embryos and sperm are collected and frozen on site.

E. Rederivation: Fertilized embryos are collected from pathogen harboring mice and transferred recipient mothers.

Mission — The Biostatistics and Data Management Core seeks collaborations that lead to a smooth transition from hypothesis formulation and efficient experimental design through quality-controlled data management, statistical analysis and summary presentations, and provide objective interpretation of research findings. The Biostatistics faculty offer expertise to ensure rigorous statistical integrity of research in the basic, population and clinical sciences. The faculty is strongly encouraged to pursue independent research in statistical theory and methods relevant to the PBRC 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's duration; 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 PBRC data and Non-PBRC data. This development and data storage paradigm allows the team to work with both intramural and extramural researchers.

Clinical Chemistry Core



Jennifer C. Rood, Ph.D.
Professor

FACULTY:

Jennifer C. Rood, Ph.D., DABCC, FACB

STAFF:

Stacey Roussel, M.T. (ASCP), Stephen Lee, M.T. (ASCP), Sandra Richard, M.T. (ASCP), Carla Kimmel, M.T. (ASCP), Margaret Graves, M.T. (ASCP), Denise Stein, M.T. (ASCP), Elizabeth Soroe, M.T. (ASCP), Jamie Tuminello, M.T. (ASCP), Estrellita Bermudez, B.S., Amanda Lyons, B.S., Jennifer LeGlue, B.S., Tania Hicks, B.S., Brandy Snowden, B.S., Carlo Milo, Donald Lewis, Lisa Jones, Sharon Thomas

Mission — to develop innovative methodology, provide accurate and timely tests results and foster a climate of personal and professional achievement, while promoting health and wellness through nutritional research.

The Core is divided into the following departments: phlebotomy, accessioning, chemistry, hematology, urinalysis, special chemistry, and point-of-care testing.

The laboratory follows rigorous quality control assurance practices and is certified by the Health Care Financing Authority 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.

A major asset to researchers at the Center is having access to a laboratory that is continually developing and implementing new methodologies. New assays developed during 2006-2007 include the following: obestatin, amino acid profiles, endotoxin, ghrelin, ppy 3-36, thyroglobulin, and cytomegalovirus antibodies,

In 2007, a new Varian atomic absorption graphite furnace spectrophotometer was purchased to allow for state of the art measurement of zinc, copper, selenium, and cadmium.

The Core performs over 250 different clinical assays to support clinical trials, basic researchers, the U.S. Army Institute of Environmental Medicine, and contracting clients. During 2006, over 625,000 assays were performed.

Dietary Assessment and Food Analysis Core

Exercise Testing



FACULTY:

Catherine M. Champagne, Ph.D., RD

STAFF:

H. Raymond Allen, Ph.D., Eric A. LeBlanc, B.S.,
Dawn R. Turner, B.S., Mary Marlene Afton

Catherine M. Champagne, Ph.D., RD
Professor



FACULTY:

Conrad Earnest, Ph.D.

STAFF:

Stephanie Anaya, M.S.

Conrad Earnest, Ph.D.
Assistant Professor

Mission — to provide accurate information on dietary intakes of research participants and to provide menu design for specific nutrient targets of clinical and behavioral trials.

The core uses the current version of Moore's Extended Nutrient Database, MENu 6 (2005), a data set of more than 21,000 files from the following sources:

- Release 19 of the USDA Nutrient Database for Standard Reference (August, 2006).
- The Food and Nutrient Database for Dietary Studies 2.0 (June, 2006). *What We Eat in America*, NHANES 2003-2004 Documentation: Dietary Interview - Individual Foods -- First Day (DR1IFF_C). (2006, September).
- Supplementary information from scientific literature or other reliable food composition tables.
- User defined foods - nutrient data of menu items for which an appropriate food match cannot be found.
- Recipes input to the Center's unique recipe calculation system.

Food Diary Program. While menu and recipe analysis is an important activity using the MENu system, several current research protocols use the Food Diary Program. Food Diary utilizes the MENu 6 Food Composition Files to analyze dietary intakes of research participants. In 2006 and 2007, the core processed approximately 34,460 lines of dietary intake data.

Food Frequencies. In association with most major research projects involving collection of dietary intake data by food records, a number of studies also use food frequency questionnaires to capture intakes over a longer period of time. Currently we use scannable questionnaires with results exported as an electronic file. The core processed about 1,779 food frequencies during the last two years.

Mission — to provide the consistent, valid and reliable assessment of the assessment of physiologic, cardiorespiratory and muscular strength parameters of exercise performance for Pennington Biomedical Research Center Scientists examining interventions involving exercise.

The Exercise Testing Core serves the needs of clinical investigators who wish to characterize the cardiorespiratory 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 accurate assessment of these parameters is essential to clinical trials given the overwhelming influence of exercise for the prevention and treatment of cardiovascular disease, obesity, and diabetes.

Operating under internationally recognized guidelines put forth by the *American College of Sports Medicine* and *American Heart Association*, The Core is equipped with a Trackmaster 425 treadmill, Lode Excalibur Sport bicycle ergometer and Parvomedics True Max 2400 Metabolic Measurement Cart metabolic analysis system for examining cardiorespiratory fitness. The Core currently uses the Cybex II Isokinetic testing system for assessing muscular strength.

Imaging Core



Steven R. Smith, M.D.
Professor

FACULTY:

Steven R. Smith, M.D., Harris Lappin, M.D.
(Adjunct), Bradley Newcomer, Ph.D. (Adjunct)

STAFF:

Kori Murray, M.S., Randy Niederhofer, R.T. (R)
(M), Julia St. Amant, ARRT R.T. (R), Denise
Jarreau, M.S., Kimberly Landry, R.C.T., Randell
Deen, R.T. (R)

Inpatient Unit

FACULTY:

Steven R. Smith, M.D.

STAFF:

Crystal Traylor, R.N., W.H.N.P., Amy Braymer, L.P.N., Kim Croftwell,
L.P.N., Lisa Dalfrey, L.P.N., Lorraine Eames, L.P.N., Rhonda Hilliard,
L.P.N., Katrina Prescott, L.P.N., Stephanie Tatum, R.N., Bridget
Taylor, L.P.N., Susan Thomas, R.N., N.P., Valerie Toups, L.P.N., Celeste
Waguespack, R.N., Onolee Thomas, R.N., Erin Wimberly, Linda Stockton

Mission — The Imaging Core is a comprehensive, dynamic group of people and state-of-the art instrumentation to provide turn-key solutions for the clinical investigator who needs high quality measures of body composition and function.

The Core places in the hands of researchers a variety of instrumentation and technical services, including:

- A QDR4500A dual energy x-ray absorptiometer (DEXA) for the measurement of whole body composition and site specific bone mineral density.
- Oasis™ based coordination of multi-center DEXA studies.
- QuickScan™ whole body NMR body composition.
- A Toshiba Powervision™ ultrasound / Doppler for cardiac imaging general purpose imaging, carotid ultrasonography and studies of post-ischemic reactive hyperemia (brachial artery flow mediated dilatation)
- Assistance with special projects requiring image analysis of CT, MRI, or ultrasound images, including multi-center clinical trials.

Most recently the core added significant capability with the construction of a new Magnetic resonance spectroscopy (MRS) lab. The lab consists of a GE 3T MRI/MRS, a series of specialized coils and instrumentation for magnetic resonance spectroscopy, and clinical facilities oriented towards patient comfort and convenience. This instrument allows researchers to non-invasively 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)
- Future capabilities include ¹³C spectroscopy (combined with stable isotopes to measure TCA flux) and ¹³C spectroscopy to measure glycogen flux in the liver.

The inpatient unit serves the needs of clinical investigators for the conduct of advanced clinical endpoints in clinical 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.
- three rooms dedicated for the conduct of euglycemic hyperinsulinemic ‘clamps’
- a procedure room for oral glucose tolerance testing, IV glucose tolerance testing, pharmacokinetic studies, and other related procedures
- a dedicated biopsy room for adipose tissue and skeletal muscle biopsies
- a satellite clinical chemistry sample processing and accessioning room
- a room dedicated to the measurement of food intake and macronutrient selection
- a fully equipped Inpatient Unit / Eating Laboratory Metabolic Kitchen
- a lounge/sunroom for volunteers where they can watch TV / DVDs, surf the internet and play games
- a large nursing station that includes a remote pharmacy, internet/intranet access and work table
- a psychology data collection area for questionnaire completion
- immediately adjacent facilities: DEXA , echocardiography, ultrasound, 3T MRI/MRS and pulmonary function testing units

The unit is staffed 24 hours, 7 days a week except major holidays.

Library and Information Center


DIRECTOR:

Lori Steib, B.A., MLIS, AHIP

STAFF:

Marilyn Hammond, B.A.

Lori Steib, B.A., MLIS, AHIP

Director, Library and Information Services

Mass Spectrometry Core


FACULTY:

Jennifer C. Rood, Ph.D., DABCC, FACB

STAFF:

Bruce Toth, B.S., M.A., Evest Broussard, B.S., M.S., Sunny Brogan, B.S., Paige McCowan, B.S., Eric Gravois, B.S., Charlene Townshend, B.A.

Jennifer C. Rood, Ph.D.

Professor

The Library & Information Center provides all employees with specialized print and electronic publications as well as reference and information services, interlibrary loan processing, bibliographic instruction, and access to electronic databases. The Center each year also provides search and delivery of approximately 5,000 requested journal articles, books, abstracts and other informational items.

Open twenty-four hours a day, seven days a week, the Center is a member of the National Network of Libraries of Medicine and LOUIS, The Louisiana Library Network. In 2006, the Center was named as a key partner in the implementation of the Louisiana Go Local Project, a MedlinePlus initiative of the National Library of Medicine.

The Center also provides a computer learning lab comprised of four complete workstations, software and peripherals, including color printers, color scanners, external zip and floppy drives, and internal CD writers. Information Center personnel provide instruction and support for these resources, which are linked to PBRC network servers.

Information Center databases – available via faculty computer workstations – are Medline via PubMed and EbscoHost; Science Citation Index, Social Science Citation Index, and Arts & Humanities Citation Index and Journal Citation Reports via ISI's Web of Knowledge. The EbscoHost suite includes such databases such as Agricola, PsychInfo, Social Science Abstracts, Biological Abstracts, as well as the full text journal databases Biomedical References Collection and Psychology and Behavioral Sciences Collection. The Pennington Library and Information Center continues to keep pace with the developing electronic resources and programming technologies.

The Mass Spectrometry facility provides core services in two areas: energy expenditure and metabolism. Stable isotopes, or heavy atoms, are used as tracers to study human metabolism. Since stable isotopes are nonradioactive, they pose no hazards to our volunteers and can be used in adults and children. However, the lack of radioactivity makes detection and quantitation more difficult, necessitating high-technology measuring equipment. The laboratory has four Finnigan isotope ratio mass spectrometers (a Delta S, a Delta XP, and two MAT 252s). The laboratory also has automated sample preparation devices interfaced to the mass spectrometers. Two gas benches are used for Oxygen 18 sample preparation and three H devices are used for the sample preparation of deuterium. With these instruments, we can accurately and precisely measure the amount of heavy isotopes, such as Oxygen-18 and Hydrogen-2, in relation to the common isotopes, ¹⁶Oxygen and ¹Hydrogen, for the measurement of energy expenditure in studies of obesity. The instruments are also used to measure total body water. In addition, the Mass Spectrometry Laboratory has two Agilent gas chromatographs with mass spectrometry detectors. These instruments are used to measure stable isotopes such as 6,6 d-2 glucose. This technology can be used to examine cholesterol metabolism in studies of cardiovascular disease, and glucose, amino acid and fatty acid metabolism in studies of obesity and diabetes.

Metabolic Chambers



Lilian de Jonge, PhD,
Instructor

FACULTY:

Lilian de Jonge, Ph.D.

STAFF:

Matthew DeCalongne B.S., Nigel Fontenot B.E.,
Henry Anderson

Mission — to perform and provide reliable and reproducible assessments of energy expenditure and substrate oxidation in humans.

The core uses Metabolic carts (Deltatrac II metabolic monitors) for measurements under resting conditions and for the assessment of both the acute and chronic effect of possible thermogenic compounds as well as for the assessment of responses to dietary interventions over time.

The core uses whole-room indirect calorimeters to measure energy expenditure and substrate oxidation on a 24H basis. The core operates two of these rooms, each of which measure 10x10x8 ft. and provide a pleasant ambiance to our participants. The software allows for minute to minute data output, making the chambers not only useful for the measurements of 24H energy metabolism but also

for the assessments of acute effects. Oxygen and CO₂ levels in the chambers are measured using a SIEMENS OXYMAT O₂ magneto-pneumatic oxygen analyzer, and an ABB Advanced Optima Uras14 infrared CO₂ analyzer.

On every test day the chambers are calibrated, before the participant enters the chambers, and for determination of the accuracy and precision of the calorimeters, 24H propane combustion tests are performed on a monthly bases. The accuracy of our chambers is 99.9% and 97.0 %, for O₂ and CO₂, 98.3% and 98.3 %, for O₂ and CO₂ for chamber 1 and 2, respectively.

Between September 1993 and October 2007, researchers used the metabolic chambers for 2457 subject days over 23 clinical studies.

Outpatient Clinic Core



Frank Greenway, M.D.
Professor

FACULTY:

Frank Greenway, M.D.

STAFF:

Yolanda Robertson, N.P., Anne Chatellier, R.N., Allison Strate, R.N., Aimee Yoches, B.S., LPN, Amber Torres, R.D., Angela Eldridge, B.S., Aubrey Windham, B.S., Carolyn Johnson, LPN, , Chrystal Duncan, LPN, Cindy Puckett, R.D., Dawn Rachal, B.S., Diane Crow, LPN, Heidi Millet, B.S., Jana Ihrig, R.N., Jennifer Arceneaux, R.N., Karen Jones, R.N., Marisa Smith, B.S., Melody McNichol, B.S., Nancy Rajapho, M.S., Natalie Currier, R.D., Patricia Pinsonat, R.N., Stacie LaPrarie, R.N., Susan Mancuso, R.N., , Jennifer Perrault, Elizabeth Tucker, B.S., Mary Beth Burnett, Melissa Lingle, B.S., Janet Fahr, B.S., Annette Hutchison, B.S., Charles Sides, RPh., Claire Hazlett, RPh., Lura Reed, Linda Guy

Mission — The Outpatient Clinic Core supports clinical trials by screening volunteers, and collecting research data. Screening involves initial phone screening and screening in the clinic for those that pass the initial screening.

The Outpatient Clinical Core is on the first floor of the clinical research building which occupies 16,485 square feet of space plus eight trailer annexes housing 49 offices and one conference room. There are ten examination rooms, a phlebotomy laboratory, three electrocardiogram rooms, three weight and blood pressure stalls and four interview rooms.

The core also has three eating monitors, a DEXA and NMR body composition area, an exercise laboratory, and a vascular ultrasound lab.

The Outpatient Clinic employs 35 people: A clinic administrator, two physicians, a nurse practitioner, a nurse supervisor, eleven nurse coordinators, six study coordinators,

four dietitians, a medical record librarian with two assistants, three secretarial personnel, a data entry supervisor and two part-time pharmacists.

During 2006 there were 6984 telephone screenings, 2213 screening visits and 1,200 subjects randomized into clinical trials. There were 35 new clinical trials directed by 12 principal investigators with funding from the federal government, industry and foundations. The Outpatient Clinic participates in multi-center trials, and collaborates with industry to develop new products. Most of the studies performed in the Pennington Biomedical Research Center relate to obesity or its associated complications, including diabetes, abnormal cholesterol metabolism, high blood pressure and atherosclerotic vascular disease. The level of activity is growing rapidly, and expansion of the clinical facilities is a priority.

Recruitment



Tim Church, Ph.D.
Professor

FACULTY:

Tim Church, M.D., Ph.D.

STAFF:

Ruben Rodarte, MS, CCRP, Ami Parks, B.S., Grace Bella, B.A., Brenda Dahmer, B.S., James Edmonds, B.A., Mary Jessica Beech, B.S., Latrica Peters B.S., Annalane Brogdon, Maria Sanchez

Mission — to facilitate clinical trial participation at Pennington Biomedical Research Center by promoting research opportunities with effective marketing campaigns and community outreach efforts.

Recruitment services for clinical trials are coordinated by the Recruitment Core. The Core manages all marketing activities for clinical trials, such as the design and placement of advertisement and screens all incoming calls to determine study eligibility. Incoming calls are directed to a Uniform Call Distributor (UCD) equipped call center and tracked using a message tracking application to assess efficacy of a marketing campaign. Over its 20 year history, a total of 21,531 volunteers have screened for a clinical research trial and nearly 11,000 have been enrolled into a study

Traditional advertisement mediums that are utilized include newspaper, radio, television, and direct mailing, while more novel methods have been employed including online advertisement and mass email campaigns. A listserv was developed to manage the email campaigns and future web-based recruitment enhancements are being developed. The core also has access to demographic information for approximately 20,000 past participants who can be targeted for future studies.

Research Kitchen Core

RESEARCH KITCHEN EXECUTIVE COMMITTEE:

Courtney Brock, BS, Marlene Most, Ph.D., R.D.; Corby K. Martin, Ph.D.; Crystal Traylor, WHNP

STAFF:

Marlene Afton, B.S., Kelly Atteberry, B.S., RD, , RD, Betty Fisher, Mandi Harvill, B.S., Marlene Most, Ph.D., RD, Mallory Purvis, B.S., Renee Puyau, B.S., RD, Rachel Romaine, B.S., and Dawn Turner, B.S.

Mission — to support nutritional research as an integrated component of the Center by designing, preparing, and serving meals to meet study-specific criteria and produce valid scientific results.

The Research Kitchen is immediately adjacent to the Clinical Research areas. In addition to providing an outstanding physical facility, the Research Kitchen is staffed by an experienced research oriented team. The Research Kitchen is led by an Executive Committee to oversee menu planning, food production, and daily management of the operation. Research Dietitians are responsible for managing the dietary component of specific study protocols. Research specialists and food service workers prepare and serve the research-designated diets.

Approximately 225 meals per day can be prepared in the facility. In addition to routine 'standard' diets, the Research Kitchen's RDs use nutritional analysis programs to precisely design menus and recipes to meet the requirements of each study protocol. The Research Kitchen is integrated into the clinic scheduling system of the Center and the Research Kitchen's RDs work directly with Principal Investigators as they plan research and design study protocols. The Research Kitchen also works closely with the Inpatient Unit and Ingestive Behavior Laboratory, providing meals to these testing areas as well as collecting food intake data by weighing food provision and plate waste; these data are entered into the PBRC Clinical Database for the automated calculation of total caloric and macronutrient intake.

Taken together, the research kitchen provides state-of-the-art nutritional research support as a core to support the Pennington faculty in an efficient and precise manner.



**“It has been
two very good decades for
this still-young institution, and
these first 20 years give us great
hope for continuing success
in the future.”**

Ralph Underwood
Associate Executive Director
for Administration and Finance

Message from the Associate Executive Director for Administration & Finance



Ralph Underwood
Associate Executive Director

The year 2008 will mark the 20th year of the Pennington Biomedical Research Center. This, the ninth issue of our *Scientific Report*, is an appropriate time to look back at where we have been and how far we have come. It has been two very good decades for this still-young institution, and these first 20 years give us great hope for continuing success in the future.

The generous gift from Claude “Doc” Pennington and his wife Irene allowed the creation of the Pennington Biomedical Research Center (PBRC) in the early 1980s. However, Doc made it clear that the gift was not intended to be used for operating money but for construction of buildings and other capital needs. In retrospect, this was a wise decision, but in PBRC’s earliest years it created a hardship. A lack of operating funds meant that in the beginning the financial focus at the PBRC was simply on surviving as a going concern. The US Department of Agriculture, through efforts of US Senator J. Bennett Johnston and Congresswoman Lindy Boggs, had provided a \$9 million grant for the purchase of research equipment, but there was a severe shortage of funds for day-to-day operations. The Center officially opened in late 1988 using operating money cobbled together through support from the Louisiana Public Facilities Authority, the US Department of Defense, and some individual and corporate gifts. Within a few months, the Baton Rouge Area Foundation stepped up with an important and generous grant which enabled PBRC in 1989 to hire its first executive director, Dr. George Bray. Dr. Bray joined Dr. Donna Ryan and Bill Silvia who were already at the Center to form the first executive management team that nurtured PBRC through its somewhat uncertain infancy and into a robust and healthy institution.

The single most significant event to help ensure the

financial survival and eventual flourishing of the Pennington Biomedical Research Center was the \$5 million annual state appropriation first provided by the Louisiana Legislature in the summer of 1990. The strong support of then-Governor Buddy Roemer was critical in making this happen. This annual appropriation provided base support which PBRC scientists used to generate research data that very soon resulted in the awards of sponsored research grants from federal and private sources. The state appropriation remained at about \$5 million per year for 10 years until in 2001 the Louisiana legislature, at the urging of Governor Mike Foster, increased the appropriation to \$8 million per year. This additional investment by the State of Louisiana allowed PBRC to attract new, highly productive research faculty and staff to develop new research programs that quickly attracted new grant and contract dollars. Most recently, the Legislature has increased the appropriation twice, by \$1 million in 2006 and by \$3 million in 2007, both during the administration of Governor Kathleen Blanco. State appropriations in fiscal year 2007-08 stand at \$17 million.

These state dollars, although they historically account for less than 25-percent of the annual operating budget of PBRC, are critically important. Without these it would be very difficult to grow the Center, and it would have been impossible for the Center to have experienced the impressive growth that has occurred in the past 20 years. These state dollars provide the seed money for new research programs. Historically, new research programs very quickly result in new federal and private research funds flowing into Louisiana from outside the state, creating new, clean, high-paying jobs and new wealth in our state. This process of PBRC scientists leveraging state dollars into multiple dollars of sponsored research funding began with the first state

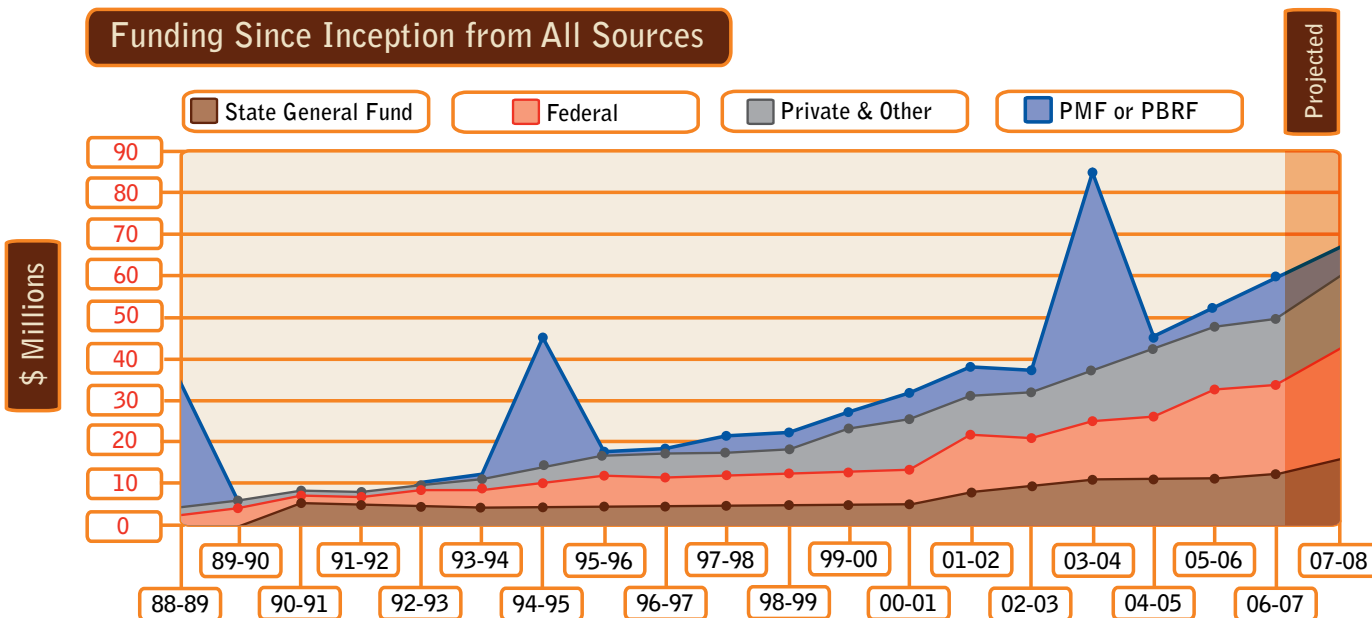
appropriation and has continued unabated and with great success ever since. In fact, when viewed over our previous 19 years, PBRC has leveraged the total state appropriations into an additional \$427 million of federal and private funding for its research efforts, a return of \$3.72 for every dollar invested by the State of Louisiana.

The Bureau of Economic Analysis (BEA) of the U.S. Department of Commerce has calculated the economic multiplier for research expenditures in the greater Baton Rouge area to be 1.89. Applying this multiplier to the \$427 million of federal and private funding reveals that PBRC scientists have attracted research funding resulting in an economic impact of more than \$800 million on our community and state in the past 20 years.

Research funding at PBRC has included, at various times, federal research grants and cooperative agreements from the National Institutes of Health, NASA, the Department of Defense, USDA, and the National Science Foundation. Private research support has come from the American Heart Association, the American Cancer Society, the American Diabetes Association, other health associations, food and pharmaceutical companies, and other private entities, both for-profit and not-for-profit. This has provided a diversified funding base that speaks well for the continued success of the Center.

Yes, it has been an outstanding first 20 years, and we are confident that the best is still in the future.

Funding Since Inception from All Sources



Communications



Glen Duncan
Director

Glen Duncan, B.S., M.J., M.S., APR; Alan Pesch, B.G.S.; Tim Nguyen, B.A.

Mission — Communications as sophisticated and effective as our research.

The communications team supports our researchers with in-house printing of full-color posters for scientific sessions, creative and effective website development for various projects and laboratories, photography, video, and developing content for various publications. The team is also meeting increased requests for consulting and assistance in specialized areas, such as – budget planning for communications or education components of research projects, use of videotaping as outreach and documentation, creation of educational posters, hand-outs and other materials, and communications and media planning as a means of furthering the objectives of specific studies. Our primary means of reaching to the community at large, at the local, national and international levels, is through timely and engaging news releases. However, we have instituted a strategy of increasing first-hand knowledge of our community members by re-introducing on-site tours, actively seeking speaking engagements and participating in community events.

Computing Services



Guy LaVergne
Director

Guy LaVergne B.S., CCNP, David Alexander, B.S., Claire Lassalle, B.S., Cherie Gravois B.S., B.A., M.B.A., Ray Allen, Ph.D., Barry Buchanan, CNE, Stephen Acosta, B.S., Archana Acharya, M.S., Jason Brakel, B.S., Kavitha Challa, M.S., Clint Duffy, B.A. Michael Gelpi, B.S., Jennifer Gonzalez, B.S., Jeff Hannaman, B.S., Diana Holmes, B.A., M.S., Eric LeBlanc, B.S., Sean Marshall, B.S., Andy Miner, MCSE, Andrew Russell, B.S., Brad Euggino, Michael LeBlanc, Shawn LeBlanc, Thomas Ramsey, Brittnay Strange

Mission — to assist the Center in the pursuit of its mission by providing exceptional technical support in technology, collaborative tools and customized application development.

The department focuses on the design, development, implementation, and application of information technologies that will support Center research and business operations. Computing Services provides all phone, network, server, desktop, and application support for the Center through its four functional groups: Administrative Computing, Nutritional Computing, Technical Support and Education, and Infrastructure. With more than 600 users to support, the department delivers many high-end applications and services using 40 enterprise servers through our fiber optic networks. Users have access to a robust enterprise network of servers with a storage capacity of more than 7 terabytes and a computational capacity sufficient to support the research and administrative demands of the Center.

Computing Services places a high value on staying abreast of new technological advances and integrating them into our services in order to increase collaborative opportunities for our faculty and decrease the burden for our administrative staff. By introducing new and novel computing tools and techniques, we are able to enrich the computing environment, thus doing our part to improve overall efficiency and enhance the Center's research activities. One way the department achieves this mission is by ongoing training and refining the talented professionals in our department. The high level of distinction and professionalism achieved by Center scientists serves as an excellent example which Computing Services strives to emulate. We are proud to be associated with the science produced by our institution and gladly welcome the opportunity to serve the Center's research community in its pursuit of excellence.

Facilities Management



Bob McNeese
Director

Facilities Management provides operation and maintenance services to support the mission of the Center.

Facilities Management is charged with responsibilities for the interior environmental control of the facility; building maintenance and equipment repairs; utility services; grounds maintenance; custodial services; shipping and receiving; property control; and security. Facilities Management also provides overall project design supervision and monitors construction activity for facility additions and renovations, and coordinates equipment acquisitions funded by the Pennington Medical Foundation. The department supervised the completion of a 15,000 sq.ft. addition to the Claude B. Pennington, Jr. Building which will house new Population Science initiatives. Design coordination and supervision for our new Clinical Research Building, along with various other renovations of existing research facilities were also provided.

Receiving Department

Dwayne Lambert and Barrett Mabile

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. The present value of moveable equipment is approximately \$26,000,000, and all pertinent information is maintained in a computerized inventory database and certified to the state each year. All requests for furniture moves and office personnel relocations are also coordinated through this department.

Bob McNeese, B.I.E., Marilyn Hughes, B.A.S., Walter Legett, B. Architecture, Darryl LeJeune, B.S., Arthur Broussard, Wendy Brown, Barbara Cantrell, Gloria Davis, Walter Farr, Adam Fauchaux, James Hall, Jerrol Jackson, Clinton Jarrett, Cornelius Johnson, Paul Johnson, Sherrie Mabile, Bryan Marks, James Palmer, and Ken Wesley.

Security Department

Hal Taylor, Capt., Scott Bertrand, B.S., Lakeisha Borel , Jason Chambers, Jennifer Heckert, B.A., Steven Kirby, Karen Quebedeaux, and Lionel Smith.

The Security Department was reorganized in 2005 when control was transferred from the LSU Police Department to the Pennington Center. Security officers are responsible for the safety and well being of employees and property, and an officer is on duty at the Center at all times. The Security Department issues employee identification cards and parking tags, and regulates and issues temporary cards for contractors, outside technicians, and other visitors. The Department also issues all keys and maintains records that document the assignment of keys. Officers also make rounds monitoring critical plant equipment and recording temperatures of numerous ultra low freezers ensuring that they are in the proper temperature range.

Stores

Richard Caro, B.S., Errol Broussard, B.S., Hilary Polito, B.A., M.S., Rodney Bynum, Brad Guidry

Pennington Stores is a full-service storeroom that offers research, medical, and office supplies to Center employees. Products not in stock can be special ordered. The operation of this auxiliary enterprise, formerly operated under the auspices of the LSU Health Science Center, has been transferred to PBRC.

Fiscal Operations



Mark Alise
Director

Mark Alise, M.B.A., Ph.D., Thomas Blalock, B.S., Joey Cyrus, B.S., Pam Fisher, BS, Steve Kelly, M.S., Ph.D. (Cand.), Charlie Mackles, B.S., Monica Mougeot, M.S., CPA, Matt Zylicz, M.S., Annette Potter, Mary Simpson, Yvette Stokes, Juanita Westly, and Diane Lowrey.

Human Resource Management



Gena Doucet
Director

Gena Doucet, B.S., M.B.A., Adrienne Davis, B.S., M.B.A., Becky Guillot, Sharon Hebert, B.A., Jason Hymel, B.S.

Fiscal Operations managers serve the research process as the Pennington Biomedical Research Center providing individualized financial management of research and clinical funding. Detailed management of the accounting and reporting requirements of grants and contracts by Fiscal Operations affords Center faculty the opportunity to focus on the science of their funded research.

The management services provided by Fiscal Operations include payroll, purchasing, processing vendor invoices for payment, sponsored projects accounting, contracts audit, budget preparation and monitoring, travel reimbursement audit, collection of university revenues, in addition to assisting in portions of the employment process including services for international students, scholars, fellows, and faculty.

Fiscal Operations is also responsible for all financial accounting and reporting for the Pennington Biomedical Research Center relative to all state, federal, and industry funding.

Mission — to provide efficient and effective support services in such areas as recruitment, employment, benefits, and retention and reward of faculty and staff.

Human Resource Management is committed to provide services, which support the strategic goals of the Center to recruit, retain, develop, and reward faculty and staff. HRM is also dedicated to ensure compliance with all federal, state, and local employment laws, which includes the development and implementation of policies and procedures relating to employment and equal opportunity.

Intellectual Property, Legal and Regulatory Affairs



Anne Jarrett
Director

Anne Jarrett, Ph.D., JD, LL.M., MBA, MPH, Janice Warren, B.A.,
Betty Rushing

The Director of the Office of Intellectual Property, Legal and Regulatory Affairs (IPLRA) reports directly to the Executive Director and oversees activities involving economic development, commercialization of research, legal, regulatory and compliance functions.

Economic Development and Commercialization

The economic development mission of the Office of IPLRA is to commercialize PBRC's intellectual property – new ideas, inventions and discoveries, such as obtaining patents and copyrights, seeking licensees and business partners in the U.S. and worldwide, and licensing technologies for the benefit of PBRC, the inventors, and society.

The most recent commercialization successes include a \$9 million license in 2007 for a cancer-fighting compound which became the basis for a Louisiana-based start-up company, Esperance Pharmaceuticals, LLC. PBRC inventors William Hansel, PhD, and Carola Leuschner, PhD, along with other LSU researchers, figured prominently in the cancer compound's discovery and development. This unique, targeted anticancer fusion protein is selectively toxic to cancer cells. The potent cytolytic peptide portion of the compound kills cancer cells. Initial studies show regression of well-established cancer and the company is preparing to conduct proof of concept human trials in the near future.

Another successful Louisiana start-up company, NuPotential, LLC, was founded by PBRC research Kenneth Eilertsen, PhD. At the end of 2007, NuPotential received \$3 million in new venture capital funding from Louisiana investors. NuPotential is advancing cell therapy technologies that enable researchers to more quickly and precisely develop new regenerative medicines for diseases such as Alzheimer's, diabetes, severe burns, and others.

A recent discovery by Andrew Butler, PhD, has uncovered a novel peptide which is being shown to improve insulin sensitivity and reverse certain metabolic syndromes linked to obesity. A multi-year research agreement has been awarded to Dr. Butler by an American biotech company, which

holds an option to license the technology. This research has shown promising results to date with plans to move toward developing a compound for use in human trials.

A cutting edge interactive approach to body image and related behavioral assessments is being developed by Tiffany Steward, PhD, in a new start-up company created in 2007 with funding from Themelios Venture Partners. The software-based technology company is in the process of applying state-of-the-art computer technology to more accurately assess a specific individual's real body image and provide for interactive feedback, which can be used as a behavioral tool for psychologists dealing with eating disorders and other body image issues.

Two new collaborations are also being developed on the global level, with initial collaborations taking place in 2007 and planned to continue in 2008. Key PBRC researchers and several prominent Taiwanese researchers and biotechnology entities will meet again in Taiwan in early 2008 to further develop collaborative research and development interests. Similar efforts have begun in France, both at the Paris Chamber of Commerce, and at BioPole, a Poitiers, France, biotechnology research incubator housing several start-up companies. Ongoing activities are planned to further develop these promising collaborations in France.

IPLRA provides service-oriented assistance – supporting PBRC researchers and businesses through every step of the technology transfer process. The office serves as a portal for the business community to identify interesting areas of research and to ensure that interested parties are put in touch with the proper laboratories and centers. The process of identifying and protecting discoveries with commercial potential and providing proper guidance toward success requires specialized techniques and skills which are provided by the IPLRA Office.

The number of technology disclosures, patent applications, license agreements, joint ventures, new business start-ups, and other economic development activities continues to grow at PBRC.

Intellectual Property (cont.)

Sponsored Projects



Winona Ward
Director

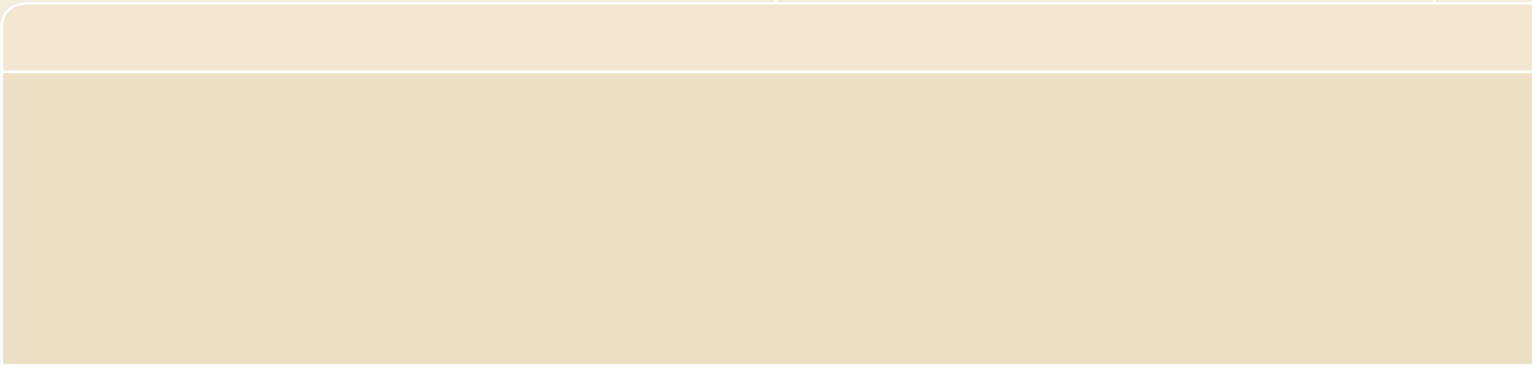
Winona Ward, B.A, Danielle Johnson, B.A.,
Katie Thudium

Legal, Compliance and Regulatory Affairs

The Office of IPLRA also functions as the compliance office for PBRC and the liaison to other regulatory offices and programs at the Center. The Director of IPLRA acts as the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Compliance and Privacy Officer. In addition, the Director works closely with the Institutional Review Board (IRB), the Biosafety Committee, and all other PBRC compliance components. The Director also oversees legal activities for PBRC.

Mission — The Office of Sponsored Projects provides a full range of pre- and post award services to faculty, principal investigators, and project directors for grants, clinical trials, and other sponsored research.

Sponsored Projects provides services that include proposal review, budget development, contract development, and negotiation of award terms and conditions. Sponsored Projects also tracks and reports grant and contract awards and current and pending support and locates and targets sources of research funding. Sponsored Projects assists faculty with locating funding information, initiating and processing proposals, and administering awarded sponsored projects. It also acts as a liaison between investigators and other offices on grant or contract-related matters. It is our goal to remove the administrative burden of sponsored research activity from the faculty in a manner that is both conducive and effective as it relates to the mission of the Center.





“That our scientists are influential in the world of science is evidenced by the more than 180,000 citations that their research has received in scientific literature.”

Dr. Claude Bouchard

Executive Director

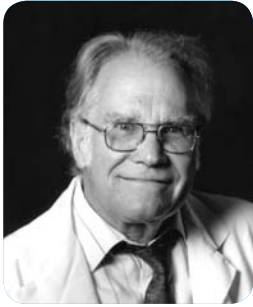
Pennington Biomedical Research Center

Adjunct Faculty 2006-2007

Baker, David, Ph.D.		
Bavister, Barry, Ph.D.	Professor	University of New Orleans; Department of Biological Sciences
Bazzano, Lydia, Ph.D.	Assistant Professor	Tulane University School of Public Health and Tropical Medicine - Dept. of Epidemiology
Bellanger, Eric D., M.D.	Instructor	Vista Surgical Hospital, Baton Rouge, LA
Bennett, Peter H., M.B., FRCP	Professor	NIDDK, NIH, Phoenix, AZ
Blair, Steven. PED	Professor	University of South Carolina, Arnold School of Public Health
Bombet, Leon, M.D.	Instructor	The Baton Rouge Clinic, Pediatrics, Baton Rouge, LA
Brenner, Carol, Ph.D.	Associate Professor	University of New Orleans
Brown, Sandra, Ph.D.	Professor	Southern University, Grad. Nursing Program, Baton Rouge, LA
Caprio, John T., Ph.D.	Professor	LSU, Biological Science Dept.
Cassidy, William, M.D.	Assistant Professor	LSUHSC, Department of Medicine
Cohen, Deborah A, M.D., MPH	Professor	Rand Corporation, Santa Monica, CA
Colvin, Lisa A., Ph.D., FACS	Professor	University of Louisiana, Department of Kinesiology, Monroe, LA
Copeland, Amy, Ph.D.	Associate Professor	Louisiana State University, Department of Psychology
Elkind-Hirsch, Karen, Ph.D.	Associate Professor	Women's Research Institute, Research Dir., Department of Reproductive Med.
Finley, John W., Ph.D.	Professor	LSU Ag Center, Department of Food Science
Fonseca Vivian, Ph.D., MBBS	Professor	Tulane University, Armed Forces Medical College
Garitty, Earl James, M.D.	Instructor	LSUHSC, Earl K. Long Medical Center, Department of Otolaryngology
George, Julia, J.D.	Instructor	LA Dept. of Culture, Recreation and Tourism, Office of the Secretary, Deputy General Counsel
Gordon, Stewart, M.D.	Assistant Professor	LSUHSC, Earl K. Long Medical Center, Dept. of Pediatrics
Guidry, Jimmy, M.D.	Assistant Professor	LA Dept. of Health & Hospitals, Office of Public Health
Hasek, Barbera, Ph.D.	Instructor	Baton Rouge Community College, Biology Department
Hebert, Larry, M.D.	Professor	Retired
Hulver, Matthew, Ph.D.	Assistant Professor	Virginia Polytechnic Institute and State University
Jazwinski, S. Michal, Ph.D.	Professor	LSU Health Services Center, N.O. Professor Dept. of Family Medicine
Johnson, Jolene, M.D.	Assistant Professor	LSUHSC-N.O., Dept. of Clinical Medicine; Earl K. Long Medical Center, Dept. of Internal Medicine, Baton Rouge
Jones, Glenn, Ph.D.	Associate Professor	Earl K. Long Medical Center, Adult Psychology & Center for Primary Care Research
Keenan, Michael, Ph.D.	Associate Professor	LSU, School of Human Ecology, Dept. of Human Nutrition and Food
Lammi-Keefe, Carol, Ph.D.	Professor	University of Minnesota, Dept. of Nutritional Studies
LeBlanc, Monique M., Ph.D.	Instructor	LA GEAR UP, Baton Rouge
Liu, Zhijun, Ph.D.	Professor	LSU Ag Center, Medicinal Plants Lab

Lovejoy, Jennifer, Ph.D.	Professor	Bastyr University, Nutrition and Exercise Science Dept., Seattle, Washington
Luftig, Ronald, Ph.D.	Professor	LSUHSC, Department of Microbiology, Immunology and Parasitology
Martin, Pamela, Ph.D.	Assistant Professor	Private Practice, Behavioral Medicine
McKnight, G. Tipton, M.D.	Instructor	LA Office of Group Benefits, LA State Police Training Academy
McLaughlin, Leslie, D.V.M.	Assistant Professor	LSU School of Veterinary Medicine, Department of Pathobiological Sciences, Baton Rouge
Newcomer, Bradley, Ph.D.	Associate Professor	University of Alabama, Dept. of Diagnostic and Therapeutic Sciences, Birmingham
Ochoa, Augusto, Ph.D.	Associate Professor	LSUHSC, Tumor Immunology Program
Paige, John T., M.D.	Assistant Professor	LSUHSC, School of Medicine
Phelps, Donald, LLB (J.D.)	Instructor	Our Lady of the Lake Regional Medical Center; Hospice Foundation, Baton Rouge
Quintana, Humberto, M.D.	Professor	LSUHSC, Department of Psychiatry
Raskin, Ilya, Ph.D.	Professor	Rutgers University, Cook College, Biotech Center, Rutgers, NJ
Raum, William, M.D., Ph.D.	Professor	LSUHSC, Department of Medicine & Surgery
Ribnicky, David, Ph.D.	Professor	Rutgers University, Cook College, Biotech Center, Rutgers, NJ
Richards III, Edward, J.D. M.PH.	Professor	LSU Paul M. Hebert Law Center
Rodriguez, Paulo, Ph.D.	Instructor	LSUHSC, Stanley S. Scott Cancer Center, Department of Pediatrics
Sjostrom, Lars, Ph.D.	Professor	Göteborg University and Sahlgrenska University Hospital, Sweden
Sothorn, Melinda, Ph.D.	Associate Professor	LSUHSC, School of Public Health, Section of Health Promotions
Stephens, Jacqueline, Ph.D.	Professor	LSU, Department of Biological Sciences
Stewart, Laura K., Ph.D.	Assistant Professor	LSU, Exercise Physiology Department
Volaufova, Julia, Ph.D.	Professor	LSUHSC, School of Public Health
Whisenhut, Brooke, Ph.D.	Assistant Professor	Missouri State University, Department of Psychology, Springfield, MO
White, Marney, Ph.D.	Assistant Professor	LSU, Department of Psychology
Woltering, Eugene, M.D.	Professor	LSUHSC, School of Medicine, Dept. of Surgery

Faculty Emeritus



Samuel M. McCann, M.D.
Professor Emeritus

Samuel M. McCann, M. D., Professor Emeritus

September 8, 1925 - March 16, 2007

Dr. McCann received his medical training at the University of Pennsylvania School of Medicine. He was subsequently commissioned a 1st lieutenant and then captain in the U.S. Army, serving in the Medical Corps at Walter Reed Army Medical Center.

Dr. McCann developed a long medical career and research career in neuroendocrinology, leading to membership in the National Academy of Sciences and the American Academy of Arts and Sciences, among many other honors. He arrived at the Center in 1995, where he held the United Companies Chair. He made many important discoveries and was one of the most influential scientists of his generation.

Dr. McCann was the center's first Professor Emeritus.

Doctorate Honoris Causa

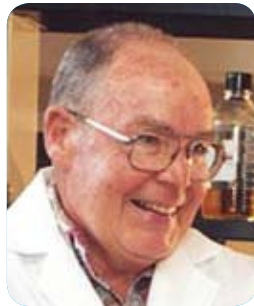
In cooperation with the Louisiana State University Health Science Center, the Pennington Biomedical Research Center granted its first Doctorate Honoris Causa in the Spring of 2005. The first recipient of this degree was Douglas Coleman, Ph.D.

Douglas Coleman, Ph.D.

Douglas Coleman earned his Ph.D. in biochemistry in 1958 from the University of Wisconsin. Until his retirement, Coleman conducted his research at the Jackson Laboratory in Bar Harbor, Maine. His work on what he called the “satiety factor” was a critical in the later discovery of leptin, now known as a major molecular player in the onset of obesity.

Coleman was awarded the Doctorate Honoris Causa for his life’s work on diabetes and obesity that, according to a description accompanying the degree, “provided the foundation for spectacular advances in the understanding of the central and peripheral regulation of energy balance in mammals, including humans.”

Energy balance is the body’s attempt to balance food intake with energy expenditure in order to maintain weight. Coleman’s work, published more than 30 years ago, provided the foundation for the understanding of how our brain interacts with peripheral tissues in order to maintain energy balance.



Douglas Coleman, Ph.D.

Albert J. Stunkard, M.D.


Albert J. “Mickey” Stunkard, a native of New York, received his M.D. in 1945 from the Columbia University College of Physicians and Surgeons. During his distinguished and productive career as psychiatrist and scientist, he concentrated his efforts on obesity and eating disorders.

Dr. Stunkard’s research career has spanning more than 55 years was continuously supported by the National Institutes of Health, and he has written more than 400 peer reviewed publications, making numerous contributions to our understanding of the genetic epidemiology of obesity through adoption and twin studies. He first described the night eating syndrome, as well as binge eating disorder, and the role they play in the predisposition to obesity.

Dr. Stunkard developed an eating inventory instrument used around the world to assess fundamental eating behavioral traits, and his career provides a superb illustration of exemplary experimental and clinical research.



Albert J. “Mickey” Stunkard, M.D.



“Several discoveries have been made by our scientists over the years, and many of the advances in science made by others would not have been made in a timely manner if our scientists had not contributed some important observations or facts to the knowledge base.”

Dr. Claude Bouchard
Executive Director, Pennington Biomedical
Research Center

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“There is no greater investment for our personal health and the community’s economic health than to help PBRC reach its tremendous potential.”

John Noland

Chair

Pennington Biomedical
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A Message from our Chair—Pennington Medical Foundation

Dear Friends,

The Trustees of the Pennington Medical Foundation held their first meeting on April 17, 1980. I was excited and proud to be a member of that initial board. All of us hoped that the journey that we were beginning would lead to the fulfillment of my grandparents' dream. Today, I can honestly report that the journey has been exciting and the dream to become a world leader in nutrition has been achieved.

The Pennington Biomedical Research Center facilities are not only among the finest in the nation, but indeed the entire world. However, our work is not complete. The need to provide additional research and support space, both clinical and basic, continues. In the past year, the Pennington Medical Foundation's highest priority was to secure funding for the Clinical Research Building.

The Pennington Medical Foundation contributed approximately \$2.5 million towards the planning, design, and site development for this facility. Fortunately, the 2007 Legislature appropriated \$21 million to begin construction and the Governor's Office of Facility Planning and Control is working to have architects assigned and the project placed on the market.

We anticipate that construction on the new Clinical Research Building will begin in April of 2008 and should be completed during the last quarter of 2009. This new facility will guarantee that the Pennington Biomedical Research Center's research will continue to be on the forefront of developing strategies to both combat and prevent the chronic diseases that afflict the citizens of our state, region, and beyond.

The completion of the new Clinical Research Building will mark the end of one important project, but the beginning of others. In today's intensely competitive international research environment one cannot take even a brief pause. The Center must be positioned to take advantage of every opportunity to grow and advance medical knowledge – the fleeting nature of opportunity demands that we press forward.

During 2008 we will celebrate the 20th anniversary of the opening of the Pennington Biomedical Research Center. Through the careful stewardship of the Board of Trustees, my grandparents' initial gift of \$125 million has enabled the Pennington Medical Foundation to provide approximately \$145 million in cumulative capital and operating support to the Center. On behalf of the Board of Trustees of the Pennington Medical Foundation, I extend our deep gratitude for all of the support that the Center has received from public and private funds, from individuals, corporations and charitable foundations.

Sincerely,



Paula Pennington de la Bretonne
Chair



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A Message from our Chair—Pennington Biomedical Research Foundation

Dear Friends:

On behalf of the Board of Directors of the Pennington Biomedical Research Foundation, I am proud of our efforts to support the Pennington Biomedical Research Center. I suggest there is no greater investment for our personal health and the community's economic health than to help PBRC reach its tremendous potential. The Pennington Biomedical Research Foundation supports the work of the Center by providing vital funding and advocacy for its important research.

As we celebrate the 20th anniversary of outstanding research at PBRC, it is important to thank and recognize the many individuals, companies and foundations that have been instrumental in generating support through the Foundation. Their names are reflected in the historical PBRF board listing, indicating those individuals that have voluntarily provided inspired leadership to these efforts throughout these 20 years. Additionally, the donor listing recognizes the individuals and entities that have given generous financial resources to support and sustain the Center through the years.



I served as President of the Baton Rouge Area Foundation in 1988 when it made the first of several grants of philanthropic community support to the Pennington Biomedical Research Foundation for the benefit of PBRC. Twenty years ago I stated, “The board felt it especially important to make this grant at this early stage of the Center’s development in order to make a strong statement to the community of our keen interest in Pennington.” Today that interest is as strong as ever and most importantly, the need for continued support is as critical as in those first days.

While we pause to celebrate all that has been achieved in the past 20 years, I am most excited to consider the opportunities that await us in the future. It is with that continued vision and optimism for the future that the Pennington Biomedical Research Foundation looks to make an impact on the Center.

Sincerely,

A handwritten signature in black ink that reads "John B. Noland". The signature is written in a cursive, flowing style.

John B. Noland
Chair

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United Companies/Harris J. Chustz Chair Abba Kastin, M.D.	United Companies	1991
Hibernia National Bank/Edward G. Schlieder Chair Jeffrey Keller, Ph.D.	Capital One (formerly Hibernia National Bank)/ Edward G. Schlieder Educational Foundation	1992
George A. Bray, Jr. Super Chair in Nutrition Claude Bouchard, Ph.D.	Pennington Medical Foundation	1999
Douglas L. Gordon Chair in Diabetes and Metabolism Eric Ravussin, Ph.D.	Edward G. Schlieder Educational Foundation	2001
LPFA Chair in Nutrition Peter Katzmarzyk, Ph.D.	Louisiana Public Facilities Authority	2002
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Peggy M. Pennington Cole Endowed Chair in Maternal Biology & the Risk of Obesity Claudia Kappen, Ph.D.	Irene W. & C. B. Pennington Foundation Community Foundation for Southeastern Michigan	2004
John S. McIlhenny Endowed Chair in Health Wisdom Tim Church, M.D., M.P.H., Ph.D.	Coypu Foundation Trust	2004
John W. Barton, Sr. Endowed Chair in Genetics and Nutrition Under Recruitment	Various Donors	2005
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George H. Bray Professorship Hans Berthoud, Ph.D.	Various Donors	1999

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**“While the dreams have
become realities, and the realities
are now memories, the Pennington
Biomedical Research Center is not a
finished product.”**

George Bray, M.D.
former Executive Director
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