



BASIC RESEARCH

SCIENTIFIC REPORT | 2008–2009



PENNINGTON BIOMEDICAL RESEARCH CENTER



CLINICAL RESEARCH



POPULATION SCIENCE

LOUISIANA STATE UNIVERSITY SYSTEM



The Pennington Biomedical Research Center is a campus of the Louisiana State University System and conducts basic, clinical and population research. The research enterprise at the Center includes 80 faculty and more than 40 post-doctoral fellows who comprise a network of 53 laboratories supported by lab technicians, nurses, dieticians, and support personnel, and 19 highly specialized core service facilities. The Center's nearly 600 employees occupy several buildings on the 234-acre campus.

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During the years 2008 and 2009, the span of time covered by this issue of the Scientific Report, we have achieved some significant milestones, including expansion of our clinical facilities, launching the first statewide discussion of children's obesity, and embarking on new and exciting research in dementia to name but a few.

We are grateful to the Louisiana State University System Board of Supervisors, the Louisiana Board of Regents, and the Commissioner of Higher Education, Dr. Joseph Savoie and later Dr. Sally Clausen, for the support they have given to our efforts. We are especially grateful for the support given by LSU System Board Chairman, James Roy and subsequently R. Blake Chatelain, and System President, Dr. John Lombardi.

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

Our deepest gratitude goes to the men and women who serve on the boards of our two supporting foundations: the Pennington Medical Foundation and the Pennington Biomedical Research Foundation. Mrs. Paula Pennington de la Bretonne, chair of

the Pennington Medical Foundation, leads a group of dedicated individuals who have made it possible for the Pennington Biomedical Research Center to break ground on new facilities and to acquire sophisticated equipment and technologies on a regular basis. Likewise, John Noland and now Tim Barfield, 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 past two decades years would not have been possible without the dedication of our faculty, staff and management team. Their devotion to our research and education efforts makes the Pennington Biomedical Research Center an inspiring place to work.

Our mission remains: *to promote healthier lives through research and education in nutrition and preventive medicine*. What has continued to develop is the breadth and depth of our science and our ability to achieve our mission. In this report, you will discover a wide spectrum of research programs and projects. You will also get a brief introduction to the process leading to new discoveries. To learn more about our science and 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



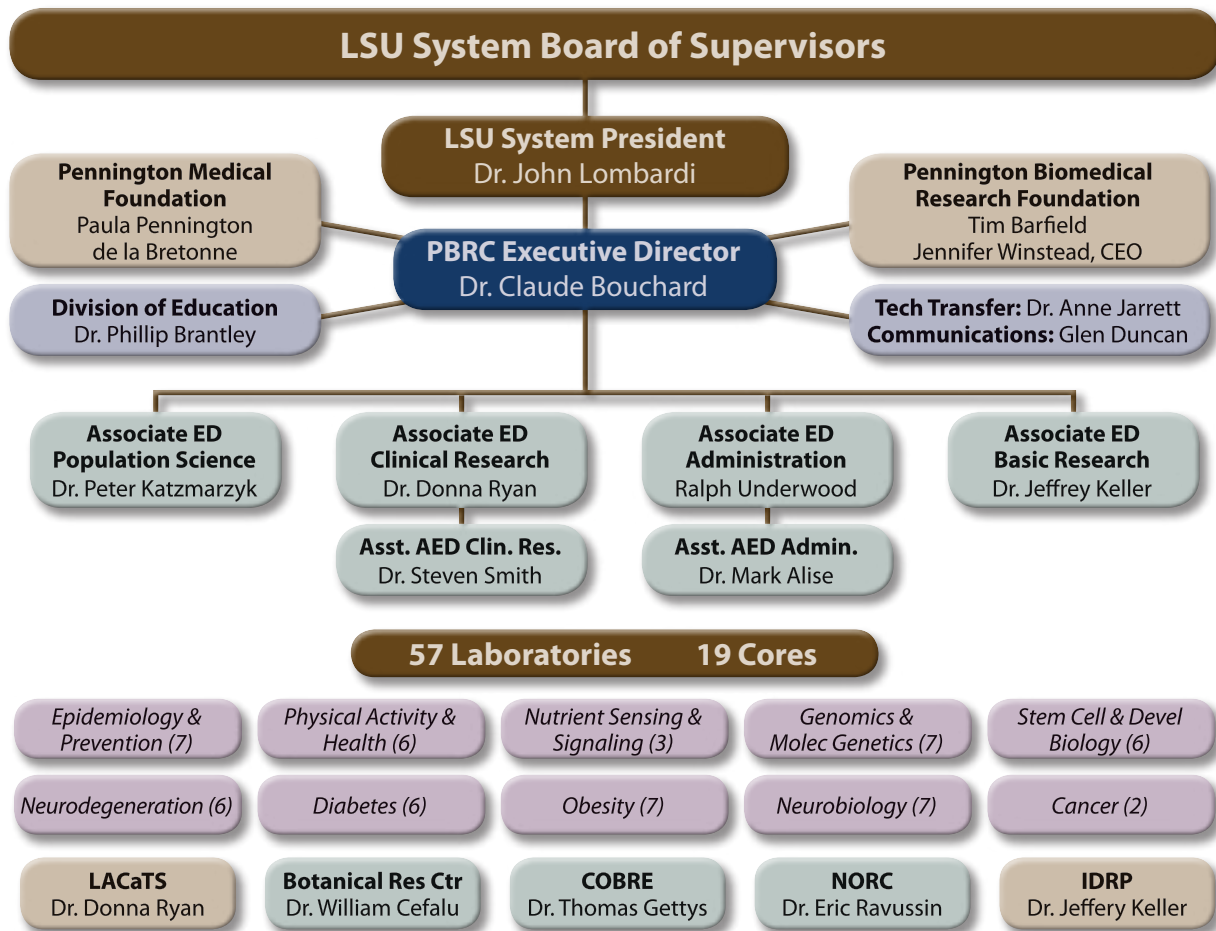
Claude Bouchard, Ph. D.
Executive Director
George A. Bray, Jr. Super Chair in Nutrition

In 2010, the Pennington Biomedical Research Center will reach a true milestone — the completion of its new clinical research space. A new 90,000 square foot building devoted to clinical research will stand as a testament to our vision of growing our science along three large research components: basic research, clinical research and population science. The new clinical research facility is the third expansion project undertaken in recent times and is sorely needed as our clinical research laboratories, staff and number of participants have outgrown our original building. In this Scientific Report, you will find a description of the clinical, population and basic

research activities as well as the various other programs of the Center. You will also read about the core facilities that provide cutting-edge technologies and high quality support to our research enterprise. This report will provide information on the challenges and opportunities, and the economic impact potential of the Center as we continue to experience growth in clinical research but also in basic research and population science.

Organization the Center

As of this writing, the Pennington Biomedical Research Center employs about 600 full-time and part-time people,



including 85 faculty and 40 postdoctoral researchers. In addition, the Center benefits from the contributions of more than 75 adjunct faculty. The scientists are grouped among 57 laboratories covering basic, clinical and population research areas.

Moreover the research enterprise of the Center is supported by the resources of 19 core facilities. During the period of time covered by this report, the Center re-organized its research efforts, turning from a broad divisional structure to a network of “program areas”, a more clearly identifiable structure closely linked to the research strengths and activities of the Center. These program areas are depicted on the Organizational Chart. Note that the number of laboratories for each program area is listed in parentheses in the chart.

The Pennington Biomedical Research Center is home to three centers of excellence funded by the National Institutes of Health: the Botanical Research Center, The Nutrition and Obesity Research Center (NORC), and the Center of Biological Research Excellence (COBRE). You will read about these entities later in this report.

Our latest endeavors which will undoubtedly prove to be highly significant over time as units of concentrated leadership and research are the Institute for Dementia Research and Prevention (IDRP) and the Louisiana Clinical and Translational Science Center (LACaTS). The latter, LACaTS, results from a collaboration among PBRC and the three medical schools of our State plus key research universities and research organizations with a mission to develop clinical and translational science, to increase the quality and quantity of clinical research conducted in Louisiana, and to train the next generation of clinical research scientists.

These entities are all depicted in the organizational chart at the bottom of page 4.

External Advisory Board 2008

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 2008 and its composition was as defined herewith.

Claude Lenfant, M.D., CHAIRMAN

Former Director, National Heart, Lung and Blood Institute

Harvey Anderson, Ph.D.

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Stephen Woods, Ph.D.

University of Cincinnati



New Clinic

Expansion and Renovation of Facilities and Major Equipment Acquisition

With the support of the LSU System and Board of Supervisors, the Louisiana Board of Regents, the Baton Rouge Area Chamber and the Louisiana Department of Economic Development, the Louisiana Legislature, along with the backing of the Governor and the Commissioner of Administration, allocated special dedicated funds for the expansion of the Center. Since 2007, the State of Louisiana has provided \$71 million to the Center for construction, renovation, research instrumentation, and infrastructure improvements. During the 2007 Regular Session, the Legislature allocated a total of \$21 million to build a new Clinical Research facility. This new 90,000 square foot building will be completed in the summer of 2010 and will allow us to compete for more clinical research studies from the National Institutes of Health and accept more industry sponsored contracts. Then in a special session of the legislature focusing on economic development in March 2008, the Governor supported new funding in the amount of \$50 million to develop expansion opportunities at the Center. These funds are being used to complete the financing of the new Clinical Research Building, build a state-of-the-art Imaging Center, construct a new Central Utilities Plant and Medical Storage Facility, and renovate the existing Clinical Building. In addition, the Center is using some of this special appropriation for infrastructure upgrades, research equipment, and faculty recruitment equipment. These investments into PBRC by the State of Louisiana will pay off with increased funding from external sources and health research contributions in the coming decades.



Imaging Center

Endowed Chairs and Professorships

Thanks to the generous contributions of many philanthropists, the hard work of the Pennington Biomedical Research Foundation and the strong support of the Eminent Scholars Program of the Board of Regents, the Center enjoys the use of 11 endowed chairs and 3 professorships. The list of these chairs and professorships along with the names of the donors who made the initial gifts is provided at the top of page 7.

Economic Impact

A report later in this document will contain more detail on the economic impact of PBRC. However, it is well worth noting that one sector is growing and stands to create significant future returns to the Pennington Biomedical Research Center, the LSU System and the State: new start-up companies based on findings of Center researchers. Among these, and perhaps most notably, is Esperance Pharmaceuticals, Inc. Investors created this company to take a potent cancer treatment compound from the laboratory bench to the first human clinical trials. It is significant, that when the FDA reviewed this drug, it was not just examining a new drug

Message from the Executive Director

	Chair:	Donor:
1	United Companies/Harris J. Chustz Chair <i>Abba Kastin, M.D.</i>	United Companies
2	Claude Bernard Pennington Chair <i>Leslie P. Kozak, Ph.D.</i>	C.B. “Doc” Pennington
3	Hibernia National Bank/Edward G. Schlieder Chair <i>Jeffrey Keller, Ph.D.</i>	Edward G. Schlieder Educational Foundation Capital One (formerly Hibernia National Bank)
4	George A. Bray, Jr. Super Chair in Nutrition <i>Claude Bouchard, Ph.D.</i>	Pennington Medical Foundation
5	Douglas L. Gordon Chair in Diabetes and Metabolism <i>Eric Ravussin, Ph.D.</i>	Edward G. Schlieder Educational Foundation
6	LPFA Chair in Nutrition <i>Peter Katzmarzyk, Ph.D.</i>	Louisiana Public Facilities Authority
7	Marie Edana Corcoran Chair in Pediatric Obesity and Diabetes <i>Under Recruitment</i>	Our Lady of the Lake Foundation
8	Peggy M. Pennington Cole Endowed Chair in Maternal Biology and the Risk of Obesity <i>Claudia Kappen, Ph.D.</i>	Irene W. and C.B. Pennington Foundation Community Foundation for Southeastern Michigan
9	John S. McIlhenny Endowed Chair in Health Wisdom <i>Timothy Church, M.D., Ph.D., M.P.H.</i>	Coypu Foundation Trust
10	John W. Barton, Sr. Endowed Chair in Genetics and Nutrition <i>Under Recruitment</i>	Various Donors
11	Fairfax Foster Bailey Endowed Chair in Heart Disease Prevention <i>Under Recruitment</i>	Laura and James Bailey, III, Virginia and John B. Noland, P. Foster Bailey
	Professorship:	Donor:
1	Douglas L. Manship Professorship in Diabetes <i>William Cefalu, M.D.</i>	Douglas L. Manship, Sr.
2	John Stauffer McIlhenny Professorship in Nutrition <i>Donald Williamson, Ph.D.</i>	Coypu Foundation Trust
3	George H. Bray Professorship <i>Hans Berthoud, Ph.D.</i>	Various Donors

in an existing category. This compound represents an entirely new category of drug, which seeks out and destroys cancer cells. Created here by Dr. William Hansel and collaborators, particularly Drs. Carola Leuschner and Fred Enright, this new category of drug, if it works as well in humans as in animal models, could well save thousands of lives.

In addition, Dr. Ken Eilertsen, scientific leader of one of our stem cell research laboratories, created NuPotential, LLC, in an effort to capitalize on a new technology for somatic cell reprogramming. This technology may one day allow a physician to treat a patient suffering from damage to an organ (as in type 1 diabetes, Parkinson and the like) by harvesting the patient’s

healthy cells from another tissue and “re-programming them” to generate new, healthy cells and tweaked them to assist the dysfunctional organ.

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

The Challenges We Face

The most important challenge we face is that of adequate funding from the Louisiana Legislature. Although significant legislative support has helped us expand our clinical research facilities, and to plan a state-of-the-art imaging facility and physical plant as well as to renovate existing facilities, current budget restrictions have created an unusual scenario. When our new clinical research building opens in 2010, we may not be able to hire physician scientists, clinical physiologists and behaviorists who have the ability to win competitive research grants and contracts that are needed to make the clinical research enterprise a success. Another challenge is that of being able to generate endowed research chairs in the range of \$3 to \$5 million so that we can compete in the national and international market place for the best and brightest scientists. The availability of chairs endowed at these levels will play a key role in the future of the Center.

Competition for the best minds has always been very keen. In the case of PBRC, there are now several institutions in the United States that are attempting to emulate its success, and a number of these institutions have a much larger endowment. We have already lost three senior faculty in 2008 and 2009 to other institutions with superior funding. It is therefore imperative that we be in a position to offer high quality employment opportunities and generous start-up funds to star faculty candidates and adequate retention measures to highly successful scientists who have made PBRC their scientific home. As the governor and legislature scrutinize higher education, it is imperative they reflect on the high value return to the citizens generated by cutting edge biomedical research. Adequate state funding is a critical investment, particularly in an environment where the level of federal funding for biomedical scientific research has not increased to any significant extent over the last four years.

The Opportunities We Have

There are great opportunities ahead for the Center and we are poised to take advantage of them. We are in a very strong position as a result of the high quality of our faculty and a portfolio of research grants and private research contracts that is equally strong. Each PBRC full time scientist at the level of assistant-professor and above brings in more than \$500,000 of external research funds every year. Also, PBRC’s scientists have excellent scientific productivity as shown by the fact that they published more than 400 scientific papers during the last academic year alone. Moreover, they are influential in the world of science as evidenced by the more than 245,000 citations that their research has received to-date in the world scientific literature.

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

In addition, the global field of disease prevention research presents a great future filled with exciting opportunities. To take advantage of these opportunities, our strategy has been and continues to be one of investing in cutting-edge basic science areas that will allow us to contribute to the definition of the next generation of best practices in public health and preventive medicine. Nutrition remains one of the key research pipelines, but it is complemented by strong programs in other behavioral areas and in the biological sciences.

Strategic Position of PBRC

As the population gets older and with many more Americans reaching 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 that

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

A Final Word

To remain on the path to success and greatness, it is obvious to me that the Center will need to continue to recruit outstanding faculty, expand its research facilities, augment its corps of star scientists, stay at the forefront of innovation in scientific instrumentation, and make growing contributions to the economy of the State of Louisiana.

After ten years at the helm, I am convinced that the Pennington Biomedical Research Center, despite its relative youth, has the potential to be a leading player on the international scene in nutrition and preventive medicine research if granted an adequate level of support.

I would like to thank you all for giving me the opportunity to serve the PBRC community over the last decade. These 10 years have been very rewarding and exciting. In particular, I owe a great deal of gratitude to the three Presidents of the LSU System with whom I negotiated my move to Baton Rouge or had the pleasure of working for as Executive Director of PBRC: Drs Allen A. Copping, William L. Jenkins and John V. Lombardi. I am grateful to those who served PBRC loyally as associate executive directors over the years, to William Silvia, Jennifer Winstead and Brad Jewell from our foundations, and to my office staff, particularly Anne Duke, Toni Finn and Nina Laidlaw. To my colleagues on the

PBRC faculty: I appreciate the support you have given me and your confidence in my leadership over the last 10 years. I am now looking forward to going back to science and hopefully making some contributions in the Human Genomics Laboratory while supporting the mission of the Center.

In 2005, we launched a PBRC Strategic Plan covering the period from 2005 to 2010 (http://www.pbrc.edu/pdf/pbrc_vision2010.pdf). In 2007 we published an interim status report on the Strategic Plan (<http://www.pbrc.edu/pdf/VISION07update.pdf>). This chapter of the Scientific Report will serve as the final report on what has been accomplished in the context of our 2005-2010 plan of action.

When we released our five-year strategic plan, called Vision 2010, we called for significant growth in the breadth of our research, in our physical facilities and in our support functions. Our vision was clear: *“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 was to significantly raise our sights within four 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
4. Contribute to the economic development of the State of Louisiana.

To achieve that ultimate success, we needed to recruit senior researchers with proven abilities to compete for large research grants, and then to equip them with outstanding facilities. We have achieved a great deal of that part of our vision as well as meeting many of ten priority areas we announced. Here is short summation of those priorities and the progress we have made under each from 2005 to today.

Top Ten Priorities

1. *Establish a Division of Nutrition and the Brain.*

Early on we established this division. It has since been re-organized under two program areas, one in Neurobiology, the other in Neurodegeneration. Since the plan was launched in 2005, Drs. Don Ingram, Maria Barnes, Stefany Primeaux, Heike Muenzberg, Paul Pistell, Jeffrey Keller, and Annadora Bruce-Keller have joined the ranks of these two neuroscience-focused program areas.

2. *Expand comparative biology and enhance transgenic animal core.*

Dr. Barry Robert 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. More vivarium space is needed to accommodate the growth of the basic science programs, and the planning for that is underway. We have added considerable human and equipment resources to the Transgenics Core and Dr. Jingying Zhang has joined the Core.

3. *Increase expertise in developmental biology and genetic epidemiology.*

Our recruitment was completed for the Peggy M. Pennington Cole Chair in Maternal Biology (Dr. Claudia Kappen), and for other key areas such as regulation of gene expression (Drs. Michael Salbaum and Nancy Arbour-Delahaye), neuroendocrine immunology and aging (Dr. Vishwa Dixit), adipose tissue, (Dr. Yourka Tchoukalova), cell biology and cell imaging (Dr. David Burk), infection and adipose tissue biology (Dr. Nikhil Dhurandhar), neuropeptides and metabolism (Dr. Greg Sutton), cancer prevention, (Dr. Sita Aggarwal), DNA Repair (Dr. Vijay Hegde), free radicals and oxidative stress (Dr. Krisztian Stadler), thermogenesis (Dr. Rea Anunciado-Koza), and physiology and metabolism (Drs. Darcy Johannsen and Sudip Bajpayi). Additionally, Dr. Indu Kheterpal joined the Center and expanded a core service, now called the Proteomics and Metabolomics Core. She is also the leader of the structural protein biology laboratory.

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

Dr. Peter Katzmarzyk joined the Center as our first associate executive director for Population Science. He was tasked with the responsibility of developing population science programs. A new 15,000 sq. ft. Population Science wing was added to the Claude B. Pennington, Jr. building. It houses population science faculty and support staff. Additions to the faculty in clinical and population science include Drs. William Johnson and Ron Horswell (biostatistics), Dr. Stephanie Broyles (contextual risk factors), Dr. Gang Hu (chronic disease epidemiology), Dr. Afschin Gandjour (health economics), Dr. Catrine Tudor-Locke (walking behavior), and Dr. Marc Hamilton (inactivity physiology).



Completion of our new 90,000 sq. ft. Clinical Research building remains a top priority for the Center, as is the completion of a new Imaging Center, now in the design phase. Three years ago, we established a new Magnetic Resonance Spectroscopy laboratory, which is now fully operational.

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: exercise testing and functional foods, (Dr. Conrad Earnest), clinical psychology (Dr. Valerie Myers), 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 Nutrition Obesity Research

Center (NORC) 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 secured an NIH planning grant to create the Louisiana Clinical & Translational Research Center (LACaTS), and are underway in seeking permanent funding from the NIH. The LA CaTS center is a collaboration among all medical schools and key research universities and research organizations, led by the Pennington Biomedical Research Center, with a mission to develop the discipline of clinical and translational science, to increase the quality and quantity of clinical research conducted in Louisiana, and to train the next generation of clinical research scientists. LACaTS will be headquartered in the new PBRC Clinical Research Building beginning in the summer of 2010.

7. Expand the postdoctoral program.

We now have two NIH T-32 institutional training grants designed to train junior scientists to become independent researchers. We have been successful in obtaining a competitive 5-year renewal on our NIDDK T-32 training grant entitled Obesity from Genes to Man that funds four postdoctoral fellows per year for up to three years of training. We have recently been awarded a 5-year NCCAM T-32 entitled Botanical Approaches to Combat Metabolic Syndrome. This new grant offers up to three years of training for seven additional postdoctoral positions per year. New coursework including an overview course in complementary and alternative medicine is being added to existing instruction in nutrition science, grant writing, professional development and the responsible conduct of research. We continue to experience an increase in competitive applications for our postdoctoral positions and our current postdocs appear satisfied with our training programs. In a recent article on best places for postdocs to train, PBRC was ranked at 26 among well over a hundred postdoctoral training institutions. The National Institutes of Health received a ranking of 32.

8. Expand community and professional education efforts.

The Division of Education continues to increase the number of community and professional symposia and educational activities we offer. We conduct two to three scientific symposia each year that allow international scientists to visit Baton Rouge and interact with our faculty. We continue to partner with the LSU Agricultural Center to develop internet based health educational materials, the Pennington Nutrition Series, designed especially for citizens of Louisiana. These materials are particularly popular with Louisiana school teachers and Agricultural Extension agents conducting health education programs throughout our state. We have also partnered with Blue Cross Blue Shield of Louisiana to offer a web-based program for promoting healthy eating and physical activity entitled the “Louisiana 2 Step.” The Division also offers “Take 5 for Diabetes” an American Diabetes Association recognized program in diabetes prevention and management for community adults. Finally, the center promotes community health fairs such as the Annual Irene Pennington Women’s Wellness Day and public forums to discuss health concerns affecting the citizens of Louisiana such as the recent town meeting on dementia.

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

The Wellness Center project had been delayed due to conditions in national financial markets, inflationary concerns in the construction industry, and projected negative operating budget cash flows. Financial markets have stabilized but considerable uncertainty and apprehension about future turmoil remain. Rapidly rising costs in the construction industry have subsided and construction costs appear to be returning to more reasonable and predictable levels. Cash flow issues remain and the Wellness Center project must be self-financed and essentially self-sustaining as no state assistance will be forthcoming. In addition, both the Pennington Medical Foundation and its partner, Our Lady of the Lake Regional Medical Center, currently are not in a position to underwrite construction and operating costs.

We continue to pursue solutions to debt service loads and operating budget issues. Our goal is to construct a prototype facility that combines scientific studies, medical services, and fitness services as an integrated affordable approach to health and wellness.

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. Recent legislative budget cuts have forced us to allow some positions to go unfilled and to curtail new hiring.

Summary of the financial progress underlying Vision 2010

A cornerstone of Vision 2010 was 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 operating revenue growing from \$45 million in 2005 to \$65 million by 2010. We can report that the operating budget for the current fiscal year will exceed \$65 million.

The annual appropriation from the State of Louisiana is currently \$15.8 million, a decrease of almost 10% compared to the previous year. Historically, state appropriations comprise less than one quarter of the Pennington Biomedical Research Center’s operating budget, but those dollars are critically important to the success of the Center. Unrestricted state dollars

are used to cover some of the campus infrastructure costs, to fund pilot studies that result in new grants and contracts and as seed money to recruit new research faculty and build new research programs at the Center. In return for its investment, the state receives an inflow of research dollars from sources outside of the state and the birth of new knowledge-based businesses, creating new jobs and new wealth in Louisiana.

While state operating support of the Center decreased in the most recent fiscal year, PBRC has received a very important one-time investment of state funds equaling \$71 million for construction, renovation and upgrade to facilities and equipment. These funds are being used to upgrade and renew research equipment and for a number of construction and renovation projects that will enhance the Center's competitive position in the highly competitive arena of biomedical research.

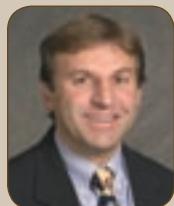
Perhaps the most noteworthy project funded by the \$71 million one-time state appropriation is the construction of a new 90,000 sq. ft. Clinical Research Building. In recent years the Center has been forced to turn away clinical trials due to lack of space and is utilizing 8 temporary trailers for clinical research. The new facility has the potential over time to add \$20 million in yearly clinical research revenue. After an initial ramping up over three years, approximately 300 new faculty and support staff jobs may be created. There is also the potential to create two hundred additional indirect jobs, and at full operation this new building has a predicted net impact of \$38 million annually. This growth is dependent upon state funding for operations and to assist in clinical faculty recruiting.

In addition to the new Clinical Research Building, the one-time state investment allows the construction of an Imaging

Center that will complement the new Clinical Research Building and accommodate MRI, CT and PET scanning units, and other state of the art imaging equipment as well as faculty offices and support space. Also included in the facility is space for a future cyclotron instrument. This building will provide a competitive edge in attracting new faculty and additional grant funding, as well as expanding economic development opportunities to attract related high-tech research entities.

During the five year period covered by the strategic plan, the Center has continued to grow and solidify its diversified base of operating funds comprised of federal grants and cooperative agreements, private grants, contracts, and gifts. While revenues from each of these sources have fluctuated over the past five years, the trend for each source has been clearly upward and overall funding of the Pennington Biomedical Research Center has grown in spite of recent difficult economic conditions worldwide. At the close of 2010, the Center has met the financial goals set forth in Vision 2010, with \$353 million total expenditures in the five-year period.

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. The Center's researchers continue to be very productive. We are eager to fill the new clinical research building with equally productive scientists. In 2008, we celebrated the 20th anniversary of the opening of the Pennington Biomedical Research Center. Based on the advances that we witnessed during the five years covered by the 2005-2010 Strategic Plan, one can easily predict that the next decade will be one of great achievements for the Center.



William T. Cefalu, M.D.
Director

Mission: The mission of the Center for Research on Botanicals and Metabolic Syndrome is to pursue an integrated understanding of the molecular, cellular and physiological mechanisms by which select botanicals may prevent or reverse the development of insulin resistance, the key pathophysiologic feature of the metabolic syndrome.

The Botanical Research Center was funded in 2004 with a 7.9 million dollar grant obtained from the National Institutes of Health. Our currently funded Botanical Research Center is a collaborative effort between the Pennington Biomedical Research Center and the Biotechnology Center for Agriculture and the Environment of Rutgers University. Collaboration for a specific project is also with investigators at the Center for Advanced Nutrition, Utah State University.

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

Goals

The key scientific goal of our 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 center, during the first funding cycle, consisted of three specific research projects, an Animal Core, a Botanical Core and an Administrative Core. Each of the research projects evaluated a specific botanical and assessed the effect on

pathogenic mechanisms leading to the development of insulin resistance. Specifically, the botanicals chosen for initial study were *Artemisia dracunculus 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. Moreover, the botanical core has identified botanical leads that have been 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 and will be evaluated for future planned projects.

Our center has encompassed the disciplines of nutrition, plant chemistry/characterization, metabolism, physiology and endocrinology, molecular and cellular biology, and genetics and spanned both the basic and clinical sciences. Thus, our interdisciplinary approach has allowed for a comprehensive evaluation of botanicals on pathogenic processes by evaluating multiple cellular mechanisms of action. However, during the course of the first funding cycle for our center, we have expanded our investigations of botanicals with use of exciting new technologies that include metabolomic and proteomic assessments. We are the first center in the country to now have an in vitro TIM unit [TNO gastrointestinal Model (TIM)] that will allow us to simulate all in vivo conditions of the upper gastrointestinal tract of humans and to evaluate bioaccessibility of botanicals. As such, based on observations to date and when combined with exciting new technologies that have been put in place by the collaborating institutions, our Botanical Research Center proposes to move in an exciting new direction.

Collaborative institutions and faculty within the Botanical Research Center include:

Pennington Biomedical Research Center:

William T Cefalu, M.D., Zhong Q Wang, M.D., Jianping Ye, M.D., Aamir Zuberi, Ph.D., William Johnson, Ph.D.

Center for Advanced Nutrition, Utah State University:

Michael Lefevre, Ph.D.

Biotech Center, Rutgers University, New Brunswick, New Jersey:

Ilya Raskin, Ph.D., David Ribnick, Ph.D.



Eric Ravussin, Ph.D.
Director

Mission: The mission of the Nutrition and Obesity Research Center (NORC) is “to facilitate and promote collaborative and multi-disciplinary interactions that will foster new research ideas and enhance the translation of basic nutritional research findings into the clinical arena and ultimately into practical application.”

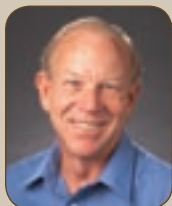
More specifically, NORC has chosen “**Nutritional Programming: Environmental and Molecular Interactions**” as a central focus for the NORC to develop. This focus is based upon convincing basic science and clinical data indicating that an interaction between genes and early life environmental conditions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

The National Institutes of Health (NIH)-funded research base on which the NORC has been established includes basic and clinical research addressing the most prominent causes of morbidity and mortality in the United States related to nutritionally induced chronic diseases, many of them linked to obesity. The NORC’s platform includes three scientific Cores: a Molecular Mechanisms Core (genomics and cellular), very closely related to a Human Phenotyping Core (characterization of phenotypes predisposing to obesity and the metabolic syndrome and behavioral interventions to counteract those) and an Animal Models and Phenotyping Core. Furthermore, the NORC supports clinical investigation addressing the etiology of nutritionally induced chronic diseases across the entire age span, from gestational and perinatal development through childhood and adolescence, to young and middle-aged adults up to elderly individuals. The resources of the NORC assist investigators at the Center and at Louisiana State University in Baton Rouge and New Orleans to address the pathophysiology and molecular mechanisms leading to different facets of the metabolic syndrome. These research programs are conducted to instigate the effects of gender, racial and ethnic background within a context of cultural factors.

The NORC is bringing to the established research base at Pennington Biomedical Research Center (PBRC) a structured system to provide core services to:

- a) support the research base, and
- b) promote novel investigation around our chosen theme of molecular mechanisms of nutritional programming induced by environmental factors.

The NORC provides a mechanism to enable both PBRC and the NIH to maximize the effect of research funding. As of September 2009, there are more than 90 members of the NORC including people outside of PBRC. One of the most successful programs provided by this Center Grant is the yearly funding of Pilot and Feasibility grants to implement new innovative research around our theme of nutritional programming. Such pilot and feasibility studies allow young investigators to collect adequate preliminary data as the basis for NIH larger research grants. Since the start of the NORC in 2005, a total of 26 pilot & feasibility grants have been awarded from our funding (approximately \$20,000-30,000/award). From these projects, already 11 grants have been submitted and 5 have been funded (4-NIH, 1-American Diabetes Association).



Thomas Gettys, Ph.D.
Director

Mission: Within the Pennington Biomedical Research Center (PBRC) is the Center for Biomedical Research Excellence (COBRE). The mission of the COBRE is to understand the cell and molecular biology of obesity and diabetes.

Nearly two-thirds of the U.S. population is either clinically overweight or obese, and eight-percent of the population is affected by adult-onset diabetes. The impact of these diseases on our economy and the quality of life of our citizens is enormous. Louisiana is disproportionately affected because of the higher incidence of both maladies in our state.

The **Specific Aims** of COBRE are to: **(a) expand the critical mass** of investigators in the cell biology of obesity/diabetes research; **(b) recruit, mentor and retain junior faculty displaying great promise** to develop into productive, independent scientists; **(c) implement evaluation criteria for our developing investigators** that enhance their ability to acquire continuous independent extramural funding; **(d) foster a collaborative and interactive research environment** in which Junior Investigators conduct nationally recognized research, and **(e) strengthen the research infrastructure** for obesity/diabetes research by establishing and maintaining state of the art Bioimaging and Genomics core facilities here at the PBRC.

The investigators of the COBRE are focused on discovering fundamental cellular mechanisms that are involved in the development of obesity and diabetes. The impetus to translate fundamental knowledge into more effective treatment strategies,

new drugs, and products is in our best interest, both in the nation but particularly in our state. The National Institutes of Health (NIH) recently developed a comprehensive strategy whose overall goal is to more effectively translate medical discoveries into improvements in people's health. This NIH Roadmap outlines several strategies for accomplishing this goal, including

- 1) place emphasis on mentoring and developing young scientists to power the discovery process.
- 2) build our collective understanding of the precise molecular events that lead to disease states.
- 3) develop a better understanding of the networks of molecules that function in an integrated manner in our cells and tissues.
- 4) enhance multidisciplinary approaches involving research teams with complementary expertise to better tackle the complexity of the research questions we're asking and the technical problems we're addressing.

The COBRE embodies the critical elements of the NIH Roadmap, structured with an emphasis on training our young scientists to make fundamental discoveries of the underlying mechanisms of obesity and diabetes. Through our COBRE, we are expanding the research base and infrastructure that will provide the discoveries and intellectual property that can be translated into products and treatments that will, in due course, lessen the burden of chronic disease and improve the quality of life of our citizens.

<http://cobre.pbrc.edu/>

Pennington Biomedical Research Center COBRE Project PIs, Mentors and members of the External Advisory Committee – March 2009





Jeffrey N. Keller, Ph.D.
Director

Mission: Recently created at the Pennington Biomedical Research Center (PBRC), is the Institute for Dementia Research and Prevention (IDRP). The mission of the IDRP is to improve the quality of life for individuals in Louisiana by generating world class research programs focused on dementia prevention and providing vital educational opportunities for individuals affected by dementia.

The IDRP was established in 2008, and is directed by Dr. Jeffrey N Keller. The goal of the Institute is to fulfill the mission through four principle approaches. These efforts include the establishment of a longitudinal study of aging and dementia, developing a therapeutic screening program, bringing much needed clinical trials for dementia to Louisiana, and conducting conferences and outreach on the latest in dementia prevention.

In just one year the IDRP has established one of the largest longitudinal studies of brain aging and dementia in the United States, consisting of over 500 individuals. These participants receive annual neuropsychiatric exams (or brain physicals) in order to understand how age-related dementia occurs, and develop better tools to detect and quantify dementia, and thereby develop interventions to prevent dementia from occurring. Additionally, this study will allow for us to begin to understand how factors such as obesity, diabetes, and nutrition impact the development of dementia. An added benefit of these efforts is that they will attract clinical trials and access to the latest in dementia therapies to the citizens of Louisiana. The second goal of the Institute is to provide a research platform and infrastructure for researchers to identify therapeutics for the prevention of dementia, and additionally build a base of talented and productive scientist in Louisiana who are dedicated to the eradication of dementia in the elderly. These efforts will include cutting edge models for identifying therapeutic compounds in the treatment of dementia, and will enlist the expertise across a broad range of scientific disciplines. Lastly, the Institute will conduct conferences which promote education on the latest in dementia and dementia prevention to the citizens and caregivers in Louisiana. These efforts will include an annual conference at the PBRC as well as numerous community events throughout

Louisiana. Our First Annual meeting “Meet the Experts: a town hall forum on dementia” was a tremendous success with over 500 attendees.

While private philanthropy is essential to the success of the IDRP, we will be submitting an increasing number of grants to the NIH and private foundations in order to grow the IDRP and fulfill its mission.



BASIC RESEARCH

BASIC RESEARCH



Jeffrey N. Keller, Ph.D.

*Associate Executive Director for Basic Research
Hibernia National Bank/Edward G. Schlieder Chair*

At the Pennington Biomedical Research Center (PBRC) basic science research efforts have traditionally centered on the study of obesity, nutrition, and diabetes. While retaining a world class reputation in each of these scientific areas, and continuing to make significant advances in each of these fields of research, we have seen a tremendous expansion in the scope of work being conducted by the faculty in basic science at the Center. Some examples of this expansion include the existence of vibrant programs studying aging, cancer, immunology, and dementia. Each of these new areas of research retain a firm footing in the scientific strengths of the Center, examining the role of metabolism and aspects of nutrition in modulating aging, cancer, and dementia.

Growth in the basic science research at the Center is evident not only by the addition of new faculty, but is evident from the investment of PBRC into the basic science Core Facilities. Millions of dollars have now been invested to ensure that the Cores for genomics, proteomics, metabolomics, cell biology and cell imaging, and metabolism/behavior are both cutting edge and world class. The productivity and vitality of these Cores allows our basic science faculty to continue to push the envelope of what can be done in the realm of scientific discovery, and allows our scientist to make some of the most important findings in their respective field.

Despite the declines in available National Institutes of Health (NIH) dollars and the intense competition for NIH grants, our basic research faculty have been extremely competitive in their ability to secure NIH funding. In our last fiscal year, our basic researchers produced more than \$12 million in NIH grant funding. Receiving these awards is clear indication of the high quality of the work conducted by our basic research faculty. In addition to NIH dollars, Basic science faculty have been successful in securing grants from the National Science Foundation and a number of National and International Research Organizations. In addition to the securing of funding,

the number and high quality of publications from basic science faculty continue to place us in the elite class of research institutions. Last year alone our basic researchers produced 224 peer-reviewed publications. Lastly, in the last year our faculty members in basic science have given keynote presentations, invited lectures, and countless presentations on their work around the world. Together, these efforts serve to acknowledge the world class reputation of the PBRC Basic science faculty.

The future of basic science research at PBRC is sure to involve the incorporation of an increasing amount of “bench-to-bedside” type of research, and research that involves increasing amounts of collaboration. The “bench-to-bedside” concept is what is commonly referred to as translational research, where the research findings are rapidly “translated” to the understanding of human disease or to develop therapeutic interventions. An increasing majority of basic science faculty hold active protocols for conducting research involving human subjects. That fact is one of the strongest testaments to the importance basic scientists at the Center place on doing translational work. Similarly, basic science researchers have worked together to submit an increasing number of large Program Project and Center grants, that involve bringing together unique expertise and skill sets. These collaborative efforts lay the groundwork for doing “Bigger Science”, and will continue to be an ever increasing important aspect of basic science work here at PBRC.

Now is an exciting time to be involved in basic science at the Center. Not only does it provide an opportunity to work with a world class group of researchers, but it also affords the opportunity to conduct cutting edge research in a stimulating and supportive environment. The future of PBRC basic sciences appears well poised to build off of our past successes, and to assure that the Center continues to make some of the most important findings in regards to health and preventative medicine.

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

Cancer

- DNA Damage and Repair
W. Deutsch, V. Hedge
- The William Hansel Cancer Prevention Laboratory
W. Hansel, S. Aggarwal

Diabetes

- Antioxidant and Gene Regulation
J. Ye, Z. Gao
- Molecular Endocrinology
S. Smith
- Oxidative Stress and Disease
K. Stadler
- John S. McIlhenny Botanical Research Laboratory
W. Cefalu, Z. Wang
- Mechanisms of Diabetes Complications
I. Obrosova

Genomics and Molecular Genetics

- Epigenetics and Obesity
R. Koza
- Functional Genomics
A. Zuberi
- Gene-Nutrient Interactions
R. Mynatt, J. Zhang
- Human Genomics
C. Bouchard, T. Rankinen
- Molecular Genetics and Thermogenesis
L. Kozak, R. Anunciado-Koza
- Regulation of Gene Expression
J. M. Salbaum, N. Delahaye
- Taste Genetics
B. K. (Smith) Richards

Neurobiology

- Nutrition and Neural Signaling
M. J. Barnes
- Autonomic Neuroscience
R. Rogers, G. Hermann, M. Barnes
- Leptin Signaling in the Brain
H. Münzberg-Grüning
- Neurobehavior
R. Martin
- Neurobiology and Nutrition I
H. Berthoud, H. Zheng
- Neurobiology and Nutrition II
R.A. Travagli, K.N. Browning
- Neurosignaling
C. Morrison

Neurodegeneration

- Aging and Neurodegeneration
J. Keller
- Blood Brain Barrier I
W. Pan, R. Sulaimankutty
- Blood Brain Barrier II
A. Kastin, H. Tu
- Inflammation and Neurodegeneration
A. Bruce-Keller
- Neurotrauma and Nutrition
G. Holmes, S. Primeaux
- Nutritional Neuroscience and Aging
D. Ingram, T. Utsuki, P. Pistell

Nutrient Sensing & Signaling

- Nutrient Sensing and Adipocyte Signaling
T. Gettys
- Neuroendocrine Immunology
V. Dixit
- Protein Structural Biology
I. Kheterpal

Obesity

- Dietary Obesity
G. Bray
- Infection and Obesity
N. Dhurandhar

Stem Cell & Developmental Biology

- Developmental Biology
C. Kappen, C. Kruger
- Epigenetics and Nuclear Reprogramming
K. Eilertsen
- Protein Deficiency and Developmental Biology
G. Sutton
- Regenerative Biology
B. Kozak
- Stem Cell Biology
J. Gimble
- Ubiquitin Biology
B. Floyd



Andy Deutsch, Ph.D.
Professor



Vijay Hegde, Ph.D.
Instructor

Faculty:

Andy Deutsch, Ph.D., Vijay Hegde, Ph.D.

Research Team:

Sridevi Yadavilli, Ph.D.

Focus: to understand the individual pathways involved in protecting human DNA from changes that can lead to the onset of cancer and accelerated aging.

Most cancers arise through changes that occur in the genetic blueprint deoxyribonucleic acid (DNA). A variety of deleterious agents including free radicals that are produced by normal metabolism are known to cause DNA damage. One change that we have been studying is the free-radical mediated alteration of the normal DNA base guanine to 7, 8-dihydro-8-oxoguanine (8-oxodG), which is highly mutagenic and found at elevated levels in a variety of cancers such as lung cancer.

Our laboratory has discovered that ribosomal protein S3 (RPS3) that was previously thought to be only involved in protein synthesis also has a very high binding affinity for 8-oxodG. We have found that RPS3 is translocated into the nucleus when cells are exposed to DNA damaging agents. The nuclear destination of RPS3 has been further traced to the presence of 8-oxodG.

In studies to determine the biological relevance of RPS3 binding to 8-oxodG, it was found that RPS3 binds to the tumor suppressor protein p53, and that the interaction can take place at sites of 8-oxodG. Further studies revealed that RPS3 was in fact protecting p53 from degradation by the E-3 ubiquitin ligase MDM2.

In an attempt to find other interacting partners of RPS3 we used Pathway Focused PCR Array analysis. It was subsequently found that RPS3 interacts with a DNA repair protein MUTYH that acts at a DNA base that is mis-incorporated opposite 8-oxodG during DNA replication.

The above findings have led us to hypothesize that RPS3 is acting to prevent the simultaneous repair of 8-oxodG and the base mis-incorporated opposite it. Otherwise the coincident repair could lead to DNA being broken on both strands (double strand breaks or DSBs), resulting in genomic instability. If however DSBs are formed, the ability of RPS3 to stabilize p53 would then lead to cellular death (apoptosis) therefore preventing the existence of abnormal cells.

We have created transgenic mice over expressing RPS3. These mice appear to be similar to wild-type mice until they are roughly 15 months old. At this time the transgenic mice appear to have a higher tumor burden than wild-type mice. The transgenics also have a high level of DNA damage that is a characteristic of aging. It therefore appears that the protection that RPS3 provides to the cell erodes over time. To further test this hypothesis, our future plans include the development of a strain of mice where RPS3 can no longer enter the nucleus to participate in pathways of DNA repair and/or apoptosis.

Research in this laboratory is supported by grants from the National Institutes of Health and a PBRC Pilot and Feasibility Award.



William Hansel, Ph.D.
Professor



Sita Aggarwal, Ph.D.
Instructor

Faculty:

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

Research Team:

Robert Hammer, Ph.D., (Adjunct), Rajasree Solipuram, Ph.D., Qingxia Wang, Ray Mack

Focus: The goal of this laboratory is to prolong and improve the quality of life of cancer patients by developing effective treatments and methods to prevent recurrence of cancer after treatments.

In previous studies, our team developed a new class of drugs (lytic peptide conjugates) that proved quite effective in targeting and destroying human cancer cells in tumors and in metastases in test mice. These drugs, which bind to hormone receptor molecules on the cancer cell membrane, may be likened to a guided missile (the hormone) bearing a warhead (the lytic peptide) which destroys the cell membrane. These conjugates

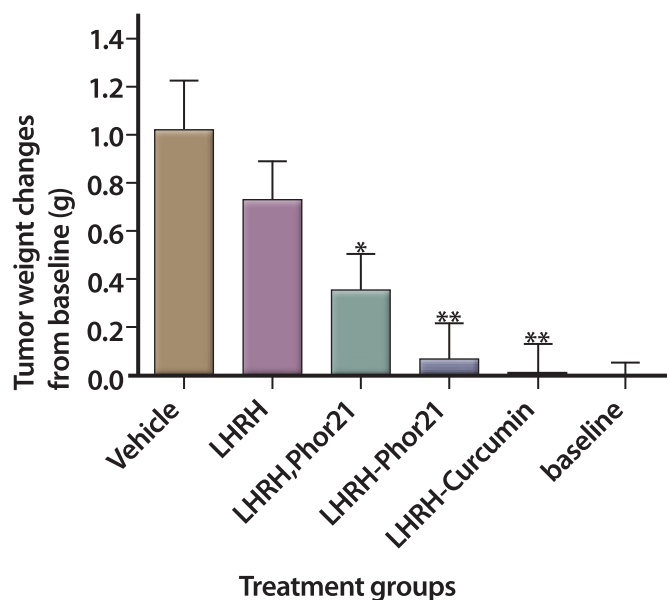


Figure 1

Tumor weight changes in nude mice (8 per group) bearing MIA PaCa2 pancreatic cancer cell xenografts and treated with LHRH, LHRH and Phor21 (unconjugated), LHRH-Phor21 (conjugated), and LHRH-Curcumin (conjugated). Baseline weights are the tumor weights of a group of mice necropsied before treatment. Both LHRH conjugates significantly ($P < 0.05$) reduced tumor weights compared to vehicle, LHRH, and LHRH plus Phor21 to baseline levels.

of a hormone such as luteinizing hormone releasing hormone (LHRH) and a lytic peptide, such as Phor21, effectively target and destroy prostate, breast, ovarian, and testicular cancers in the nude mouse model.

Current Projects:

Since pancreatic cancer cells express LHRH receptors and normal cells do not, we decided to study the oncolytic effects of LHRH-Phor21 and another conjugate, LHRH-Curcumin, in vitro and in vivo in our nude mouse model. Pancreatic ductal adenocarcinomas are invariably lethal. Gemcitabine, the only approved chemotherapeutic drug, extends survival time only a few weeks. Previous research suggested that Curcumin, extracted from the spice Turmeric, inhibits cancer cell growth, but its insolubility and poor absorption from the gut, made its oral administration impractical and its intravenous administration impossible. However, when we conjugated it with LHRH, it became readily soluble and could be injected intravenously.

After synthesizing LHRH-Curcumin and testing its effect on pancreatic cancer cells in vitro, we conducted an in vivo study in which we compared the effects of LHRH-Curcumin, LHRH-Phor21, LHRH alone and LHRH plus Phor21 (unconjugated) in nude mice bearing human pancreatic cancer cell tumors (MIA PaCa2 cells). The results are shown in Fig. 1. Clearly, treatments with each LHRH conjugate (LHRH-Phor21 and LHRH-Curcumin) prevented growth of the pancreatic cancer cell tumors and, in some cases, caused complete regression of the tumors. These results suggest that these drugs might be developed into effective treatments for pancreatic cancers.

Research in this lab is supported by grants from private donors, the Pennington Biomedical Research Foundation and Esperance Pharmaceuticals, Inc.



Jianping Ye, M.D.
Professor



Zhangou Gao, Ph.D.
Assistant Professor

Faculty:

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

Research Team:

Jun Yin, M.D., Ph.D., Jin Zhang, Ph.D., Xin Ye, B.S., and Fen Xu M.S.

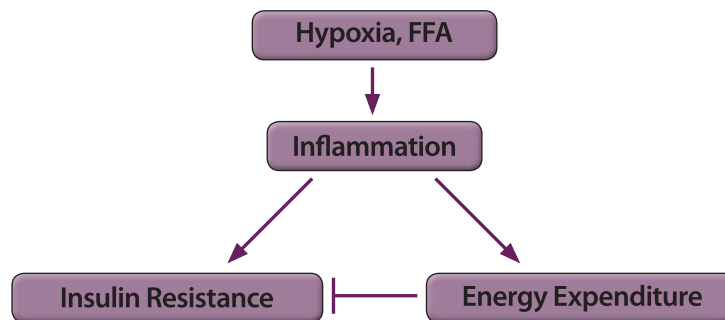
Focus: Our research in the past two years has brought exiting insight into cellular and molecular mechanisms of inflammation in obesity. The progress is on two questions: (1) Why inflammation occurs in obesity; (2) How inflammation induces insulin resistance.

Inflammation contributes to the pathogenesis of many diseases including type 2 diabetes, metabolic syndrome, fatty liver and atherosclerosis. Chronic inflammation occurs in the adipose tissue in obesity. The local inflammation may lead to a systemic metabolic disorder through disruption of adipose tissue function. It acts by inhibiting adipogenesis, inducing adipocyte degeneration, stimulating lipolysis, and suppressing adiponectin expression. The molecular mechanism is related to suppression of C/EBPs, and PPARg activities by inflammation. However, it has been unclear why the low grade inflammation occurs in adipose tissue, and what is the biological benefit of inflammation. Our study suggests that adipose tissue expansion leads to a hypoxia response within the tissue, and the adipose tissue hypoxia is a primary cause of the chronic inflammation (1). The hypoxia response induces expression of inflammatory cytokines and macrophage infiltration. The molecular mechanism is related to activation of transcription factors HIF-1a and NF-kB. In addition to inflammation, the hypoxia response also induces insulin resistance, lipolysis and apoptosis in adipocytes (2). These events contribute to the mechanism of hypoxia inhibition of adipose tissue function. In addition to the negative effect, our data suggests that hypoxia serves as a signal to stimulate angiogenesis in adipose tissue. Macrophages may contribute to the angiogenesis through secretion of angiogenic factors (3). Based on our observations, we proposed a concept of “adipose tissue hypoxia (ATH)” to explain the biological significance of the hypoxia response (4).

Insulin resistance leads to metabolic disorders in glucose and fatty acids. The molecular basis of insulin resistance is impaired signal transduction at the downstream of insulin receptor. Our data suggest that inflammation inhibits the insulin signaling pathway through activation of the IKK2/NF-kB pathway. IKK2 reduces IRS-1 function by induction of serine phosphorylation in IRS-1 protein directly and indirectly. The serine phosphorylation occurs at multiple serine residues. Our recent study suggests that S6K1 mediates the IKK2 signal to phosphorylate IRS-1 at four residues (5). In the nucleus, NF-kB mediates IKK2 signal to inhibit PPARg function (6). The inhibition contributes to insulin resistance and adipocyte degeneration.

In the phenotype study of NF-kB p50-KO mice, our data suggests that inflammation also protects insulin sensitivity (7). The mechanism is related to protection of IRS-1 through induction of energy expenditure. The energy expenditure may reduce lipotoxicity by reducing fatty acid accumulation in the body. In conclusion, the obesity-associated inflammation is a feedback signal in adipose tissue. It occurs in response to hypoxia and has at least two effects: (a) induction of insulin resistance; (b) promotion of energy expenditure. The energy expenditure may attenuate insulin resistance. The net effect is determined by the balance of the two activities (Figure). This possibility may explain why anti-inflammation therapy is not effective in the treatment of insulin resistance and type 2 diabetes in clinic. The therapy may block both activities.

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





Steven Smith, M.D.
Professor

Faculty:

Steven R. Smith, M.D.

Research Team:

Hui Xie, M.Ap.Stat., Sudip Bajpeyi, Ph.D., Sheila Costford, Ph.D.,
Diana Albarado, M.S.

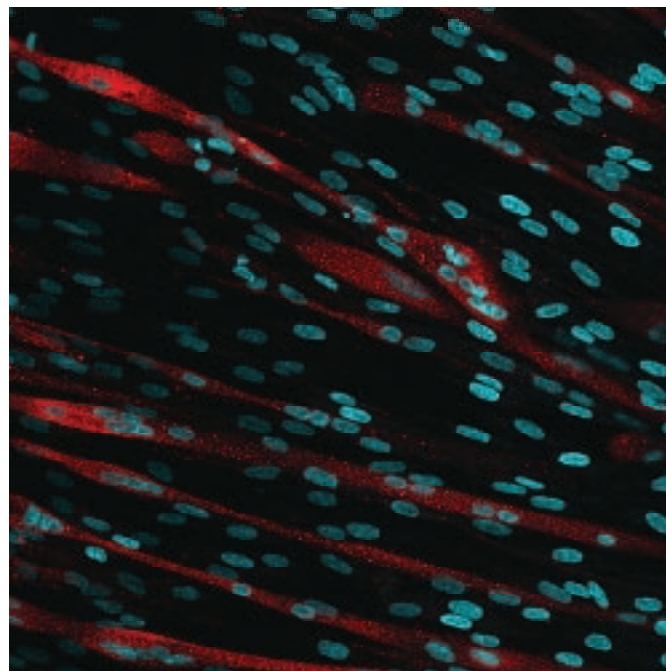
Focus: To understand the physiological, cellular and molecular connections between obesity and type 2 diabetes and use this information to develop better approaches to treat these common chronic diseases.

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.

Recent work from the lab also suggests that the adipose tissue plays a key role in the ability of people to switch from burning fat to sugar. Recent work published in the journal *Diabetes* demonstrates that when people become obese and the adipocytes become larger they outgrow the blood supply leading to low oxygenation and disturbances in the ability of insulin to turn off fat breakdown also known as lipolysis. This work in humans parallels work from Dr. Jianping Ye's laboratory where these same changes were first observed in mice. This suggests novel new ways to treat the metabolic complications of obesity.

Over the last 3 years, in collaboration with Dr. Kevin Conley in Seattle, we have developed non-invasive tools to measure mitochondrial function in skeletal muscle using magnetic resonance spectroscopy and optical spectroscopy. We are now using these tools to probe the mitochondrial responses to caloric restriction in collaboration with Dr. Ravussin in the CALERIE study.

We've also discovered that the pattern of genes that are turned on in muscle vary widely across individuals with diabetes and the genes active in adipose tissue and skeletal muscle predict the response to a weight loss intervention. These results suggest that



■ Type-1 myotubes ■ Nucleus

Human skeletal muscle cells grown in culture.

Endocrinology lab researchers use these human cells, derived from biopsies, to probe signaling systems and metabolism of muscle tissue. In this photomicrograph, nuclei are stained blue and oxidative type I fibers red. Oxidative fibers are better able to burn fat.

there are different 'subtypes' of both diabetes and obesity and opens the possibility of new approaches to treat these diseases based on the concept of 'personalized' medicine.

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, Unilever, and Novartis.



Krisztian Stadler, Ph.D.
Assistant Professor

Faculty:

Krisztian Stadler, Ph.D.

Focus: to understand the role of free radicals - reactive oxygen and nitrogen species – in the development of various diseases and symptoms, with the emphasis on diabetes, obesity and insulin resistance.

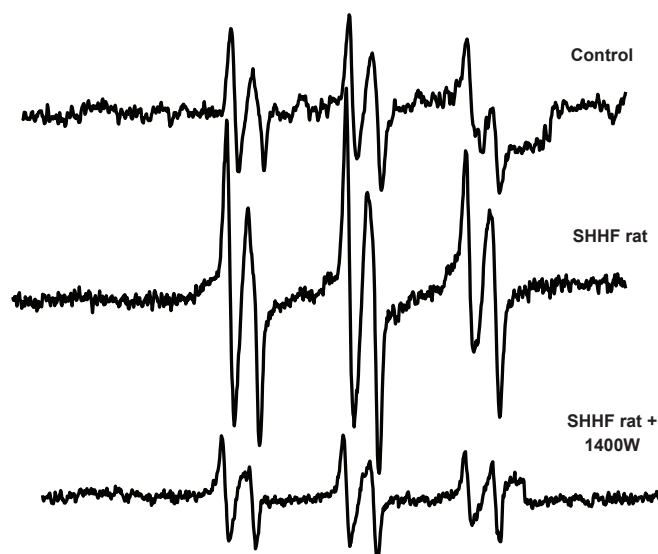
Diabetes mellitus is a chronic metabolic condition where oxidative stress has often been implicated in the pathogenesis of the disease. Free radical production has been demonstrated in both type 1 and type 2 diabetes and possibly contributes to the development of complications through diverse mechanisms. However, the detailed mechanisms responsible for the pathogenesis of certain diabetic complications, metabolic imbalance and insulin resistance are still largely unknown.

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

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

Currently, we are interested in a) how the accumulation of toxic lipid metabolites interferes with the insulin receptor signaling pathway in rats with hyperglycemia, hypertension and heart

failure and participates in the development of insulin resistance; b) developing new strategies to make an attempt to reduce, postpone or prevent oxidative stress related tissue damage in diabetes and to restore or improve the insulin signaling pathway as well; c) how mitochondrial oxidative stress contributes to metabolic imbalance in different diabetes or obesity models.



*Lipid free radical generation as detected by *in vivo* spin trapping in control and obese SHHF rats. The figure shows representative spectra of lipid radical adducts in the control, SHHF diabetic or 1400W treated diabetic group. Inhibition of the inducible nitric oxide synthase enzyme with its specific inhibitor 1400W significantly decreased the EPR-detectable lipid radical products in SHHF rats, revealing iNOS as a major source of the primary radical generation.*



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



Zhong Wang, M.D.
Instructor

Faculty:

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

Research Team:

April Stull, Ph.D., Yongmei Yu, Ph.D., Xian Zhang, B.S.,
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 provide pre-clinical evaluation for promising compounds from plants that may prove valuable in addressing the underlying pathophysiologic parameters contributing to obesity, metabolic syndrome and type 2 diabetes.

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. Our recently completed study demonstrated that in a well-characterized cohort of type 2 diabetic subjects representing a wide phenotype range, e.g. lean to obese, and including both insulin sensitive and insulin resistant subjects, there was not a consistent effect of chromium supplementation to improve insulin action. Chromium levels in subjects did not relate to the clinical response. However, in subjects responding to chromium, the effect of chromium to improve glycemia was secondary to enhanced insulin sensitivity in muscle. There was no effect of chromium on liver metabolism or on body weight/fat distribution. In addition, in those subjects responding to chromium, fasting glucose and A1c were significantly higher and insulin sensitivity significantly lower when assessed before treatment. Thus, the individual most likely to respond to chromium are patients who are insulin resistant, and who have more elevated fasting glucose and A1c levels.

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, an extract of Russian Tarragon, i.e. 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. Thus far, our data suggests that the extract was demonstrated to: 1) increase cellular signaling through the insulin receptor, i.e. increasing PI-3 Kinase activity and Akt phosphorylation; 2) modulate negative regulators of insulin action in skeletal muscle, i.e. protein phosphatases (PTP1B); 3) exhibit a genetic background-dependent effect on improving overall insulin sensitivity in mice (32); 4) reduce lipid intermediates in skeletal muscle; and 5) increase whole body insulin action in early phase human studies.

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



Irina G. Obrosova, Ph.D.
Professor

Faculty:

Irina G. Obrosova, Ph.D.

Focus: To understand the pathogenesis of diabetic complications, especially neuropathy.

This laboratory studies the role of oxidative-nitrosative stress and related mechanisms in diabetic complications, primarily, diabetic neuropathy. Our new data revealed the important role for 12/15-lipoxygenase (LO), the enzyme of arachidonic acid metabolism, in neuropathic changes in animal models of diabetes and prediabetes/obesity.

In particular, we have shown that LO overexpression and activation [assessed by the LO product, 12(S)-HETE, accumulation] is present in the peripheral nerve and spinal cord of streptozotocin-diabetic mice (a model of type 1 diabetes) and high-fat diet fed mice (a model of prediabetes and alimentary obesity). LO-deficient mice were used to dissect the role for this mechanism in peripheral diabetic neuropathy.

The results of behavioral, physiological, and morphometric studies in streptozotocin-diabetic mouse model are presented in the table. Thermal hypoalgesia, tactile allodynia, and motor (MNCV) and sensory (SNCV) nerve conduction velocity deficits were clearly manifest in diabetic wild-type mice, and were essentially prevented or alleviated in diabetic LO^{-/-} mice. Diabetic wild-type mice developed tibial nerve axonal atrophy (reduction in myelinated fiber diameter and myelin thickness) and intraepidermal nerve fiber loss. LO gene deficiency prevented diabetes-associated axonal atrophy, but not intraepidermal nerve fiber degeneration. Apparently, the 12/15-LO mechanism plays more important role in diabetes-induced degeneration of large myelinated fibers, than small unmyelinated fibers. The latter is

not truly unexpected considering that the lipid-like compounds such as 12(S)-HETE and its derivatives are the most likely to incorporate into and affect lipid moieties of the peripheral nerve myelin sheath.

Variables of peripheral diabetic neuropathy in control and streptozotocin-diabetic wild-type and LO-deficient mice (Mean ± SEM, n = 5-12).

MNCV and SNCV – motor and sensory nerve conduction velocities. ^a – intraepidermal nerve fiber density is expressed in nerve fiber profiles per mm. *** p < 0.05 and < 0.01 vs corresponding non-diabetic mice; ^{*,##} p < 0.05 and < 0.01 vs diabetic wild-type mice.

LO gene deficiency partially protected from nerve conduction velocity deficits associated with prediabetes and obesity. However, high fat diet-fed LO^{-/-} mice were not protected from development of sensory disorders such as thermal hypoalgesia and tactile allodynia. High fat diet feeding was not associated with either intraepidermal nerve fiber loss, or axonal atrophy of large myelinated fibers.

Thus, our findings suggest an important role for LO in peripheral neuropathy associated with diabetes and prediabetes/obesity. The results provide the rationale for development and further studies of LO inhibitors and LO inhibitor-containing combination therapies.

My laboratory is also involved in other projects evaluating the roles for Na⁺/H⁺-exchanger-1 and endoplasmic reticulum stress in diabetic neuropathy and other diabetic complications (cataract, early retinopathy).

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

Variable	LO ^{+/+}	LO ^{+/+} diabetic	LO ^{-/-}	LO ^{-/-} diabetic
Initial body weight, g	26.4 ± 0.7	26.1 ± 0.8	25.9 ± 0.7	26.5 ± 0.9
Final body weight, g	40.4 ± 1.6	28.8 ± 0.7**	38.5 ± 1.2	29.5 ± 0.8**
Initial blood glucose, mM	9.2 ± 0.8	15.2 ± 1.0**	8.8 ± 0.7	16.3 ± 1.3**
Final blood glucose, mM	8.9 ± 0.5	25.7 ± 1.3**	9.1 ± 0.7	27.2 ± 1.8**
Thermal response latency, s	9.6 ± 0.4	18.9 ± 0.97**	10.0 ± 0.41	14.0 ± 1.3***
Tactile response threshold, g	2.79 ± 0.18	0.40 ± 0.06**	2.54 ± 0.17	2.08 ± 0.16**
MNCV, m s ⁻¹	50.3 ± 2.0	36.4 ± 1.1**	49.3 ± 1.6	48.9 ± 2.7 [#]
SNCV, m s ⁻¹	35.8 ± 1.1	28.5 ± 0.6**	34.4 ± 0.4	31.4 ± 1.1* [#]
Myelinated fiber diameter, μm	5.57 ± 0.10	5.02 ± 0.07**	5.53 ± 0.095	5.65 ± 0.22 [#]
Myelin thickness, μm	1.80 ± 0.06	1.22 ± 0.06**	1.73 ± 0.03	1.73 ± 0.10 [#]
Intraepidermal nerve fiber density ^a	22.27 ± 1.07	17.52 ± 1.43**	23.97 ± 1.098	16.63 ± 1.58**



Robert Koza, Ph.D.
Assistant Professor

Faculty:

Robert Koza, Ph.D.

Research Team:

Renu Joseph, B.S.

Focus: To identify epigenetic determinants of obesity and related metabolic disorders.

Obesity arises from a multi-factorial interaction between the nutritional and physical environment with genetics and other factors. Studies have shown that nutritional status during development can permanently alter an individual's susceptibility to developing diseases such as obesity and diabetes, however, very little is known regarding the biological mechanisms that cause these changes. To identify these non-Mendelian or 'epigenetic' contributions to obesity, we have characterized a dietary obesity susceptible inbred mouse population reared in controlled

environmental conditions. After feeding the mice a high fat diet large variations in body weight and adiposity develop. Global gene expression analyses of adipose tissue from mice with low and high weight gain identified several genes expressed in adipose tissue that are associated with variations in obesity among individual mice. These include imprinted genes, developmental genes; and, genes involved in Wnt signaling, angiogenesis, vascularization and cytoskeletal organization. Because individual mice within our inbred mouse population are virtually genetically identical, we hypothesize that epigenetic mechanisms underlie the regulation of genes associated with the development of obesity.

Mesoderm specific transcript (*Mest*), an imprinted gene known to be regulated by epigenetic mechanisms, showed the largest variation in gene expression (~80-fold) among adipose tissue depots in the mice. *Mest*, also known as paternally expressed gene 1, belongs to the α/β hydrolase family of proteins and is only expressed from the paternal allele. Many studies have established a role for *Mest* in growth and development and we have shown that *Mest* is strongly associated with fat mass expansion under conditions of positive energy balance. We are presently determining how epigenetic factors regulate *Mest* in adipose tissue of adult mice.

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

Research in this laboratory is supported by grants from The National Institutes of Health, PBRC's Nutrition and Obesity Research Center and PBRC's Center of Biomedical Research Excellence.

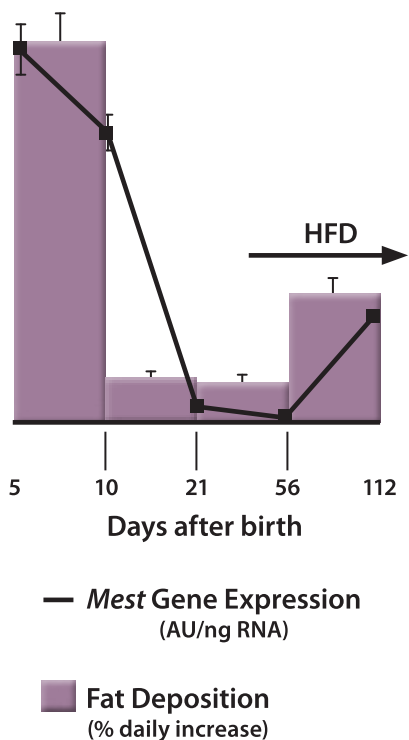


Illustration showing association between adipose tissue Mest expression and fat mass expansion during early post-natal development and in adult mice fed an obesogenic diet.



Aamir R. Zuberi, Ph.D.
Assistant Professor

Faculty:

Aamir R. Zuberi, Ph.D.

Research Team:

Rachel Cooley, B.S., Carmel Fargason, Holly Martin and Christian Quitadamo

Focus: The Functional Genomics Laboratory is engaged in preclinical research using animal models aimed at understanding the mechanism of action of botanical extracts that promote significant health benefits to obese and type II diabetic individuals.

Despite the widespread use of Botanicals, there are few sound scientific data available characterizing their mode of action, physiological effects and possible complications. Where the results of scientific research are available, continued lack of appreciation of the complexity of plant phytochemical preparation hampers attempts in replicating the published findings.

Our preclinical research activities have focused on the effects of Russian Tarragon, a class of phytochemicals found in berries known as Anthocyanins and Shilianghua, Ginger and Ginsen on the treatment or prevention of metabolic syndrome (obesity, diabetes, insulin resistance and cardiovascular complications) in mice. For this report we will limit ourselves to the role of Ginger in the regulation of obesity and diabetes in a commonly used preclinical model, the mouse.

Fresh Ginger roots were purchased locally and chemically fractionated into organic and water soluble phytochemical fractions. Both were found to confer different biological effects when studied separately. The organic phase is enriched for one known class of bioactive phytochemicals, known as the Gingerols and chemical derivatives, the Shoagols. When obesity susceptible mouse strains were fed with this extract (at 2% of the diet) in concert with high fat diet feeding, an immediate inhibition of food intake was

observed causing a loss of body weight due to loss of body fat and a normalization of the dietary induced increase in circulating glucose (hyperglycemia). Upon a reduction of the dietary extract concentration to 0.5%, we were able to normalize the effect of the extract on food intake inhibition but we were still able to observe a significant reduction in adiposity (fat mass divided by body weight) during prolonged high fat feeding and dietary supplementation. A more complete analysis of the metabolic profile (Fig. 1) of these mice revealed an increase in physical activity during the light-off phase (when the rodents are normally active and feeding) and an associated increase in oxygen consumption, indicating an increase in energy expenditure. There was also a shift in the observed substrate oxidation profile indicating the mice supplemented with the organic phase of Ginger root extract shifted towards increased carbohydrate oxidation and reduced fat oxidation. It is possible that in the context of a high fat diet, this shift may reduce overall dietary energy bioavailability and, thus, confer, a reduction in weight gain. We are hypothesizing that the inhibition of food intake in mice fed a high Gingerol containing diet may be modulating the activity of the murine TrpV1 signaling pathway. This receptor is expressed on sensory neurons and can be found in the gut, the brain and in adipose cells. Dietary Ginger may be modulating a complex series of process including gastric motility, taste sensory regions of the brain and possibly affecting thermogenic heat output. Follow-up experiments using mouse mutants deficient in expression of TrpV1 and sub-fractionation of the organic phase are ongoing.

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

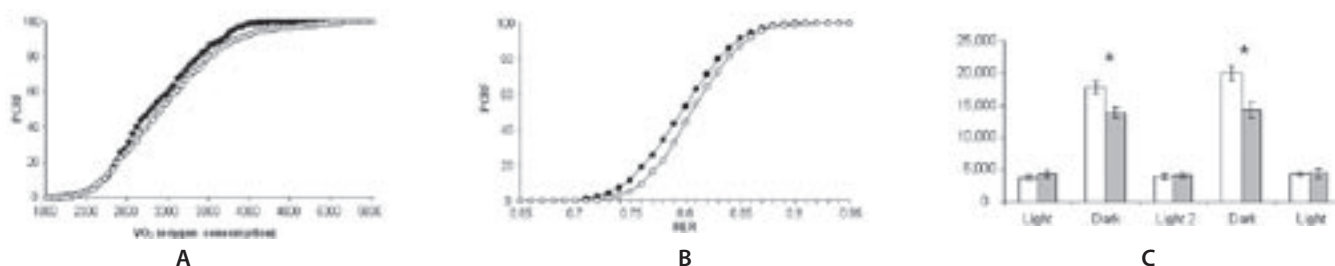


Fig. 1. Panel A. Energy expenditure (oxygen consumption) expressed as PCRf (percent relative frequency) over a 24 hr period of mice in indirect calorimetry chambers fed with high fat diet containing 0.5% organic phase of Ginger root (open symbols) or control high fat diet fed mice (closed symbols). Each plot contains data from 8 animals per group. Panel B. Substrate oxidation (RER; ratio of CO₂ produced to O₂ consumed) from the same animals is also shown as a PCRf plot. Mice fed with high fat + 0.5% organic phase of Ginger root are shown in open symbols. Control high fat diet fed mice are represented by closed symbols. Panel C. Significantly increased physical activity during the dark (active) phase caused by high fat and 0.5% organic phase Ginger root dietary supplementation. Mean infra-red beam break counts +/- SE of supplemented mice (white bars, n=8) and control mice (gray bars, n=8) are shown relative to the time intervals over which the activity was summed. Asterisk indicates *p* < 0.05. Rearing and fidgeting activities do not show significant differences between the groups (not shown).



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., Estrellita Burmudez, B.S., Christina Crane, B.S., Dieyun Ding, B.S.

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.

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.

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

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

These results provide the initial "proof-of-concept" that dietary carnitine is effective at improving insulin-stimulated glucose utilization and in reversing abnormalities of fuel metabolism associated with T2D. Key to understanding the extent of the contribution of mitochondria efflux fatty acids to the overall benefit of supplemental carnitine is the manipulation of carnitine acetyltransferase (CRAT) in mice. The reduction of CRAT activity in muscle led to a moderate increase in fat mass when fed a high fat diet. However, the CRAT KO mice had higher blood glucose values and were less responsive to insulin irrespective of diet, indicating that insulin resistance in these mice is not secondary to obesity and suggesting a direct role of CRAT in muscle for glucose homeostasis. These data support the role of CRAT as a key enzyme in mitochondrial energy homeostasis.

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



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



Tuomo Rankinen, Ph.D.
Associate Professor

Faculty:

Claude Bouchard, Ph.D., Tuomo Rankinen, Ph.D.

Research Team:

Mark Sarzynski, Ph.D., Adrian Stütz, Ph.D.,
Margarita Teran-Garcia, M.D., Ph.D., Kathryn Cooper, B.S.,
Diana Holmes, M.S., Jessica Watkins, B.S.

Focus: The Human Genomics 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 co-morbidities.

HERITAGE Family Study: The most recent set of experiments concluded the positional cloning of four QTLs of the response of cardiorespiratory fitness and hemodynamic phenotypes to regular exercise. We have reported that DNA sequence variation in the kinesin 5B (KIF5B) gene (QTL2) is associated with response of cardiac stroke volume to regular exercise, and the DNA sequence variants significantly affect KIF5B promoter activity. Our analogous inhibition and overexpression experiments showed that changes in KIF5B expression alter mitochondrial localization and biogenesis in a manner that could affect the ability of the heart to adjust to regular exercise (see the figure). Fine mapping of QTL4 on chromosome 2q34 identified cAMP responsive element binding protein 1 (CREB1) as the strongest positional and functional candidate gene for exercise training-induced changes in submaximal exercise heart rate. Interestingly, our data also suggest that at least four other gene loci within the QTL4 region contribute to the QTL-specific genetic variance.

In addition to positional cloning projects, several candidate gene studies have been completed in 2008-2009. For example, the HERITAGE Family Study was the first to report that an obesity risk marker in the fat mass and obesity associated (FTO) gene is associated with exercise training-induced changes in body composition: individuals who have two copies of the FTO obesity risk allele did not lose body fat, while subjects with no risk alleles showed a significant loss of fat mass after a 20-week exercise-training program.

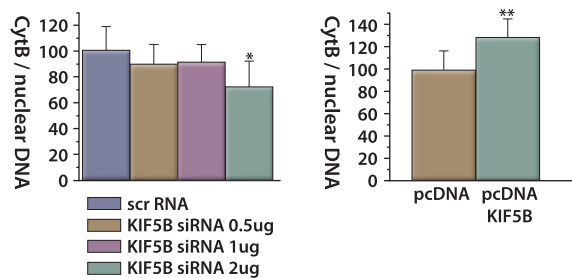
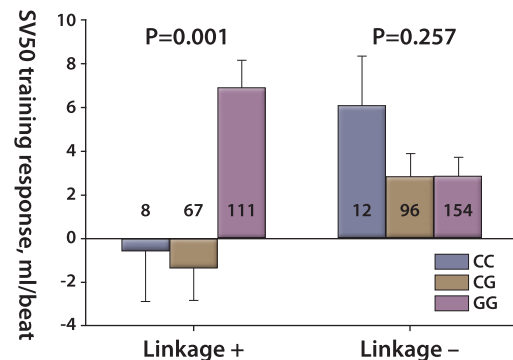
CARDIA Fitness Study: The laboratory has established a close collaboration with CARDIA Fitness Study investigators to study the genetics of cardiorespiratory fitness as well as genotype-fitness interactions on cardiovascular disease risk factors in Caucasian and African-American young adults. The first set of analyses targets over 260 SNPs representing DNA sequence variation in 17 candidate genes.

The Pennington Center Longitudinal Study (PCLS): The PCLS cohort consists of all subjects who have been screened at the PBRC clinic since 1994. The central database includes over 30,000 subjects and approximately 14,000 of them have participated in clinical studies.

The PCLS cohort is managed by the PBRC Population Science group under the leadership of Dr. Peter Katzmarzyk. The Human Genomics Laboratory has established a DNA bank for the PCLS cohort, which currently consists of over 5,000 extracted and diluted DNA samples. The overall goal is to conduct obesity and metabolic co-morbidities genetic studies using state-of-the-art genetic techniques (e.g., genome-wide association studies and deep re-sequencing). The first project is a genome-wide association study for abdominal visceral fat accumulation.

In 2008 and 2009, the laboratory published 46 (to be updated by the end of the year) peer-reviewed original papers and 5 (to be updated by the end of the year) book chapters.

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



Top panel: Association between SV50 training response and KIF5B SNP rs211302 (-835) in linkage positive and linkage negative subjects of HERITAGE.

Lower left panel: *kif5b* inhibition with siRNA reduced mitochondrial biogenesis.

Lower right panel: Transient transfection of cells with the *kif5b* expression construct increased mitochondrial biogenesis.



Leslie P. Kozak, Ph.D.
Professor, Claude Bernard
Pennington Chair



Rea Anunciado-Koza, D.V.M., Ph.D.
Instructor

Faculty:

Leslie P. Kozak, Ph. D., Rea Anunciado-Koza, D. V. M., Ph. D.

Research Team:

Tamra Mendoza

Focus: To determine the genetic, developmental and environment factors involved in the adipose tissue expansion.

Project: Thermogenesis and the regulation of obesity.

If an adult mouse, which is genetically susceptible to diet-induced obesity, is fed a high fat diet for ~8 weeks the percent body fat will increase from about 10 to 30% when the mouse is housed at an ambient temperature of 72°F. If the ambient temperature is reduced to 40°F, within one week the percent body fat will be back at 10%, despite the fact that the mouse will have increased its daily food intake by 50%. This illustrates how thermogenic mechanisms are activated to protect body temperature of the mouse, which must be maintained at 98°F, just as it is in humans, and that this process consumes enough energy from food intake and body fat stores to essentially eliminate the obese condition in only one week. The major thermogenic mechanism in mice for burning large amounts of fat to protect body temperature is located in brown adipose tissue. The mitochondrial uncoupling protein in brown fat uncouples respiration from oxidative phosphorylation to produce heat instead of ATP. Although brown fat has been known to be present in humans for many years, a renewed interest in the potential of brown fat to reduce obesity has recently arisen through the analysis of humans by positron emission tomography (PET) imaging. Although the PET imaging was being used to identify tumors with high metabolic activity, unanticipated signals were detected and confirmed to be associated with brown fat depots. Could this brown fat in humans also be activated to burn off fat in obese individuals?

We know little about brown fat in humans. Do the number of brown adipocytes increase in response to cold as they do in the mouse? Do humans vary genetically in their capacity for induction of brown adipocytes as in the mouse? How does brown fat thermogenesis vary with respect to age? Similar to mice, activation of brown fat thermogenesis may be much stronger in children and therefore more effective in reducing obesity than in adults. To acquire some basic information on thermogenesis in humans we have initiated a project to measure thermogenesis, i.e. heat production, in humans using infrared imaging with an IR sensitive camera. Unlike PET imaging that cannot be used frequently because of the inherent exposure to radioactivity (and probably not at all in children for such an application not connected with a serious disease). Unlimited numbers of IR images

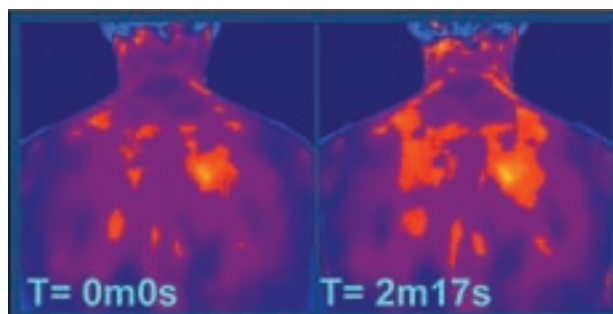


Figure 1 – Acute effects of peripheral cold stimulation on thermogenesis as detected by infrared thermo-imaging.

can be recorded acutely over a time scale of seconds or chronically over days, months or even years. IR images illustrating the thermogenic response in an adult male human exposed to the cold by submersion of feet in ice water for approximately 90 seconds is illustrated in the attached figure. Whether this change is determined by brown fat must yet be established; however, if it is abundant in some humans, brown fat can be used to reduce obesity.

It is possible that humans do not have sufficient brown fat to significantly reduce obesity. Therefore, we are pursuing a second approach to activating thermogenesis based upon skeletal muscle physiology. Skeletal muscle has evolved for one primary function: rapid movement of the body from a resting position to full flight within seconds. Even an individual asleep is able to almost instantaneous take flight. This means that the energy, ATP, for muscle function is available on demand, just like an idling car merely has to shift a gear to move. Can the heat generated by muscle in an uncoupled or idling state be used to reduce obesity by the heat generated in uncoupled muscle? With this logic we have inactivated the Ucp1 gene in brown fat to force the mouse to find alternative thermogenic processes to maintain body temperature. We have found 2 proteins in the inner mitochondrial membrane the ATP-Mg⁺⁺/inorganic phosphate transporter and the mitochondrial glycerol phosphate dehydrogenase that seem to be essential for maintaining ATP levels in cells, particularly in muscle and could be part of a mechanism controlling metabolic efficiency. The manipulation of these genes provides new and novel mechanisms of thermogenesis that could be used to reduce obesity.

Research in this laboratory is supported by a research grant from the National Institutes of Health.



J. Michael Salbaum, Ph.D.
Associate Professor

Faculty:

J. Michael Salbaum, Ph.D., Nancy Arbour Delahaye, Ph.D.

Research Team:

Jacalyn MacGowan

Focus: To understand the relationship between diabetes, nutrition, birth defects, and gene expression in the embryo.

Diabetes is a major health concern in the United States and worldwide. Both type I and type II diabetes not only severely compromise the health of the afflicted individual, but diabetes also affects embryonic development. Maternal diabetes during pregnancy has well-documented teratogenic effects that cause birth defects such as cardiovascular malformations and neural tube defects. Those effects are not well understood, but are thought to involve interactions of the embryo's genetic makeup with the intrauterine environment. The goal of this project is to understand how maternal diabetes affects the developing embryo, with focus on the early nervous system and the pathogenesis of neural tube defects.

The overarching hypothesis for this research project is that maternal diabetes during pregnancy alters gene expression in the embryo, but does not necessarily represent a metabolic disease for the embryo itself. The enigma of maternal diabetes-induced birth defects has been how a systemic condition such as diabetes and the associated high blood sugar can cause specific morphogenetic defects in the embryo. Diabetes-induced birth defects such as neural tube defects are not only characterized by the restriction of the defect to a specific tissue, but also often by a limitation to a specific region of the affected tissue. The conundrum is how this specificity is elicited with a systemic insult such as hyperglycemia, which in theory should exert its effects everywhere. We posit that this specificity is generated in two steps: (i) first, by the quantitative

effects of maternal diabetes on gene expression levels in the embryo, and (ii) second by the endogenous tissue and region-specific expression patterns of the affected genes. Therefore, understanding which genes in the embryo are affected, and how their expression is altered, is paramount to understanding the pathogenesis of birth defects brought about by maternal diabetes during pregnancy.

We have recently defined a set of genes misregulated by maternal diabetes in embryos at mid-gestation. A fraction of these genes are known to cause birth defects. Expanding on our previous work, we have now identified more than 2000 genes that are altered in their expression in maternal diabetes-exposed embryos. With respect to neural tube defects, there are at present approximately 350 genes that are known to play a role in neural tube defects. Approximately one third of these neural tube defect genes fall within the cohort of 2000 genes deregulated by maternal diabetes, demonstrating that maternal diabetes does not affect neural tube defect genes across the board. Our current studies are guided by the working hypothesis that the molecular etiology of neural tube defects in diabetic pregnancies involves those neural tube defect genes that are affected by maternal diabetes. Our analyses on the genetic as well as epigenetic level will permit an in-depth analysis for novel insights how maternal diabetes interacts locally with the expression of known neural tube defect genes during the process of neural tube closure, and how these expression changes affect distinct signaling pathways in the developing embryo.

Research in this laboratory is supported by the National Institutes of Health and by PBRC's Nutrition and Obesity Research Center.



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

Faculty:

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

Research Team:

Lisa DiCarlo, B.S., Heather Duby, B.S.

Focus: To understand the genetic factors contributing to energy and macronutrient intake.

A quantitative trait locus (QTL) is a region of DNA associated with a physical trait, or phenotype, measured on a quantitative scale. We have discovered numerous QTL contributing to nutrient intake traits, including fat, carbohydrate, and total calorie intake. Our mapping study, in the F2 generation of a C57BL/6J x CAST/Ei mouse intercross, was the first to identify genetic linkage for nutrient preference and energy intake in mammals. Highly significant associations between phenotype and genotype were found on six chromosomes, providing clear evidence for multiple genetic controls on food intake.

To isolate these QTL, test their effects, and aid in identifying the underlying genes, we developed congenic strains. Congenic strains harbor alleles within a defined chromosomal segment, from an inbred donor strain on the genetic background of a second recipient strain. We used this approach to capture regions of Chromosomes 8, 17 and 18 that contain genes influencing fat, carbohydrate, and total calorie intake, respectively. Thus we developed three unique strains which will enable us to discover the individual genes responsible for these food intake traits. One of these congenic strains possesses traits for both increased carbohydrate intake and increased physical activity. We have narrowed the interval for these phenotypes to a region on Chromosome 17. This strain provides a powerful tool for investigating possible gene interactions in the control of energy balance, because pathways regulating energy intake and physical activity may share common regulatory mechanisms. Several approaches are being used to locate the responsible gene(s), including microarray and eQTL analysis of gene expression, and high-resolution, genetic fine-mapping in a congenic F2 intercross.

We are also investigating the mechanisms by which a deficiency in short-chain acyl-CoA dehydrogenase (SCAD) alters voluntary fat intake. In an animal model of SCAD deficiency, we identified 142 genes whose expression was significantly changed in the brain and 164 genes that were deregulated in liver, when the mutant strain was exposed to a 58% fat diet. A higher-than-expected number of dysregulated genes was noted for processes involving

fatty acid metabolism, steroid metabolism, electron transport, and cell structure and motility. Further pathway analyses and qPCR verification of results will determine which genes may play a key role in the metabolic control of food intake.

The genetic contributions to ingestive behavior and spontaneous physical activity phenotypes are virtually unknown. Discovering genes that are involved in macronutrient and total energy intake is important for understanding the mechanisms underlying eating behaviors that lead to obesity. The results have potential for both basic science and clinical applications. Once candidate genes are identified in mice, they can be tested in human association studies for their relevance to nutrient intake and obesity. Although the genes discovered in our mouse model will likely not explain all the phenotypic variability observed in humans, these findings will form the basis for future translational research on the control of food intake.

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



Nutrient intake is assessed in adult mice provided with a choice between two diets: a carbohydrate/protein (C/P) or a fat/protein (F/P) mixture containing 78/22% of energy from C/P, or F/P, respectively. Equalizing the protein content in both choices prevents problems associated with the taste of protein alone.



Maria J. Barnes, Ph.D.
Assistant Professor

Faculty:

Maria J. Barnes, Ph.D.

Research Team:

Lyndsey S. Flowers, B.S.

Focus: To identify and characterize the changes within the central nervous system that contributes to the development of diet-induced obesity.

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

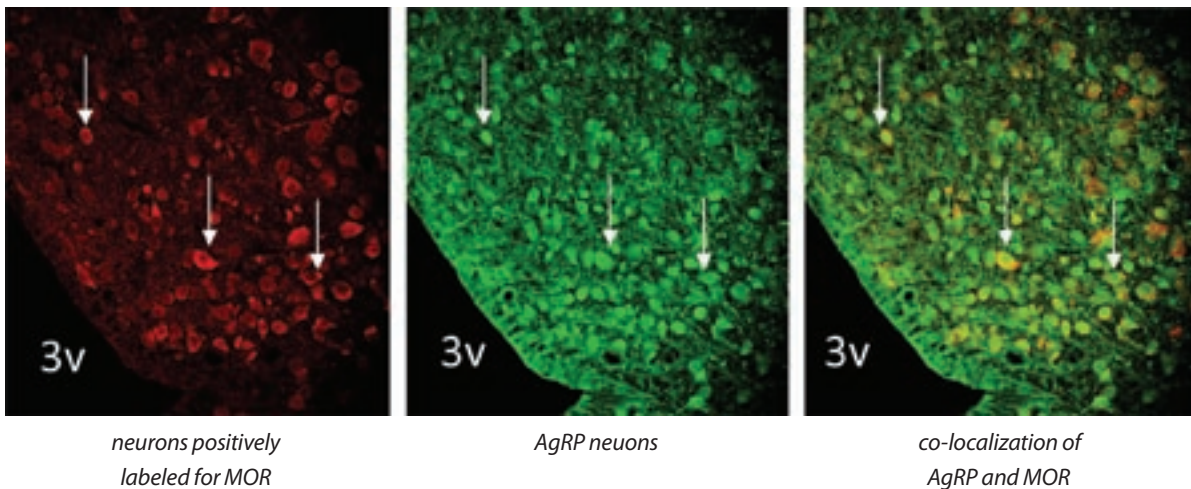
Data from our laboratory have demonstrated that within the arcuate nucleus there is a population of mu opioid receptors (MOR). Activation of this receptor population make animals increase their food intake and selectively change their dietary preference to a diet high in fat, independent of their original dietary preference. Our laboratory is interested in this receptor population because 1)

when we make animals obese the density of MOR is significantly increased in the arcuate nucleus; and 2) MOR are co-localized on neurons within the arcuate nucleus which contains the orexigenic (Neuropeptide Y, Agouti gene Related Peptide) and anorexic (pro-opiomelanocortin) peptides that plays a role in maintaining energy homeostasis. The possibility exist that changes in this receptor population is contributing to the overeating and increased fat preference that is observed in obese animals.

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

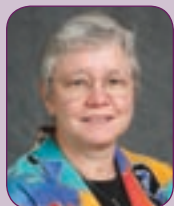
Research in this laboratory is supported by a grant from the National Institutes of Health.

Co-localization of MOR and Agouti gene Related Peptide (AgRP) neurons in the arcuate nucleus





Richard Rogers, Ph.D.
Professor



Gerlinda Hermann, Ph.D.
Associate Professor



Maria Barnes, Ph.D.
Assistant Professor

Faculty:

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

Research Team:

David McDougal, Ph.D., Tina VanMeter, H.T.

Focus: This laboratory is generally interested in determining how the brainstem controls autonomic functions related to metabolic and behavioral homeostasis.

Present activities include investigations of:

- the basic neural circuitry involved in the control of digestive processes,
- the mechanism by which immune cells in the brain activated by infection cause autonomic regulation of the stomach to fail,
- the mechanisms by which glial cells in the brainstem detect brain injury and in turn regulate neuronal control of digestion,
- the mechanism responsible for the regulation of metabolic heat production by the brainstem, and
- chemosensory functions of cranial nerve afferents.

One of our more recent publications [Hermann et al, *Journal of Neuroscience*, 2009, 29:9292-9300] deals with a phenomenon that is new to neuroscience; communication between glia and neurons resulting in changes in autonomic control as a function of disease.

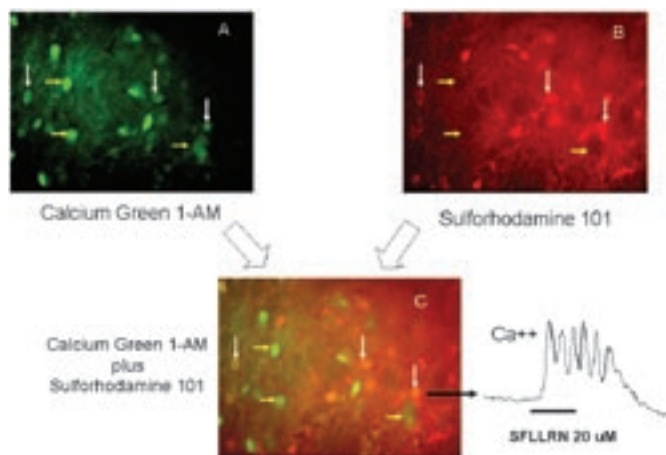
Eighty years ago, the famous physician and endocrinologist Harvey Cushing observed that bleeding closed head injuries often produced severe gastric ulcers caused primarily by a complete suppression of gastrointestinal motility. His original theory was that increases in intracranial pressure caused by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

We suspected that a critical component of the blood clotting cascade, thrombin, might be responsible for the connection between trauma and autonomic failure. The portion of the brainstem responsible for autonomic control of the gut has a high concentration of sites thru which thrombin can act to evoke changes in cellular activity. These areas of the brainstem are outside the blood brain barrier and therefore can be affected by thrombin generated either within the brain or in the periphery in response to injury. We found that thrombin and thrombin – like peptides applied to the brainstem produce gastric stasis. Surprisingly, this effect was mediated within

the brainstem by a novel interaction between glial cells and neurons. Glial cells have long been thought of as passive supporters of neurons the cells responsible for long distance electrical communications. By using live cell imaging methods developed in this laboratory, we found that thrombin first activates glial cells in the brainstem by causing the release of stored calcium. This, in turn, causes glial cells to release glutamate, normally a neuronal transmitter substance, onto adjacent neurons involved in the reflex regulation of the stomach. These gastric-control neurons are then activated, eventually causing a shutdown of gastric motility.

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

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



Live cells recorded from a brainstem slice preparation showing the identification of glia [astrocytes] and neurons plus the effect of a thrombin-like peptide [SFLLRN] to activate glial cells. Upper left; calcium green dye tracks changes in intracellular calcium changes in both neurons and glia, while the vital stain sulforhodamine [upper right] only stains astrocytes. Bottom left, merged image shows discrimination between astrocytes and neurons. Bottom right; calcium release response of a selected astrocyte to SFLLRN.



Heike Münzberg-Grüning, Ph.D.
Assistant Professor

Faculty:

Heike Münzberg-Grüning, Ph.D.

Research Team:

Yan Zhang, Ph.D., Amanda Laque B.S.

Focus: Investigation of novel leptin target neurons and their impact in the regulation of food intake and body weight.

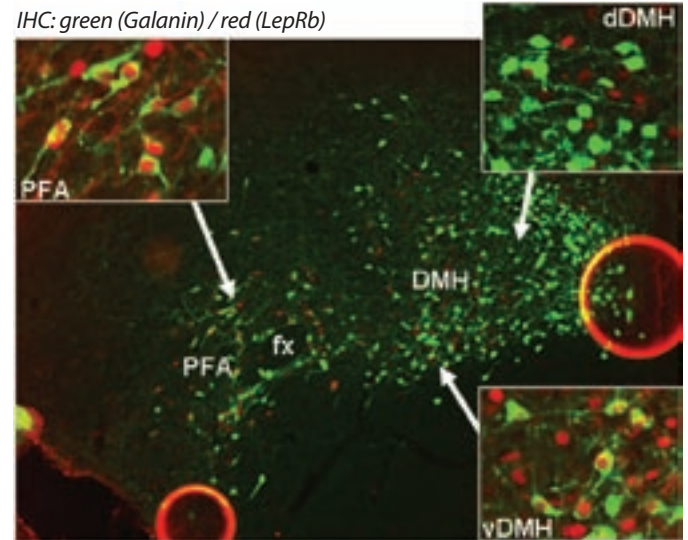
The importance of leptin action in energy balance has been established by the severe hyperphagia and obesity in humans or rodents null for leptin or leptin receptor (LepRb). While leptin is known to act via LepRb located on neurons of the arcuate nucleus (ARC) melanocortin system (consisting of orexigenic AgRP neurons that increasing food intake and anorexigenic POMC neurons that inhibiting food intake), other studies suggest that the action of leptin in the ARC alone only accounts for a fraction of leptin action to regulate food intake and body weight.

The majority of LepRb expressing neurons have not been studied and their function and contribution to anorexigenic leptin actions is unknown. For example, apart from the ARC the dorsomedial and lateral hypothalamus, which are known to importantly regulate feeding circuits, contain a large population of LepRb expressing neurons; suggesting that leptin action in these sites also contributes to the regulation of energy homeostasis.

We have discovered a large number of LepRb neurons that co-express the neuropeptide galanin (Gal), which is well known to regulate food intake thus indicating that these LepRb(Gal) neurons play an important role in the regulation of feeding and body weight regulation. LepRb(Gal) neurons are mainly located in the dorsomedial and lateral hypothalamus and a smaller population is found in the brainstem and represents a unique subset of leptin responsive neurons (see Figure).

We hypothesize that LepRb(Gal) neurons play a crucial role in mediating anorexigenic leptin actions to control feeding behavior. Our overall goal is to understand the physiologic function and underlying neuronal network of LepRb(Gal) neurons as well as to investigate the overall population of LepRb neurons in the exPFA.

We use several molecular genetic tools to investigate this specific subset of LepRb expressing neurons. First, we want to determine the role of LepRb(Gal) neurons in physiologic leptin action by targeted deletion of LepRb in galanin neurons to determine the contribution of LepRb(Gal) neurons in leptin dependent regulation of energy homeostasis. We specifically investigate any perturbation in body weight, food intake or energy expenditure in these mice with disrupted LepRb in galanin neurons.



A newly identified population of LepRb neurons co-expresses the orexigenic neuropeptide galanin (Gal). Even though LepRb and galanin are both found throughout the CNS, co-localized LepRb(Gal) neurons are largely restricted to a specific hypothalamic site (vDMH and PFA). PFA=perifornical area, vDMH=ventral DMH, dDMH=dorsal DMH, fx=fornix

Second, we investigate the regulation of LepRb(Gal) neurons. We use reporter mice to visualize LepRb(Gal) neurons immunohistochemically and define regulatory mechanisms of LepRb(Gal) neurons.

Third, we study the neuroanatomic circuits of LepRb(Gal) neurons. We will define axonal projection sites of LepRb(Gal) neurons throughout the brain by using traditional and novel tracing methods (LepRb or galanin neuron-specific tracer expression in the exPFA). Furthermore, we will identify the neurons that are innervated by LepRb(Gal) neurons or that innervate LepRb(Gal) neurons by using LepRb or galanin neuron-specific expression of anterograde or retrograde transsynaptic tracers.

Research in this laboratory is supported by the National Institutes of Health, PBRC's Center of Biomedical Research Excellence, and the American Heart Association.



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

Faculty:

Roy J. Martin, Ph.D.

Research Team:

Michael Keenan Ph.D., Carol Lammi-Keefe Ph.D.,
Anne Raggio B.S., Li Shen M.S.

Focus: Identification of bioactive food components that impact feeding behavior and health.

The long-term goal of this research is to provide evidence concerning health effects of nutrients and other bioactive food components that can be used by scientific organizations in revising or selecting endpoints for setting dietary reference intakes and tolerable upper limits for such components (e.g. omega-3 fatty acids, fermentable fiber). In addition, this research should lead to the development of novel and health-enhancing foods.

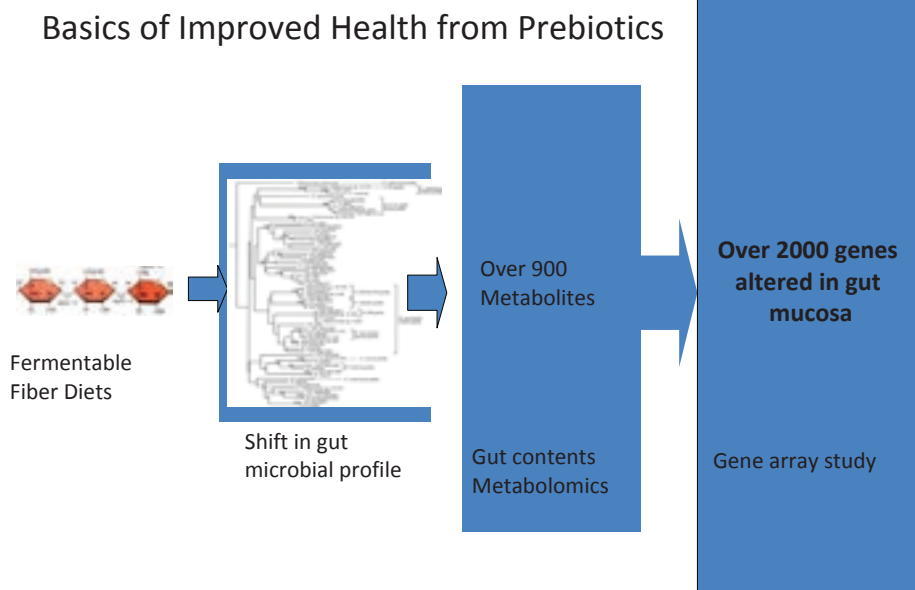
Three examples of hypotheses of health enhancing food components are currently being investigated.

- **Dietary fermentable fiber will mimic the beneficial effects of diet restriction on healthspan by attenuating age-related declines in neuronal nutrient sensing mechanism.** It is well established that diet restriction attenuates many aging processes and increases lifespan and healthspan in numerous species. Our lab found dietary fermentable fiber, in many aspects, has similar beneficial effects as diet restriction. When fed fermentable fiber, animals have decreased body fat and plasma triglycerides; improved glucose tolerance, and increased GK expression in the hypothalamus, an indicator of improved brain glucose sensing. Studying age-related changes in brain nutrient sensing and nutritional intervention will provide vital information on amelioration of abnormalities related to poor nutrition and impaired feeding behavior observed in many elderly persons.
- **Gut bacteria are important in nutrient utilization and metabolism leading to improved health.** Gut bacteria outnumber human cells tenfold and represent a combined microbial genome well in excess of the human genome. Collectively, the flora has a metabolic activity equal to a virtual organ within an organ. Over 400 bacterial species have been identified in the gut. However, it is clear that most bacterial species cannot be cultured. With new technology such as broad-range sequencing of 16S ribosomal RNA from

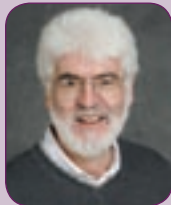
amplified bacterial nucleic acid extracted from gut contents can be used to identify and classify bacteria. The availability of bacterial sequence data has facilitated the development of molecular probes for fluorescence *in situ* hybridization, DNA microarrays and gene chips that can identify and enumerate specific species. The goal of this project is to provide a comprehensive molecular characterization of gut microflora from animals fed a fermentable fiber that has been shown to reduce obesity, blood lipids and improve glucose clearance.

- **Dietary components may act in synergy to reduce inflammation and improve health.** We have found that the gene expression profiles of rodents fed a dietary fermentable fiber and have found that the gene for tristetraprolin is up regulated. Tristetraprolin is an RNA-binding protein that suppresses inflammation by accelerating the degradation of cytokine mRNAs, specifically TNFalpha. This is consistent with the literature that supports a role of fermentable fibers in the suppression of inflammation. Since both omega three fatty acids and fermentable fibers appear to act on several different anti-inflammatory mechanisms. Their combinations in the diet may provide a synergistic response important in maintaining long-term health and decreasing the risk for chronic disease.

Research in this laboratory is supported by grants from the Gordon Cain Professorship, National Institutes of Health, and the LSU Agriculture Center.



Proposed Mechanisms of improved gut function and overall health



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



Huiyuan Zheng, Ph.D.
Instructor

Faculty:

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

Research Team:

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

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 results of these studies are expected to generate new behavioral and pharmaceutical strategies to lessen the impact of the obesogenic environment on appetitive behavior.

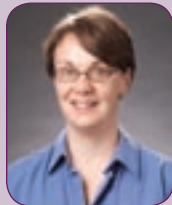
In another project, we look at the mechanisms by which longer-term and cognitive signals from the hypothalamus and forebrain are integrated with gut-related signals of satiety. We have shown that hypothalamic neurons expressing the feeding peptides proopiomelanocortin (POMC)/ alpha-melanocyte stimulating 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 molecularly fingerprinted and neurochemically characterized the specific brainstem neurons receiving both gut and descending input signals using electrophysiological, gene expression analysis, and neuroanatomical tracing strategies in the hope to find novel drug targets to fight obesity.

Finally, we have started identifying the powerful hormonal and neural mechanisms responsible for reversing obesity and type-2 diabetes after bariatric surgeries, in particular Roux-en-Y gastric bypass surgery. We are testing the hypothesis that the sustained weight loss after surgery is due to the action of altered circulating and locally acting gut hormones on various brain areas involved in the homeostatic regulatory and hedonic aspects of food intake and energy balance controls. Knowing “how bariatric surgeries work” should lead to “knifeless” pharmacological and behavioral approaches that are more effective than currently available drugs.

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



R. Alberto Travagli, Ph.D.
Professor



Kirsteen N. Browning, Ph.D.
Assistant Professor

Faculty:

R. Alberto Travagli, Ph.D., Kirsteen N. Browning, Ph.D.

Research Team:

Tanja Babic, Ph.D., and F. Holly Coleman, B.S.

Focus: For several years we have been interested in the organization of vagal brainstem circuits devoted to the control of homeostatic pathways, particularly those involved in the control of gastrointestinal and feeding functions.

From our initial studies, we hypothesized that parasympathetic brainstem motoneurons that are devoted to distinct visceral functions can be identified by a unique combination of biophysical and pharmacological properties. More recently, our studies have led to the understanding the brainstem autonomic system is segregated into functional circuits that display unique properties at several specific levels, from a neurons membrane properties, to its local network connections, its distant network associations as well as to its effector response. This type of cellular organization implies a “task matching” capability where subsets of parasympathetic and sympathetic brainstem neurons integrate vital cardiac, respiratory and gastrointestinal functions.

Functional gastrointestinal (GI) motility disorders, including functional dyspepsia, are very common, often chronic and disabling, conditions that account for a large proportion of consultations with primary care and specialist physicians. The pathophysiology of these disorders remains incompletely understood, but several lines of evidence point toward impairment of the vagal sensory-motor loop connecting the gut to the central nervous system (CNS) and

back. Visceral sensory information is conveyed to the CNS via vagal afferent nerve fibers, which terminate within the brainstem in the nucleus tractus solitarius (NTS). Neurons of the NTS assimilate this sensory information and project to integrative CNS centers involved in metabolic homeostasis, as well as to the adjacent dorsal motor nucleus of the vagus, which provides the preganglionic vagal motor output and, ultimately, coordinates GI vago-vagal reflexes.

Based on the experimental data we have generated in the last few years, we hypothesize that brainstem homeostatic circuits are not the simple, static relay networks that they have long been described as but, rather, are adapting to every-changing environmental conditions. These circuits undergo short-term adaptive plasticity to ensure that vagally regulated functions respond appropriately to a variety of intrinsic and extrinsic factors (e.g., food, stress, peripheral sensory inputs, time of day, etc.). This short term plasticity is directed toward selective and distinct neuronal subpopulation, each of which is devoted to the modulation and regulation of integrative inputs originating from higher centers (e.g., the hypothalamus, the central nucleus of the amygdala, the Barrington’s nucleus, etc.). Similarly, peripheral injury due to dietary deficiency, inflammation or neurodegenerative disease (e.g., diabetes, pancreatitis, esophagitis, Parkinson’s disease, etc.) may induce longer-term alterations in the pharmacological and synaptic organization of these homeostatic circuits.

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



Christopher Morrison, Ph.D.
Assistant Professor

Faculty:

Christopher Morrison, Ph.D.

Research Team:

Megan Purpera, M.S.

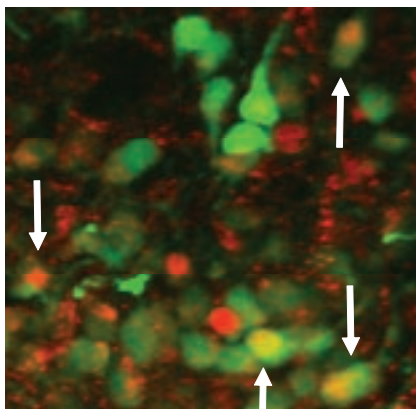
Focus: Neural mechanisms that control food intake in response to changes in nutritional status.

Key populations of neurons within the brain are critical for the regulation of food intake and body weight, and 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. Leptin acts within the brain to suppress food intake, and recent work in our lab has focused on leptin's role in the body's adaptive defense against weight gain. Using a model of experimental overfeeding, our data demonstrate that lean animals voluntarily reduce their food intake following a period of forced weight gain, and maintain this reduced food intake for many days following the cessation of overfeeding. This adaptive decrease in food intake results in a rapid normalization of body weight. Our data indicate that intact leptin signaling is required for this adaptive decrease in food intake, and thus leptin is required to effectively defend against experimentally induced weight gain. Considering that obesity is associated with a loss of brain leptin signaling, these observations suggest that this

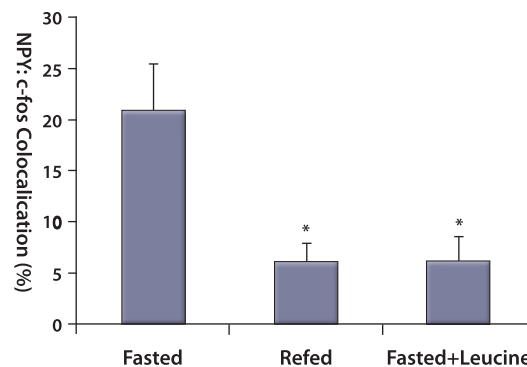
loss of leptin action may contribute to weight gain.

A second area of recent focus for the Neurosignaling Lab has been the 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. However, the identity of the "protein signal" inducing this response, as well as its site of action in the brain, is currently unclear. Our recent data indicate that injection of the amino acid leucine into the brain suppresses food intake. Leucine is also sufficient to directly regulate key populations of neurons within the hypothalamus; the same hypothalamic neurons that mediate the effects of leptin and other nutritional signals. Thus these data indicate that leptin may be a key signal of protein balance which acts at least in part by influencing the activity of neuronal populations that also respond to leptin. 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 and by the Pennington Medical Foundation.



Effect of Leucine on NPY neuron activity. NPY neurons (Green) are activated by fasting, as marked by an accumulation of c-Fos (red) within their nucleus (co-labeled neurons are marked by arrows). Refeeding produces a rapid decrease in colocalization, and this effect is reproduced by a single injection of leucine. These data indicate that these NPY neurons (which drive food intake) are acutely inhibited by leucine, and thus that leucine's ability to reduce food intake may be mediated by an inhibition of these NPY neurons in the brain.





Jeffrey N. Keller, Ph.D.

*Associate Executive Director for Basic Research
Hibernia National Bank/Edward G. Schlieder Chair*

Faculty:

Jeffrey Keller, Ph. D.

Focus: This laboratory is currently involved in a wide range of studies aimed at understanding the causes of brain aging, and identifying the basis by which aging promotes the development of brain pathology and brain diseases such as Alzheimer's disease.

The studies in our laboratory look at the molecular basis of brain aging (focusing on a vital enzyme called the proteasome), utilize animal models to understand the biochemistry and physiology of aging, utilize animal models of neurodegenerative disease to understand the basis of diseases such as dementia, and involve human studies of brain aging and dementia. Current grants for each of these projects is provided below.

The Aging and Neurodegeneration laboratory publishes routinely on the basis by which dietary restriction mediates beneficial effects on aging tissues, and has a particular interest in understanding the role of oxidative stress in both aging and Alzheimer's disease. More and more effort in our laboratory is aimed at developing pharmacological interventions for both aging and Alzheimer's disease, and advances from these efforts are anticipated to begin bearing fruit in the very near future. Two new

major initiatives in the laboratory have also recently begun to mature and have a significant impact on the direction of the laboratory. The first of these efforts is working on understanding the ability of a high fat diet to modulate brain function and brain pathology during aging. While lead by Dr Keller, these efforts are a part of a multi-group effort at the PBRC and have resulted in the submission of a Program Project Grant proposal and a half dozen publications on the topic. This work is expected to continue to develop and have important implications for understanding the basis by which metabolism regulates brain aging. Secondly, Dr Keller established and directs the Institute for Dementia Research & Prevention. This institute will include a longitudinal study of aging and dementia in individuals in Louisiana aged 60 and over, as well as include a platform for the identification of therapeutics for the prevention of dementia. Those interested in learning more on any of these research efforts, or wanting to participate in these research efforts, are encouraged to contact the IDRP at (225) 763-2973 or dementia@pbrc.edu for more details.

Research in this laboratory is supported by grants from the National Institutes of Health, the National Institute on Aging, and the Alzheimer's Association Investigator Initiated Research Grant.



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

Faculty:

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

Research Team:

Reas Khan Sulaimankutty, Ph.D., Dr. Xiaojun Wu, Ph.D.

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

Current Projects

- Regulation of the interleukin-15 (IL15) system in the CNS: IL15 is a unique T helper cell cytokine that plays important roles in CNS development and physiological functions, response to inflammation, and development of autoimmune disease. Tumor necrosis factor alpha (TNF), lipopolysaccharide, and experimental autoimmune encephalomyelitis are among the strongest inducers that activate the IL15 system in the CNS. We employ different molecular, cellular, and animal models to determine the mechanisms of regulation of IL15 and its receptors. This involves intracellular trafficking studies by use of confocal microscopy, generation and expression of different mutant constructs, analyses of transcriptional regulation by genetic studies on promoters and untranslated RNAs, studies of protein turnover, transport assays, and a series of neurobehavioral analyses. We hope to identify some novel answers about how transcytosis occurs and what mechanisms drive the upregulation of the transport.

- Functional implications of 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.

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



Abba J. Kastin, M.D., Ph.D.
Professor



Hong Tu, M.D., Ph.D.
Professor

Faculty:

Abba J. Kastin, M.D., Ph. D., Professor, United Companies/
Harris J. Chustz Chair, Hong Tu, M.D., Ph.D. instructor

Research Team:

Yi He, Ph.D, Xiajun Wu, Ph.D., Hung Hsuchou, M.S., Ling Ying

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 the way in describing 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 are 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.

Last year we published more than 10 papers on this subject and promoted our research and our institution at several international meetings. Dr. Kastin received his third honorary doctorate, this one from Uppsala University, the oldest university in Sweden (and Scandinavia). He also delivered the David Rabin Visiting Professor lectures at Vanderbilt University and was made an honorary member of the Indian Society for Comparative Endocrinology. Also in 2008, Drs. Kastin and Pan co-edited the Henry Stewart Series on Blood-Brain Barrier. This, along with publication of the 213-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.

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



Annadora Bruce-Keller, Ph.D.
Associate Professor

Faculty:

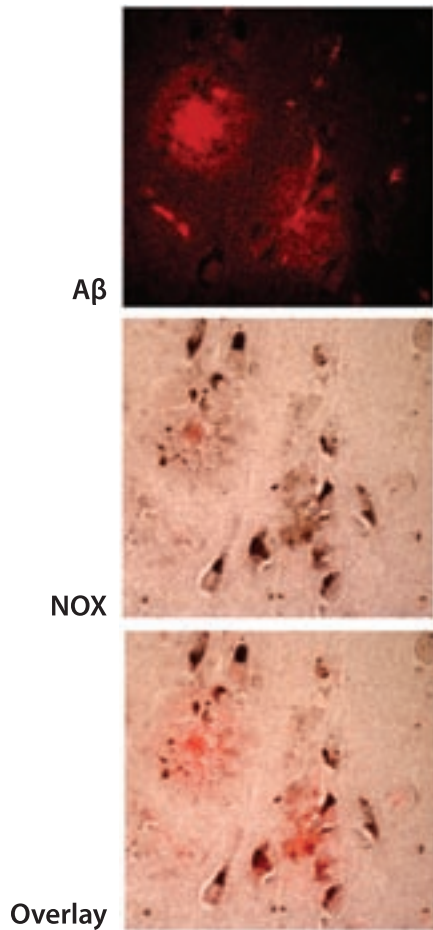
Annadora Bruce-Keller, Ph.D.

Research Team:

Sunita Gupta, M.S., Alecia G. Knight, M.S., Sun-Ok Fernandez-Kim, M.S.

Focus: To understand how brain inflammation is caused by disease and/or metabolic dysfunction, and how such inflammation impinges on brain function.

Dr. Bruce-Keller has a long history of research into the role of inflammation in brain injury, neurodegeneration, and cognitive



NOX in AD

Histological sections were prepared from formalin-fixed tissues derived from human Aβ brain, and processed to identify NOX and senile plaques (dense amyloid deposits). Images suggest that NOX-positive neurons (black) are in close proximity to amyloid plaques (red).

function. Current research funded by the National Institute of Health is focused on brain inflammation in HIV and Alzheimer’s disease. A project funded by the Institute of Neurological Disorders and Stroke (NINDS) seeks to determine the extent to which HIV-related brain inflammation and neuronal injury in cell culture and animal models is caused by the enzyme NADPH oxidase (NOX) in brain. A separate project funded by the Institute of Drug Abuse (NIDA) is part of a large Program Project grant that is funding research here at PBRC in collaboration with investigators at Virginia Commonwealth University. The objectives of this project are to understand the mechanisms whereby opiate drugs exacerbate the development and progression of NeuroAIDS in animal and cell culture models. Finally, a project funded by the Institute of Aging (NIA) is part of an additional large Program Project grant that is funding research here at PBRC in collaboration with investigators at University of Kentucky, and is designed to understand the pathogenesis of Alzheimer’s disease (AD). The objectives of this PPG are to understand the mechanisms of amyloid pathology in cultured cells, in transgenic AD mice, and in human AD patients. PROJ 4 (“Aβ and NOX in MCI and AD”) is focused on delineating the role of NOX in mediating increases in neuronal dysfunction in response to amyloid via increases in oxidative stress. The attached image shows NOX-positive neurons (black) in close proximity to amyloid plaques (red).

In addition to these ongoing projects Dr Bruce-Keller is working on several new major research efforts. First, a project is underway to understand how diets high in fats and calories can detrimentally affect the brain, with a special emphasis on aging and age-related dementia. These efforts are a part of a multi-group effort at the PBRC and are the core of Program Project Grant proposal currently under review at the NIA. Secondly, Dr. Bruce-Keller is working to understand how cognitive processes become impaired in setting of HIV infection, with specific emphases on opiate-based drugs and side effects of anti-retroviral therapies. Finally, Dr Bruce-Keller is working with others at the PBRC to build the Institute for Dementia Research and Prevention. This institute includes a longitudinal study of aging and dementia in individuals in Louisiana aged 60 and over, and includes a platform for the identification of therapeutics for the prevention of dementia.

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



Gregory M. Holmes, Ph.D.
Assistant Professor



Stefany D. Primeaux, Ph.D.
Instructor

Faculty:

Gregory M. Holmes, Ph.D., Stefany D. Primeaux, Ph.D.

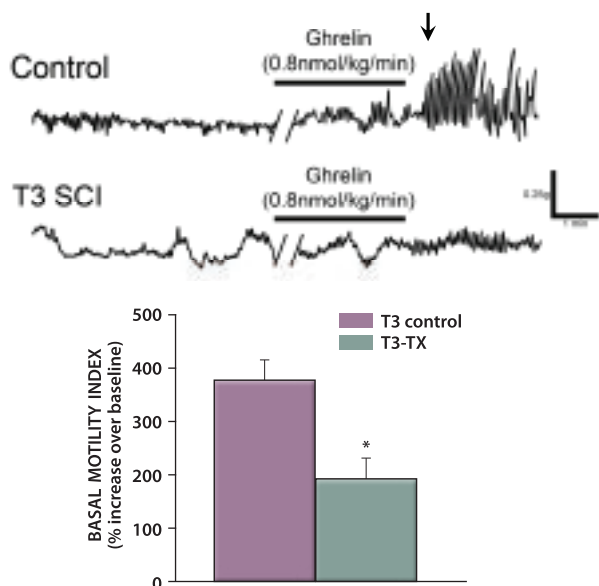
Research Team:

Melissa Tong, B.S., Emily Q. Creekmore, M.A.

Focus: To understand the mechanisms of digestive system dysfunction following central nervous system trauma.

Spinal cord injury (SCI) dramatically impairs autonomic nervous system function, including the regulation of the gastrointestinal (GI) tract and systemic blood pressure. Clinical reports indicate that GI motility is diminished in humans after spinal cord injury (SCI). The autonomic reflexes governing motility begin with sensory signals originating in the GI tract (e.g., stomach) which are relayed through the vagus nerve. These sensory fibers provide input to a complex series of neural circuits organized in the brainstem. The main projections of these circuits terminate upon neurons of the dorsal motor nucleus of the vagus (DMV) in order to regulate gastric motility through the balance of competing excitatory and inhibitory projections.

We have demonstrated profound reductions in gastric contractions and emptying of a solid test meal as early as 3 days, and persisting at least as long as 6 weeks, after experimental SCI. Furthermore, we report that reflex inhibition of the stomach in response to mild distension of the esophagus (as occurs during swallowing) is significantly decreased after SCI. Since the vagal circuit controlling the stomach remains physically intact after SCI, the esophageal and gastric dysfunction following SCI presents an intriguing paradox.



Ghrelin activation of gastric motility (arrowhead) is significantly diminished in SCI subjects.

For example, uncontrolled intestinal feedback mechanisms to the stomach may limit further gastric emptying in the SCI subject and be one mechanism responsible for the clinical reports of early satiety. Release of cholecystokinin (CCK) from small intestine endocrine cells activates inhibitory gastric feedback circuits through both peripheral endings of vagal sensory fibers and by acting directly upon neurons within the brainstem. Excessive CCK release following a meal by a SCI subject would “brake” gastric emptying. However, in contrast to the reduction in gastric motility seen after administering CCK in intact animals, we have observed limited responsiveness by CCK after SCI. Collaborative work with other scientists and PBRC has revealed that sensory fibers within the vagus nerve remain functional after SCI, but do not respond normally to CCK. Conversely, release of the peptide ghrelin is tightly linked to the nutritional status of the organism. In addition to the stimulatory effects upon feeding, ghrelin also stimulates gastrointestinal motility. Using ghrelin as a pharmacological tool to test vagus nerve drive to the stomach, we find that increased gastric motility following peripheral (0.8nmol/kg/min for 5 min, Fig. 1) or brainstem (450pmol, data not shown) administration of ghrelin is blunted in T3-SCI rats.

Our observations suggest that changes in the sensitivity of GI-vagal reflexes may be partially responsible for post-SCI gastroparesis. We propose that SCI diminishes vagus nerve function through several mechanisms that include diminished blood flow (ischemia) that instigates inflammation of the GI tract. This conclusion is based upon our observation that blood flow in the superior mesenteric artery (SMA, which supplies the upper GI tract) is significantly lower in SCI rats. Furthermore, the reflex increase in blood flow to the GI tract that occurs as nutrients pass through the intestine does not occur after SCI. This so-called postprandial hyperemia reflex is critical to meet the increased metabolic demand of the GI tract during digestion. Without this reflex, the GI tract is prone to injury and inflammation. Indeed, the expression of mRNA for inflammatory markers is upregulated following SCI.

We are only just beginning to understand the mechanisms involved in the changes to the GI tract after SCI. Our laboratory is the only one of its kind in the nation dedicated to understanding GI dysmotility and inflammation in order to develop a therapeutic strategy to alleviate gastrointestinal dysfunctions in the SCI population.

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



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.

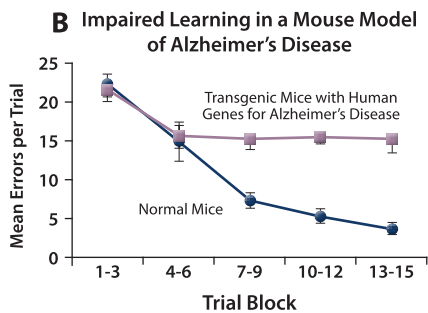
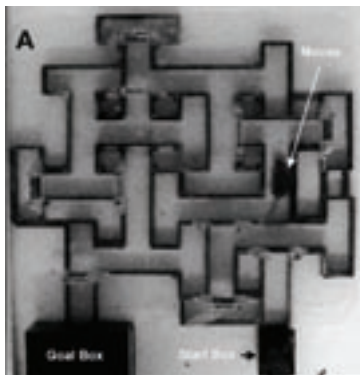
Research Team:

Jong Soon Kim

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 multiple genetic and environmental factors, with nutrition playing a major role. As a primary focus for our laboratory, we have been investigating the beneficial 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 function. This dietary regimen of caloric restriction (CR) is 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 animals, 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 dieting. Previously using a variety of animal models, we 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, we have conducted screens to discover new CR mimetics, primarily focused on inhibiting hexokinase (HK), the first step in glycolysis. We hypothesize that inhibiting glucose metabolism will trick the cell into activating a CR-like response. As the lead compound, we are examining an extract of avocado containing a high concentration of the sugar, mannoheptulose (MH), a known HK inhibitor. Addition of MH to the diet results in improved insulin function and protection against the unhealthy consequences of a high fat diet similar to beneficial effects of CR, including improved motor and cognitive function. This approach is modeled after previous studies in which we showed that the plant polyphenol found in high concentration in red grapes, resveratrol, can protect against obesity related pathology. We are currently extending our findings of MH to several other rodent models, including transgenic models of Alzheimer’s disease, in which we have recently shown that CR can attenuate pathogenesis.



(A). Overhead video image of a mouse in the 14-unit T-maze moving through water from a start box to a dark, dry goal box. (B) Decreased number of errors made by normal mice across 15 trials indicates ability to readily learn correct pathway compared to markedly impaired learning indicated by greater number of errors observed in transgenic mice expressing mutant human genes that create brain pathology similar to Alzheimer’s disease.

In other studies using rodent models of normal aging and Alzheimer’s disease, we have found that high fat diets accelerate age-related decline in memory function. To this end, we are investigating several novel drugs for preventing this impairment, including novel inhibitors of butyrylcholinesterase and phosphodiesterase. For examining learning and memory in mouse models, we have developed a new maze paradigm that is depicted in the illustration.

In addition to rodent studies, we are conducting human clinical trials in collaboration with Dr. Will Cefalu to evaluate effects of a blueberry supplemented diet on insulin sensitivity and cognitive performance in persons at risk for adult onset diabetes. Additionally, collaborating with Dr. Steven Smith, we are evaluating effects of the dietary supplement, Juvenon, containing acetyl-L-carnitine and alpha-lipoic acid, for improving memory and brain glucose metabolism. In general, the major goal of our research is to improve brain health and enhance the quality of life for the elderly.

Research in this laboratory is supported by grants from the Glenn Foundation for Medical Research, the Alzheimer’s Association, the Wild Blueberry Association of North America, Juvenon, Inc., the National Institute of Neurological Disorders and Stroke, and the National Center for Complementary and Alternative Medicine.



Thomas W. Gettys, Ph.D.
Professor

Faculty:

Thomas W. Gettys, Ph.D.

Research Team:

Ji Suk Chang, Ph.D., Eric Plaisance, Ph.D., Vivian Fernand, Ph.D., Jeho Shin, M.S., Anik Boudreau, B.S.

Focus: To investigate the sensing mechanisms which detect dietary composition and translate this information to peripheral tissues through signaling systems that communicate with and modify 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 α - 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 α 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 α which is biologically active and dynamically regulated in the context of the physiological signals which regulate the full length form of the protein. The abbreviated domain structure of NT-PGC-1 α conveys

unique properties that are both complementary to and unique from the parent protein. NT-PGC-1 α is expressed in human tissues and we propose that it plays an important, previously unappreciated role in all tissues where the full length protein is expressed. Our long term goal is to understand the *in vivo* roles of this novel protein with respect to how NT-PGC-1 α functions to enhance and complement the metabolic functions of PGC-1 α in all tissues where both forms of the protein are expressed.

Dietary Methionine Restriction Induces Substrate Cycling in Peripheral Tissues - Dietary methionine restriction (MR) limits accumulation of adipose tissue despite producing a paradoxical increase in food consumption. These responses to dietary MR involve a significant increase in fuel oxidation and corresponding reduction in metabolic efficiency. Our studies support the view that these effects involve both uncoupled thermogenic respiration and the induction of non-heat producing substrate cycles in adipose tissue, liver and muscle. For example, given the compartmentalization and highly integrated function of liver, adipose tissue, and muscle metabolism during the daily transitions between fed and fasted states, the metabolic remodeling produced by dietary MR is likely to involve changes in the way these tissues function together. An important goal of our work is to identify the non heat producing substrate cycles that are engaged by dietary MR and assess their relative impact on overall *in vivo* energy expenditure. An equally important goal is to understand the nutrient sensing mechanisms which detect dietary MR, initiate increased food consumption, and remodel the integration of lipid metabolism among peripheral tissues in a way that dissipates excess energy, enhances metabolic flexibility, and limits the accumulation of adipose tissue.

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

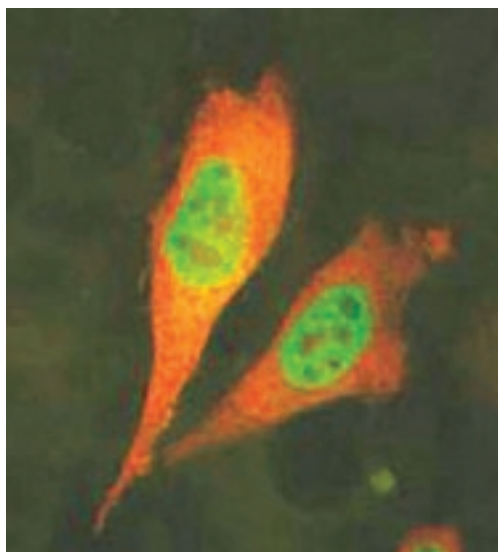


Figure 1 - Confocal image showing NT-PGC-1a tagged with red fluorescent protein in cytoplasm and PGC-1a tagged with green fluorescent protein in the nucleus. Our studies show that NT-PGC-1a moves into the nucleus under conditions which increase its involvement in regulation of gene expression.



Vishwa Deep Dixit, D.V.M., Ph.D.
Assistant Professor

Faculty:

Vishwa Deep Dixit, D.V.M., Ph.D.

Research Team:

Yun-Hee Youm, Ph.D., Bolormaa Vandanmagsar, Ph.D.,
Anthony Ravussin, B.S.

Focus: Cellular and molecular mechanisms of aging and obesity-related decline in immunity and aberrant inflammatory response.

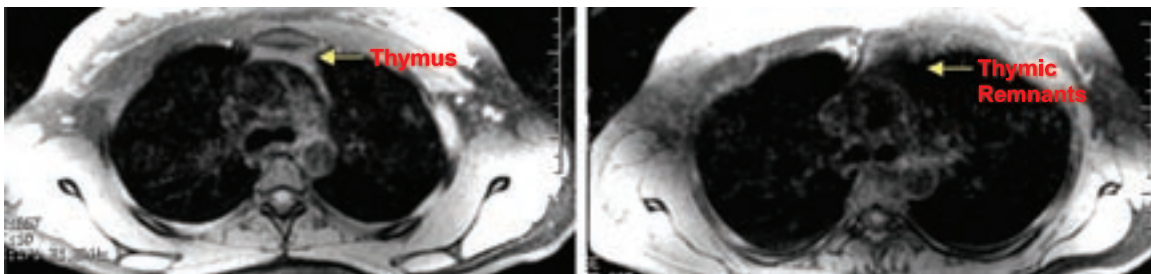
A major research emphasis of this laboratory is to study the dialogue between adipose and immune cells in relation to aging and obesity. We call this emerging area as Adipoimmunology. We define Adipoimmunology as area of research devoted to studying the interactions between adipocytes and immune cell subsets via their secreted products and cell-cell interactions within adipose and lymphoid tissue microenvironment and consequences of these interactions during disease states of obesity (insulin resistance, infection and cancer) and/or aging (immune deficiency and autoimmunity).

As we grow older, thymus, an immune-organ that produces infection and cancer fighting T cells is converted into adipose-tissue and cannot effectively generate T cells. According to the dogma, it has been believed that adipocytes or fat cells “infiltrate/invade” the thymus to “fill space” in absence of T cells. However, Laboratory of Neuroendocrine-Immunology at PBRC has challenged this dogma. The latest research work from Dixit Lab, employed genetic fate-mapping and discovered that a subset of specialized thymic epithelial cells, that are vital for T cell development, trans-differentiate, lose their function and become fat cells. Considering that hematopoietic stem cells in bone marrow develop into T cells only in thymus, loss of thymic epithelial cells and emergence of adipocyte leads to age-related decline in immune function and increased risk of influenza, shingles, infections, cancer and vaccination failures. The ongoing research in this laboratory is

focused on understanding the basic mechanisms of abnormal-adipocyte formation in immune-organs in an effort to develop future therapeutic strategies to strengthen immune system. Dixit Lab is also translating these basic research findings to the clinic by investigating if pro-longevity experimental intervention called caloric restriction can enhance immune function in humans. This study called “CALERIE” is expected to be complete in year 2013 and would be the first controlled randomized clinical trial to investigate the impact of caloric restriction on reversing or retarding the aging of thymus in humans.

As the continued deposition of adipocytes in the immune microenvironment is detrimental, similarly, the increase in immune cells in adipose tissue depots during obesity leads to type-2 diabetes. Working on the interface of Immunobiology, aging and obesity the Laboratory of Neuroendocrine-Immunology, has found that aberrant expansion of immune cells can alter 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. This laboratory at PBRC has discovered that in addition to macrophages, the adipose tissue in obese animals and humans harbors various activated immune cell subsets, including effector-T cells 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 grants from the National Institutes of Health, PBRC's Nutrition and Obesity Research Center, and the Coypu Foundation.



The MRI image showing a thymus (located above heart) of healthy 25 year woman (left), by age of 50 years (right) majority of functional thymic tissue is lost and replaced with fat.



Indu Kheterpal, Ph.D.
Assistant Professor

Faculty:

Indu Kheterpal, Ph.D.

Research Team:

Peter Scherp, Ph.D., Ginger Ku, M.S. and Carmen Ruiz, B.S.

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, not only from the perspective of human disease, but also in terms of fundamental aspects of protein folding/misfolding.

We are developing and applying hydrogen/deuterium exchange - electrospray ionization mass spectrometry (HX-ESI-MS) methods to identify and characterize molecules aimed at slowing, preventing or reversing A β amyloid formation in AD. We are also applying HX methods to probe the secondary structure of islet amyloid polypeptide (IAPP) fibrils associated with type 2 diabetes. We have developed and applied on-line HX-MS methods for structural determination of amyloid fibrils and protofibrils of the A β (1-40) peptide associated with AD. This methodology has provided insight

into the secondary structure of monomers, protofibrils, and fibrils and into the structural relationships among these states. HX-MS is fast, sensitive and is becoming a general tool to study protein structure and dynamics as well as to study protein-protein and protein-ligand interactions. The tools developed to study amyloid fibrils can be easily extended to other protein systems.

Proteomic approaches to understanding the role and mechanism of botanical 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 state-of-the-art proteomic technologies to map modifications in protein expression and phosphorylation levels due to the botanical and nutritional treatments in skeletal muscle tissues and cells in culture. These studies are providing essential data to understand the mechanism of action of botanical extracts and nutritional treatments in improving insulin sensitivity at the molecular level.

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



(A) Electron micrograph image of amyloid fibrils. Amyloid fibrils are electrosprayed (B) into the mass spectrometer and number of backbone amide protons exchanging with deuterium are measured in an ESI spectrum (C).



George A. Bray
Boyd Professor



H. Douglas Braymer, Ph.D.
Professor



Maria Barnes, Ph.D.
Assistant Professor



Stefany Primeaux, Ph.D.
Instructor

Faculty:

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

Faculty:

Katherine Pyburn, B.S.

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.

The last two years have been a time of transition for this laboratory. The 10 year MERIT Award came to an end and the renewal application was not funded.

Maria Barnes received a K01 Award to determine the role that mu opioid receptors play in the development of diet induced obesity. The level of fat in the diet, together with portion size, is thought to play a major role in promoting the number of individuals who are obese. This emphasizes the need to understand the factors that are involved in modulating not only food intake but also the high preference for fat. Of the large number of peptides, neurotransmitters, and receptor populations that affect food intake, only a few have been demonstrated to make animals overeat and increase their fat preference. Included in this list are mu opioid receptors. The precise mechanism(s) by which mu opioid receptors make animals overeat and increase the preference for a high fat diet is unknown. What is known is that in obese animals, this receptor population is significantly increased in multiple areas of the central nervous system that are known to be involved in feeding behavior. We hypothesize that the increased mu opioid receptors are contributing to the overeating and increased fat preference that is observed in obese animals. The goals of the K01 application are to determine 1) what causes mu opioid receptors to increase in obese animals; 2) potential mechanisms by which mu opioid receptors make animals hyperphagic and increase fat preference; 3) if increased mu opioid receptors potentiates the development of

obesity. The results obtained from the studies can provide a potential target to attenuate the overeating and increased fat preference that is observed in humans that are obese.

During the preparation of a new grant request focusing on the taste of fat, we examined the expression of the gene CD36 which is a fat transporter in the gastrointestinal tract (GI). Among the interesting findings was the discovery that many other genes like olfactory genes, inflammatory genes, drug-metabolizing genes and transport genes were differentially expressed in response to diet in obesity-prone and obesity-resistant rats. This implies that the GI tract may act as an extended nose and that metabolism of fatty acids or related products may be involved in the adaptation to diets. This area will clearly get more research in the future.

We have also continued experiments investigating the role of fat receptors on the tongues of obesity-prone and obesity-resistant rats. The role of the tongue and taste are very important because they provide important information about the composition of the diet. The CD36 receptor has been proposed to be the taste receptor for fat. Therefore, we examined the gene expression of CD36 receptors on the tongues of obesity-prone and obesity-resistant rats in response to a diet high in fat. Our results indicate that CD36 receptors are differentially expressed on the tongues of these two strains in response to dietary fat. We have begun studies to experimentally manipulate the expression of CD36 receptors on the tongue of obesity-prone and obesity-resistant rats and our results suggest that altering CD36 receptors significantly affects the preference for a high fat diet.

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



Nikhil V. Dhurandhar, Ph.D.
Associate Professor

Faculty:

Nikhil V. Dhurandhar, Ph.D.

Research Team:

Ronald Luftig, Ph.D., (adjunct), Olga Dubuisson, Ph.D., Rashmi Krishnapuram, Ph.D., Emily J. McAllister, B.S., Robert Oubre

Focus: To understand the role of infections as a cause of obesity.

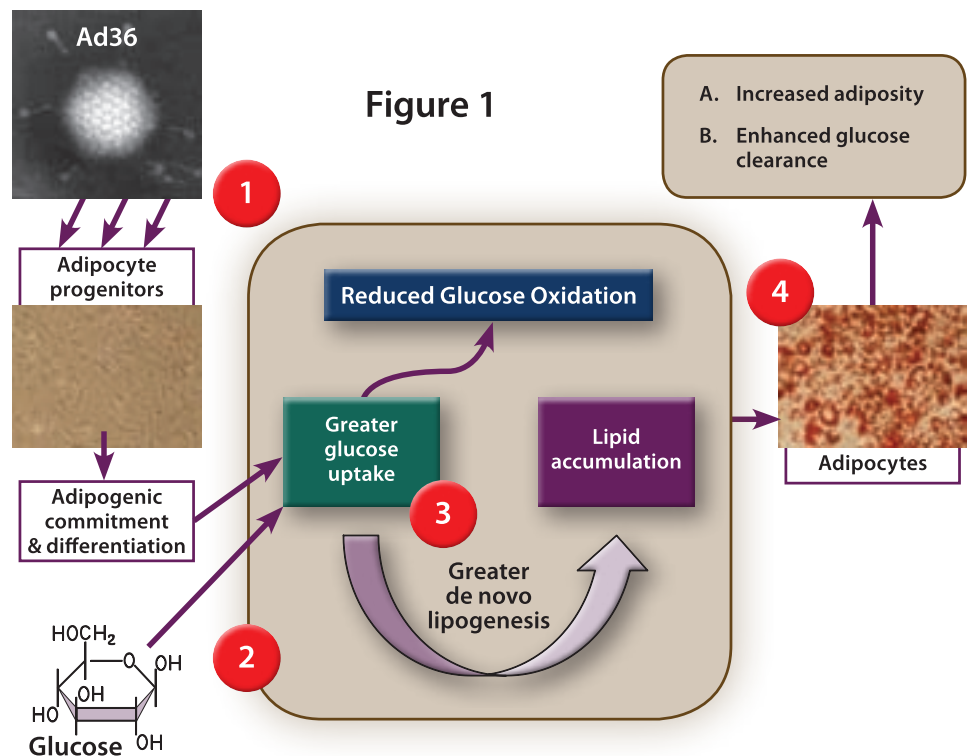
The primary interest of our lab is to discover effective strategies to prevent or treat obesity and its related comorbidities. A more complete understanding of the varied etiological factors contributing to the human obesity epidemic may lead to specific treatments and better management of this important disease. In this regard, if a subset of obesity is caused by certain infections, the strategies required for its cause-specific prevention and treatment may differ considerably from the currently available conventional approaches. In the last two decades, ten obesity-promoting pathogens have been reported, including our reports of the first human virus, adenovirus type 36 (Ad36). We showed that Ad36 causes obesity in experimentally infected chickens, mice, rats and non-human primates and reduces serum cholesterol and triglycerides. In humans, natural Ad36 infection is associated with obesity and relative hypolipidemia. Our data indicate that Ad36 increases adiposity by inducing adipogenic commitment in adipocyte progenitors and by increasing their replication, differentiation, and lipid storage. In addition to increasing adiposity, Ad36 robustly enhances glycemic control in experimentally infected animals. This effect appears to be due to an increase in glucose uptake by Ad36 in adipose tissue or skeletal muscle cells in a Ras mediated and phosphatidylinositol-3-OH kinase (PI3K) dependent manner. We recently identified the E4orf1 protein of Ad36 as a candidate, which may explain the effect of the virus on adiposity and glycemic control.

Based on the in vitro and in vivo data, Figure 1 presents a working model to explain the effects induced by Ad36 in rodents. The processes represented by numbers in the figure are as follows:

1. Ad36 infects adipocyte progenitors and promotes adipogenesis
2. Ad36 increases glucose uptake in adipocytes
3. The increased glucose entering cells is preferably converted to lipid
4. This leads to more adipocytes with greater lipid storage, but with enhanced ability for glucose clearance. Collectively, this may contribute to greater adiposity, yet better glucose handling.

The treatment and/or prevention of Ad36-induced adiposity is our long-term goal. Developing a vaccine to prevent Ad36 induced obesity is one of our objectives. Moreover, determining the role of other infectious agents in the etiology of obesity is an area of investigation that may be crucial to making progress in managing the obesity epidemic.

Research in this laboratory is supported by grants from the National Institutes of Health, the American Diabetes Association, and the Mathile Institute for Human Nutrition.





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



Claudia Kruger
Instructor

Faculty:

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

Research Team:

Xiaoying Zhang, M.D., Jacie MacGowan, Jessica Wilson

Focus: The long-term goal of my research program is to understand how information encoded in the genome is realized into a three-dimensional living organism that encounters diverse environments.

Initially, we focused on a family of transcription factor genes, the homeobox genes, which are involved in morphogenesis of the embryo. Using conditional transgenic and knockout technologies, we have developed unique mouse genetic models that allow us to study the function of these transcription factors in specific tissues, in particular the developing skeleton. Using culture of primary cells, we have identified a role for Hox genes in regulating proliferation of cartilage progenitor cells. Genetic screens have shown that this role is modulated by gene-gene interactions, as well as gene-environment interactions, because certain aspects of skeletal patterning are influenced by maternal diet in our models. Extensive expression profiling studies implicate specific developmental pathways, particularly those that regulate proliferation of precursors and their propensity for differentiation into functional chondrocytes that produce cartilage, a critical precursor to bone formation in the developing skeleton.

We have recently begun to study how maternal factors, such as nutrition or diseases during pregnancy, affect these signaling pathways and embryonic development in general. It is well established that pregnancies complicated by maternal diabetes are accompanied by a higher risk for congenital defects in progeny of affected mothers. Heart defects and neural tube defects are particularly common in infants exposed to maternal diabetes. Our efforts in the past two years have demonstrated that genes belonging to Wnt signaling pathways are misregulated in embryos exposed to diabetes. Wnt signaling is known to be critical for normal development, but its role in embryogenesis under conditions of maternal diabetes is unknown. Functional studies are now underway in my laboratory to define the contribution of Wnt pathway genes to birth defects risk caused by maternal metabolic disease. Where possible, such studies will be extended to maternal obesity during pregnancy, as this was recently identified a strong risk factor for birth defects.

Some birth defects, most notably neural tube defects, can be prevented by a diet that is rich in folic acid, an essential vitamin.

Folic acid is present in leafy green vegetables, and in folate-fortified grain and cereal products; many multivitamin supplements also contain folic acid. However, despite its wide use, the mechanisms underlying the beneficial effect of folate supplementation are poorly understood. We are using mouse models to investigate the transport of folate to the developing embryo, and the effects of folate supplementation on key morphogenetic processes, such as neural tube closure and development of the skeleton. In the past two years, we have identified the visceral endoderm as the major site of expression for Folate receptor 1, the major transporter of folate to the developing embryo prior to neural tube closure. We have also found that reduced expression of Folate receptor 4 leads to reduced fertility, and when expression is absent, to infertility in females. Our present efforts aim to determine whether embryonic development is impaired before or during implantation in Folate receptor 4 deficient animals.

Upon implantation, the placenta begins to form and assume the major role in transport of nutrients to the developing embryo, and conversely, waste products away from it. In pregnancies affected by maternal diabetes, the placenta remains smaller and exhibits abnormal gene expression, again indicating that maternal diabetes has profound effects on tissues required for normal embryonic development. Interestingly, the composition of the maternal diet modulates gene expression in placenta as well as birth defect risk, suggesting a complex interplay between genetics, environment and disease. It is now believed that this interaction of factors during intrauterine development has long-lasting consequences for the health of the individual, such that adverse exposures may raise the predisposition to disease later in life, particularly cardiovascular disease, metabolic syndrome and obesity. Our ongoing projects are now aimed at understanding how intrauterine exposures modulate risk for birth defects and risk for adult diseases. In the long term, we may be able to use the insight gained from these studies to formulate optimal diets or supplements for pregnancy, and to develop better strategies for prevention of congenital defects, as well as for promotion of long-term health in adults.

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



Kenneth J. Eilertsen, Ph.D.
Associate Professor

Faculty:

Kenneth J. Eilertsen, Ph.D.

Research Team:

Ru Gao, Ph.D., Heather Kirk-Ballard, M.S.

Focus: To understand how adult cells can be reprogrammed to a less differentiated state.

During animal development, an epigenetic memory is established in the nucleus of cells that promote tissue-specific gene expression patterns that dictate cell function. Epigenetic memory is heritable and stable, but not irreversible. Reprogramming is a process of changing a differentiated cell to a less differentiated state and involves erasure of epigenetic memory. Reprogramming can occur when a differentiated nucleus is exposed to a natural reprogramming environment such as the intact oocyte or egg. Complete reprogramming to totipotency (e.g., the capacity to develop into an entire organism) has been demonstrated by us and others through successful animal cloning using somatic cell nuclear transfer (SCNT, or cloning) technology. Partial reprogramming (e.g., reversal to a pluripotent state that is capable of differentiating into all cell types of an organism, but not an entire organism) has also been demonstrated by our group.

Approaches designed to regulate gene expression in humans has been a strategy for therapeutic intervention in human diseases. As our understanding of gene regulation has developed, it has revealed molecular mechanisms underlying disease, allowed for the identification of disease markers, and ultimately, is facilitating the development of novel therapeutics. Reprogramming is an extension of this strategy and will lead to the development of reprogrammed human cells that can be applied to cell-based therapies. Other applications include drug discovery, toxicology screening and livestock cloning.

Despite immense promise, somatic cell reprogramming still faces a critical challenge. Specifically, every method described to date can be characterized by low efficiency rates ranging from ~0.0006-1%. The low rates of success, which have not improved after a decade of intense research, limit development and application.

We have hypothesized that numerous factors limit the efficiency of reprogramming including 1) a general resistance on the part of a cell to broad epigenetic changes induced experimentally; 2) activation of programmed cell death pathways (apoptosis); and 3) suboptimal culture conditions.

To address the challenges of reprogramming, and to eventually realize the promises of this technology, our research program focuses on elucidating and understanding the mechanisms of reprogramming somatic and adult stem/progenitor cells to pluripotent and totipotent states. Ongoing studies include the identification of methods to induce expression of key genes such as Oct4, Sox2 and Nanog (Figure 1A-C); use of small molecule inhibitors of apoptosis to improve reprogramming efficiency; development of novel culture conditions; and improving livestock SCNT efficiency by reprogramming donor cells (Figure 1D & E).

Key findings have been 1) the identification of mechanisms that resist reprogramming of an adult cell to a less differentiated state and 2) improving reprogramming efficiencies by specifically targeting components that inhibit change to a less differentiated state. Lastly, we have learned that broad changes to epigenetic memory may also have undesirable consequences including induction of various pathologies. Our data suggest at least some of these pathologies may be attributable to subtle and highly specific differences in the molecular marks that establish memory.

Research in this laboratory is supported by a grant from the LSU Board of Regents Industrial Ties Research Subprogram.

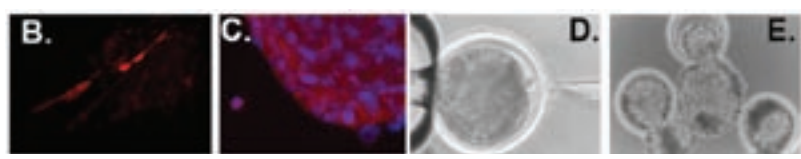
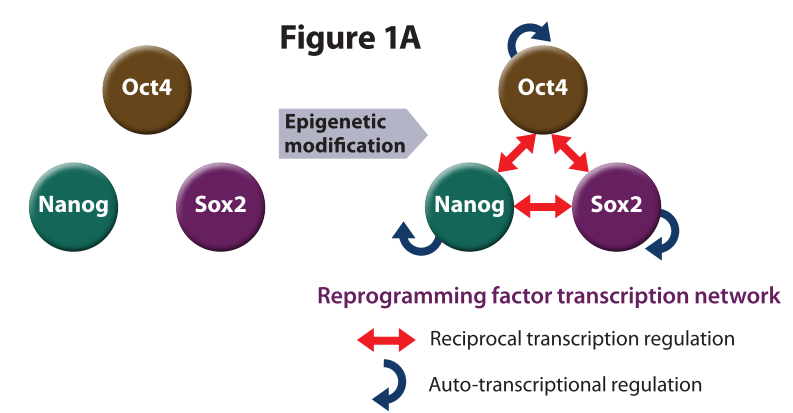


Figure 1A. Reprogramming requires activation of at least 3 key genes: Oct4, Sox2 and Nanog which in turn continue to activate themselves (blue arrows) and the others (red arrows). **1B.** Muscle progenitor cells expressing Oct4 (red) from the lentiviral transgene. **1C.** Reprogrammed human cells expressing Oct4 (red). **1D.** Bovine Somatic Cell Nuclear Transfer. **1E.** Bovine embryos produced by SCNT.



Gregory M. Sutton, Ph.D.
Assistant Professor

Faculty:

Gregory M. Sutton, Ph.D.

Research Team:

Armand Centanni, B.S.

Focus: To understand how protein malnutrition during pregnancy results in altered circadian rhythms in the offspring after birth.

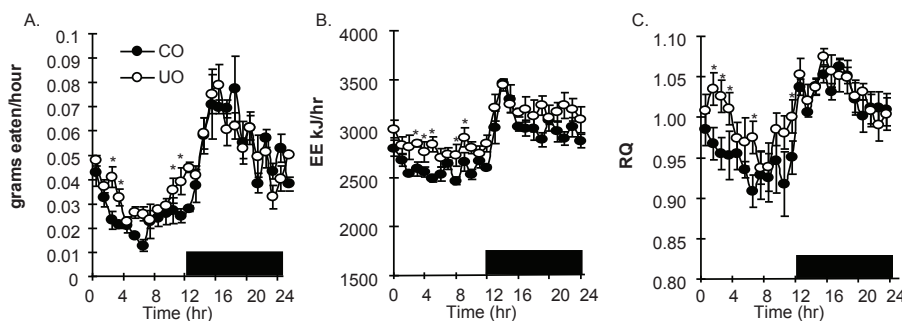
The environment encountered during fetal life and infancy appears to be strongly related to the development of adult-onset diseases such as type 2 diabetes, hyperlipidemia, hypertension, and obesity. Adaptation to variation in nutrient availability during critical periods of development is necessary to maintain homeostasis and proper growth; however compromised development can impact function via alterations in systems such as fetal cell number, gene expression, hormonal balance and sleep patterns. The process by which the intra-uterine environment plays a role in establishing the health of the offspring has been termed “fetal programming”.

Recent research indicates that maternal nutrition plays a significant role in development of the fetal central nervous system (CNS). Through unknown mechanisms, maternal malnutrition may lead to altered responses to peptides regulating satiety and neuroendocrine function leading to lifelong hyperphagia and an obese phenotype in animal models. Prenatal exposure to a low protein diet is a commonly used model mimicking fetal under-nutrition, and when administered to rat dams, results in offspring exhibiting significant changes in memory and serotonergic regulation which result in profoundly altered sleep patterns. Sleep deprivation in rodents has been shown to alter responses to neuropeptides controlling food intake and energy expenditure. Similar impairments in neuronal development may be correlative in humans exposed to malnutrition within the first 2 years of life as these children are reported to have delayed cognitive development and poor school performance.

Our hypothesis suggests that maternal protein deficiency has profound effects on circadian rhythms of physical activity, metabolism and gene expression in C57Bl/6J offspring. Mothers fed a protein deficient diet produced offspring that had a 56% reduction in nocturnal wheel running activity, coupled with an increase in daytime wheel running as well as a deregulated circadian pattern of food intake and energy expenditure as assessed by indirect calorimetry. Circadian rhythms or the 24 hour daily processes of sleep wake cycles control multiple physiological processes and proper circadian control of these processes is important in coupling day/night patterns of behavior with metabolism. Our lab studies the disruption of circadian oscillation of three critical clock genes, *Bmal1*, *Per2* and *Rev-erba*, as these genes may provide a molecular basis that could impact glucose and lipid metabolism as recent evidence suggests that cell autonomous clocks in the brain and in peripheral tissues such as liver, muscle and adipose tissue are necessary to maintain metabolic stability. We have observed that at 2 months of age, mice exposed to dietary stress have impaired glucose and lipid homeostasis as well as express signs of Type II Diabetes at 5 months of age. This phenotype is exacerbated after exposure to a high fat diet.

Future studies will characterize the circadian physiology of offspring as well as the mother’s health after dietary stressors such as protein malnutrition. We will also incorporate pharmacological strategies that may aid in reversing the metabolic syndrome observed in mice at 5 months of age that have been exposed to protein malnutrition in utero in an effort to correct metabolic instability by restoring loss of circadian function.

Research in this laboratory is supported by a grant from the American Diabetes Association.



Mice exposed to a protein restricted diet throughout gestation (undernourished offspring, UO) have altered circadian patterns of food intake (A) energy expenditure (B) and respiratory quotient (C) compared to mice exposed to normal dietary parameters (control offspring, CO). Measurements taken every hour over a 24-hour period. The 12-hour dark phase is represented by a black box along the x-axis.



Barbara Kozak, Ph.D.
Assistant Professor

Faculty:

Barbara Kozak, Ph.D.

Research Team:

Jaroslaw Staszkievicz, D.V.M., Ph.D., Heather Kirk-Ballard, M.S.

Focus: 1). To understand the mechanisms of scar-free healing (regeneration) in FOXN1 deficient (nude) mice and how this knowledge can be translated and applied to guide the wound healing process towards regeneration; 2). To investigate commitment of adult stem cells into the adipocyte lineage

1). Skin tissue is the largest organ in the body and its primary function is to protect the body's integrity from the external environment (i.e. pathogens, injuries). Post-injured skin responds to trauma by scar formation at the lesion site. Although the scarring process is beneficial for reestablishing the barrier between internal and external environments, the scar of post-injured skin tissue never regains complete functionality. Currently, there is little understanding of the molecular basis of scar formation and consequently there are no effective therapies for reducing severe scarring.

Our laboratory has determined that FOXN1 deficient (nude) mice are the only adult mammals known to exhibit a skin wound healing process with regenerative features. We demonstrated that post-injured skin tissues from nude mice differ from wild type mice with respect to deposition of collagen and hyaluronic acid. Moreover, we showed that pattern of matrix metalloproteinases (MMPs) expression, enzymes that remodel tissue and are indispensable for regeneration in amphibians, are differently regulated in nude mice. Since the nude phenotype is the consequence of a functional mutation of the *Foxn1* gene, we investigated whether the lack of nude gene (*FoxN1*) is the factor that promotes scarless skin repair. We found that: (i) skin injury evokes up-regulation of *Foxn1*; (ii) *Foxn1* expression during wound repair accompanies elevated expression of *Mmp-9* in wild type of mice; (iii) FOXN1 induces *Mmp-9* expression

in keratinocytes. The data suggest that *Mmp-9* is direct target of FOXN1 action in keratinocytes and FOXN1 participates in wound healing process through regulation of *Mmp-9* expression. Currently we are testing the mechanism of interaction between FOXN1 and MMP-9/MMP-13 expression.

2.) In our second project we focus on the identity, characteristics, and regulation of adipose-derived stem cells/progenitor cells. We aim to understand the mechanisms that determine how adipocyte progenitor cells contribute to adipose tissue expansion, a fundamental mechanism in obesity.

We showed that fat mass enlargement in C57BL/6J mice fed a high fat diet was correlated with an increase in stem cell antigen-1 (Sca-1) positive cells in the stromal-vascular fraction (SVF) of fat depots. Cultures of Sca-1+, but not Sca-1-, cells from the SVF displayed a robust accumulation of lipid droplets and had higher levels of adipogenic gene expression during differentiation. Additionally, we measured potential differences in the localization and quantity of adipose-derived stem cells in fat tissues depending on the obesity status of animals. We demonstrated the existence of stem cells/progenitor cells in fat depots that are localized to two compartments: those close to the blood vessels wall and those sparsely distributed among adipocytes. Moreover, we show that adipocyte progenitor cells are stem cell antigen 1 (Sca-1) positive. These findings support our hypothesis that Sca-1 is a biomarker for adipocyte stem/progenitor cells within adipose tissue. Currently we focus on establishing the obesogenic phenotype of Sca-1 KO mice during 30 weeks of high fat diet and low fat diet in comparison to wild type C57BL/6J mice.

Research in this laboratory is supported by funding from the Pennington Medical Foundation, the National Institutes of Health, and PBRC's Center of Biological Research Excellence.



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

Focus: To further the characterization and understanding of adipose tissue and adult stem cells for circadian, metabolic, and regenerative medical studies.

Current Projects

The Stem Cell Biology Laboratory opened at the Pennington Biomedical Research Center in August, 2003. The principal investigators in the Stem Cell Biology Laboratory focus on the following inter-related areas:

(a) Tissue Engineering and Regenerative Medicine: The isolation and expansion of adult stem cells from adipose tissue and bone marrow, using both human subjects and experimental animal models. These cells have the potential to serve as building blocks for the emerging field of regenerative medicine. Additional collaborations with investigators at the LSU School of Veterinary Medicine and the Department of Mechanical Engineering as well with biotechnology industry partners (Repair Technologies, Vet-Stem, Zen-Bio). Studies supported by NIH have determined that adipose-derived stem cells (ASCs) can be used to generate new bone formation in a spinal fusion model. Since >100,000 spinal fusion procedures are performed in the U.S. each year, the ability to accelerate fusion using ASCs has direct clinical relevance. Additional grant support has been requested to examine the value of ASCs for soft tissue reconstructive surgery in collaboration with investigators at Tufts University and for hard tissue reconstructive surgery with investigators at Columbia University.

(b) Proteomic and Epigenetics: The characterization of the “proteome” of human ASCs. Proteomics represents the next wave

Faculty:

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

Research Team:

Bruce A. Bunnell, Ph.D. (adjunct, Tulane University), Ram Devireddy, Ph.D. (adjunct, LSU), Mandi J. Lopez, D.V.M., Ph.D. (adjunct, LSU-School of Veterinary Medicine), Xiying Wu, M.D., Gang Yu, M.S., Katie Hamel, Sydney Gardner

of comprehensive biological profiling that is now feasible because of the genomics revolution. We are taking advantage of the Pennington Biomedical Research Center’s substantial investment in the Proteomic Core Facility’s infrastructure to determine how the protein content of human ASCs changes following adipogenesis. These on-going studies are conducted in close collaboration with Dr. Elizabeth Floyd, Director, Ubiquitin Laboratory, and Dr. Indu Kheterpal, Director, Proteomic Core Facility. Additional collaborative studies with Dr. Barbara Gawronska-Kozak, Director, Regenerative Biology Laboratory, and Dr. Kenneth Eilertsen, Director, Epigenetics and Nuclear Reprogramming Laboratory, are pursuing the generation of induced pluripotent stem cells by reprogramming adipose-derived stem cells.

(c) Circadian Mechanisms: The circadian biology of adipose tissue, bone, and other metabolically active peripheral tissues. Drs. Floyd, Gimble, and Mynatt, together with Dr. Ptitsyn at Colorado State University, have demonstrated that the transcriptional machinery responsible for maintaining circadian rhythms in the brain exists within bone and fat. Our work indicates that the expression level of >20% of the expressed genes in adipose tissue show a circadian oscillatory profile. This suggests that most, if not all, metabolic activity is directly linked to the circadian clock. These findings point to new regulatory mechanisms that influence adult stem cell function in vitro and in vivo and provide new targets of opportunity to use drug intervention to manipulate adipocyte and osteoblast function.

Research in this lab is supported by grants from the Board of Regents, National Institute of Dental and Craniofacial Research, the National Institute of Diabetes & Digestive & Kidney Diseases, and the National Institute of Arthritis, Musculoskeletal, and Skin Diseases.



Beth Floyd, Ph.D.
Assistant Professor

Faculty:

Beth Floyd, Ph.D.

Research Team:

Gail Kilroy, B.S., Zachary Ogea

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.

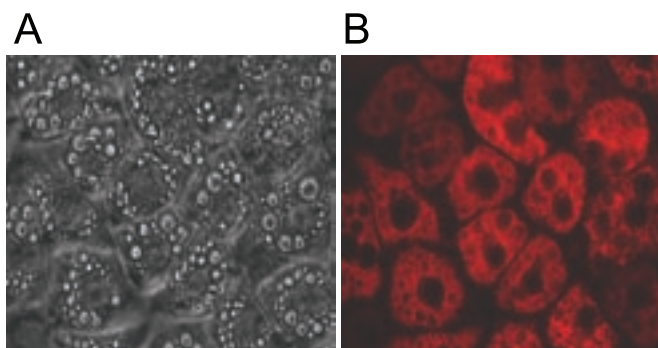
The stability of most intracellular proteins, such as PPAR γ , is determined by the ubiquitin-proteasome system. The ubiquitin-proteasome system is a highly conserved pathway that is responsible for the carefully timed degradation of proteins, making this pathway central to cellular functions. Interaction 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. Our studies show that PPAR γ activity is regulated by the ubiquitin proteasome system in adipocytes. To understand this connection between PPAR γ activity and degradation, we use cellular and molecular approaches to dissect how PPAR γ is recognized by components of the ubiquitin-proteasome pathway.

Using this approach, we found that the region of PPAR γ responsible for binding TZDs contains a signal for binding to ubiquitin and that a functioning ubiquitin system is necessary for TZD-dependent regulation of PPAR γ activity in adipocytes. Our studies are currently focused on identifying enzymes of the ubiquitin proteasome system that directly interact with PPAR γ in adipocytes. In particular, we are interested in identifying

the ubiquitin ligases involved in determining PPAR γ activity in adipocytes since these enzymes are particularly attractive targets for drug development. To accomplish this goal, we developed a novel high throughput screening method based on RNA interference technology. We used this technology to systematically examine over 225 ubiquitin ligases in adipocytes and identified a number of ubiquitin ligases that affect PPAR γ stability in adipocytes. Our ongoing studies will determine how these enzymes are regulating PPAR γ stability and if the enzymes are important in controlling PPAR γ activity in adipocytes. In addition, we know that some of these ligases also affect insulin sensitivity in adipocyte, linking regulation of PPAR γ stability by the ubiquitin system to control of insulin sensitivity.

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 Institutes of Health, PBRC’s Center of Biological Research Excellence, PBRC’s Clinical Nutrition Research Unit, and PBRC’s Botanical Research Center.



Brightfield (A) and fluorescent (B) images of small interfering RNA (siRNA) introduced into fully differentiated adipocytes. Introduction of siRNAs targeting specific ubiquitin ligases in adipocytes is being used to examine the effect of the ubiquitin ligases on PPAR γ stability and activity.

CLINICAL RESEARCH

CLINICAL RESEARCH



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

At the Pennington Biomedical Research Center (PBRC), our approach to clinical research is to provide support from inception of the research question through analysis of results and publication. This is not a do-it-yourself model. For junior investigators, ideas are refined in the Clinical Mentoring Committee. For all investigators, we provide a Peer Review Service, where we assign reviewers who provide an anonymous critique. Our Institutional Review Board provides templates online and processes research protocols in a timely manner. The Scheduling Committee assures that funding is in place for all of the 11 Core Service providers who might be needed on the project and schedules the study so that we can efficiently address needs of all our studies. Our clinic can assign a Study Coordinator if needed and our Clinical Data Management Core and Recruitment Cores are engaged early in the launch of the study. We provide on-going monitoring via our Record Library services. There are intranet applications to allow investigators to track participants and their data in real-time from investigators' desktop computers. Our Biostatistics Core is available to assist with analyses. There are online applications available to make sure that all of the investigative team has up-to-date assurance of training in privacy and HIPAA

compliance issues, in Good Clinical Practices and in Human Subjects Protections. We have made strides in the last year to assure that the underlying process measures support FDA compliance for all PBRC data. The overall approach at PBRC is one of systematic and uniform processes and a commitment to the highest quality possible in the conduct of clinical research.

Since inception of the first clinical studies in 1992, the strong infrastructure outlined above has resulted in an enviable record of completed research. As shown in the figure below, this approach has resulted in more than 15,000 patients being enrolled in more than 350 studies.

Some Research Highlights at PBRC over the last two years:

- The landmark POUNDS Lost Study demonstrated that macronutrient composition of four diets did not effect weight loss and provided strong evidence that low fat, low carbohydrate or high protein approaches do not have an independent effect on weight loss. Yes, the message remains that “calories do count” in achieving and maintaining weight loss.

Clinical Research Activity Report, Pennington Biomedical Research Center

Year	# Telephone Contacts	# Screening Visits	% Females	% Minority	# Enrolled in Studies	% Females	% 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%	7
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%	25
1999	4537	1686	61%	26%	618	58%	22%	13
2000	5458	1933	76%	32%	731	69%	24%	24
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%	29
2004	6741	2502	67%	44%	1429	66%	38%	36
2005	8576	3775	57%	39%	1723	64%	35%	16
2006	6984	2213	67%	39%	1189	68%	36%	35
2007	7501	1974	67%	42%	1011	67%	35%	32
2008	16876	2199	68%	43%	1556	66%	38%	30
TOTAL	100,326	32,856			15,332			355

- Doctors are usually pessimistic about their ability to help very obese persons lose weight. However, the LOSS Study, sponsored by the Louisiana Office of Group Benefits, demonstrated that primary care clinics, who had received brief training in obesity management, could help a subset of persons with extreme obesity achieve and sustain meaningful weight loss.
- Our work using human muscle biopsies has shown that adiponectin increases the number of mitochondria in muscle and reduces the production of harmful free radicals.
- Our metabolic inpatient unit has been engaged for the execution of first-in-man studies of new pharmacologic agents.

Trends and Emerging Areas in Clinical Research at PBRC:

- Because of the supportive environment for clinical research, we are beginning to see bench scientists move into their first human studies. Randy Mynatt, Ph.D., Les Kozak, Ph.D., and Jeff Gimble, M.D., Ph.D. are joining our cadre of clinical researchers and we expect this trend to continue, along with the great national interest in forcing more attention to “translational research.”
- PBRC has taken a leadership role in Louisiana’s translational research effort. The Louisiana Clinical and Translational Science Center (LA CaTS Center) proceeds with plans to link all the clinical and translational research enterprises in Louisiana for a Clinical and Translational Science Award (CTSA). Activities to date have been in the deployment of a member website and the development of a plan for Bioinformatics support across all institutions.
- Construction has begun on the new Clinical Research Building and Imaging Center to add more than 110,000 SF of space for

our clinical operations and tripling the size of our outpatient capacity. We have also completed plans for the renovation of existing facilities to support a Pediatric Research Clinic and to expand our inpatient capacity, including an additional two metabolic chambers.

- The Joint Endocrinology Program, under the leadership of Dr. William Cefalu, is an effort of the LSU School of Medicine and the Pennington Biomedical Research Center to enhance collaborative efforts between the Endocrinology Section in the Department of Medicine with relevant faculty at PBRC and to develop a comprehensive program of fellowship training, research and patient care delivery. This fledgling program will begin with a weight management program executed by collaborating scientists, but embedded in the LSU clinics in New Orleans.
- The future of clinical research at PBRC depends upon the pipeline of young investigators who must be supported to advance in their career paths. The Clinical Mentoring Committee has provided the structure and framework for mentoring young instructors with some notable successes. Corby Martin, Ph.D. and Robert Newton, Ph.D. have both achieved funding through K awards. Dr. Martin has also achieved an R21 and R03. Dr. Leanne Redman recently received a K99 award. Meanwhile Tiffany Stewart, Ph.D. has spun off a company to commercialize her technology to assess body image disturbances.

The future seems promising for our clinical research efforts, with new facilities and technologies coming on line within the next two years and with the maturing of our efforts in leading the clinical research efforts across the state.



Clinical Research at the Center lies within three program areas, each of which has multiple investigators and laboratories.

Diabetes

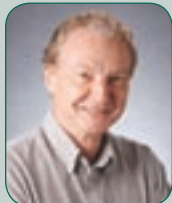
John S. McIlhenny Skeletal Muscle Physiology
Eric Ravussin, Y. Tchoukalova, L. Redman, D. Johannsen

Obesity

Behavioral Medicine
P. Brantley, V. Myers, H. Roy
 Behavior Modification Clinical Trials
G. Bray, D. Ryan, F. Greenway, S. Smith, A. Gupta
 Ingestive Behavior
C. Martin
 Pharmacology-based Clinical Trials
F. Greenway, A. Gupta
 Women's Health, Eating Behavior, and Smoking Cessation Programs
P. Geiselman

Physical Activity and Health

Exercise Biology
C. Earnest, T. Church, T. Rankinen
 Inactivity Physiology
M. Hamilton
 Preventive Medicine
T. Church, C. Earnest
 Human Physiology
Eric Ravussin, L. Redman



Eric Ravussin, Ph.D.
Professor, Douglas L. Gordon
Chair in Diabetes and Metabolism



Leanne Redman, Ph.D.
Instructor



Sudip Bajpeyi, Ph.D.
Professor



Darcy Johannsen, Ph.D.
Instructor



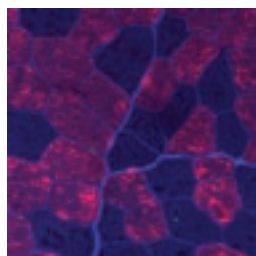
Steven Smith, M.D.
Professor

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), polycystic ovary syndrome (PCOS) and aging.

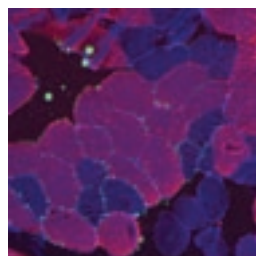
Over the past year our group has conducted cellular, molecular and functional studies in skeletal muscle samples obtained from the following clinical studies: MITO, EAT, FLEX, PRISM, CALERIE II. We use a wide array of assays to assess the metabolic, mitochondrial, and physiological characteristics of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

1. MITO: The effects of aging on skeletal muscle function. Oxidative capacity in skeletal muscle has been shown to decrease with age and may be related to increased accumulation of intramyocellular lipid (IMCL), decreased mitochondria number, and a preferential loss of oxidative type 1 muscle fibers. The purpose of the MITO study, an ancillary project of the Louisiana Healthy Aging Study, was to further investigate these relationships in elderly and young individuals. Using our newly acquired immunohistochemistry technique, we found significantly higher IMCL in elderly compared with young individuals (See Figure). However, there was no difference in the number of type1 or type2 muscle fibers between elderly and young individuals.

Young



Elderly



2. PRISM: Role of circulating factors in the pathogenesis of skeletal muscle insulin resistance in polycystic ovary syndrome. Women with PCOS have profound peripheral insulin resistance as well as intrinsic abnormalities in insulin signaling within skeletal muscle. In this study, we aim to determine whether circulating factors (sex steroids, hormones, metabolites) can modulate insulin-stimulated glucose uptake by altering insulin signaling in women with PCOS. Using a cell culture system of primary human myotubes we show that cultured human myotubes from healthy female control subjects have a decrease in glycogen synthesis when treated with serum containing elevated androgens from women with PCOS.

Faculty:

Eric Ravussin, Ph.D., Professor, Leanne Redman, Ph.D., Sudip Bajpeyi, Ph.D., Darcy Johannsen, Ph.D., and Steven Smith, M.D.

Research Team:

Jose Galgani, Ph.D., Shantele Thomas, B.S., Pamela Rogers, M.S., Jennifer Zhang, M.S., M.S., Jeffrey Covington, B.S., B.A., Clair Cook, B.S.

3. FLEX: Role of muscle mitochondrial density on metabolic flexibility. Metabolic flexibility is the ability to match fuel oxidation to availability. Skeletal muscle metabolic inflexibility has been implicated in the origin of insulin resistance due to a mismatch between lipid availability and oxidation leading to increased muscle lipid accumulation. This metabolic inflexibility to lipid is proposed to be a consequence of impaired muscle mitochondrial density and/or function. This notion is supported by the decreased mitochondrial density, function and abnormal mitochondrial morphology accompanied by higher muscle lipid content in insulin-resistant vs. insulin-sensitive individuals. The influence of mitochondrial density on metabolic flexibility to lipid may be more evident when lipid oxidative demand is increased. We are assessing the difference in metabolic flexibility to lipid in humans with a high and low skeletal muscle mitochondrial density during a prolonged moderate-intensity exercise session.
4. EAT: Fat cell size and overfeeding. The purpose of this protocol is to characterize the morphological and metabolic characteristics of both adipose and muscle tissues predisposing to ectopic fat deposition and insulin resistance before and after 8 weeks of overfeeding. The overarching hypothesis is that overfeeding will significantly increase ectopic fat deposition, insulin resistance and decreased muscle oxidative capacity in individuals with hypertrophic adipocytes more than in individuals with hyperplastic adipocytes.
5. ACTIV. Skeletal muscle mitochondrial defects and a high level of intramyocellular lipid (IMCL) content are often associated with insulin resistance in patients with type 2 diabetes mellitus (T2DM), obesity, and subjects with family history of T2DM (FH+). The objectives of our study were to compare and contrast mitochondrial capacity and IMCL measured by skeletal muscle biopsy and magnetic resonance spectroscopy (MRS) in sedentary healthy control with (FH+) and without (FH-) family history of diabetes, obese, T2DM and endurance trained athletes. We also investigated the effects of a short term exercise training regiment (~3 weeks) on skeletal muscle oxidative capacity, insulin sensitivity, and IMCL content.

Research in this lab is supported by grants from the National Institutes of Health, the Obesity Society, and various pharmaceutical corporations.



George A. Bray, M.D.
Boyd Professor



Donna H. Ryan, M.D.
Professor



Frank L. Greenway, M.D.
Professor



Steven Smith, M.D.
Professor



Alok Gupta, M.D.
Assistant Professor



Timothy Church, M.D., Ph.D.
*Professor, John S. McIlhenny
Endowed Chair in Health Wisdom*

Faculty:

George A. Bray, M.D., Donna H. Ryan, M.D., Frank L. Greenway, M.D., Steven R. Smith, M.D., Alok Gupta, M.D., Timothy Church, M.D., Ph.D.

Research Team:

Nursing, Dietary and Clinic Staff

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.

A. Diabetes Prevention Program

The study compared an Intensive Lifestyle Program versus Metformin or placebo. This study has now completed its 10th year of which the first 3.2 were double-blind. The initial Intensive Lifestyle Program produced a 7% weight loss and reduced the incidence of diabetes by 58%; 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. After these results were announced, the trial was converted into a mixed outcomes-intervention study with people taking metformin remaining on treatment and the Intensive Lifestyle group getting extra behavioral intervention. From the time the trial was converted to an outcomes study, the conversion rates were similar in all groups and corresponded to that of the initial lifestyle group i.e., everyone benefited. The trial has been refunded to 2014 to follow outcomes of diabetes.

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. The weight loss of the Intensive Lifestyle Intervention (ILI) group was 8.6% versus 0.7% in DSE group ($p < 0.001$) at year 1. This faded somewhat over the next 3 years. Mean fitness increased in ILI by 20.9% versus 5.8% in DSE ($p < 0.001$). A greater proportion of ILI participants had reductions in diabetes, hypertension, and lipid-lowering medicines. Mean HbA1c dropped from 7.3% to 6.6% in ILI ($p < 0.001$) versus from 7.3% to 7.2% in DSE. The success of the trial has led to its refunding through 2013.

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

POUNDS Lost is a randomized clinical trial conducted at the PBRC and at Harvard School of Public. It is a clinical study of the relative effectiveness of diets with 35, 45, 55, and 65% and protein at 15% or 25% and fat and 20% or 40% of daily calories. All participants received a standardized behavior and exercise program. POUNDS Lost randomized 811 overweight or obese people. This study demonstrated that you could lose weight with any diet, providing you stuck to it.

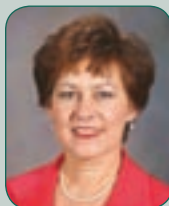
Research in this unit is supported by multiple grants from National Institutes of Health.



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:

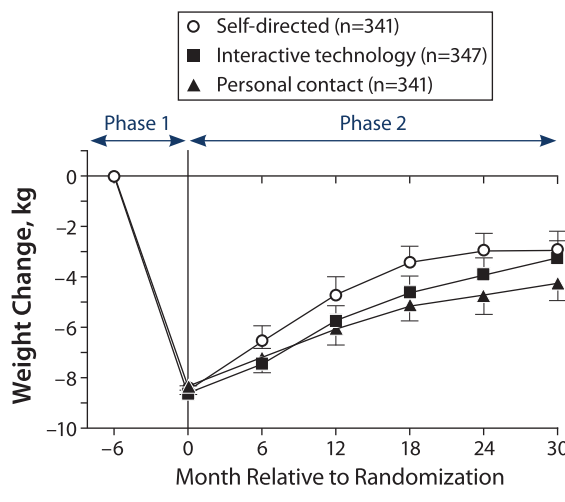
Claire Adams, M.A., Brooke Barbera, M.A.,
Patti Smith, B.A., Diana Stewart, M.A.

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 the metabolic syndrome including diabetes and cardiovascular disease.

Weight Loss Maintenance. This is the largest and most diverse multicenter trial to date for comparing strategies for maintaining long-term weight loss. We are one of four study sites. Others are Duke University Medical Center, Johns Hopkins Medical Center and Kaiser Permanente Center for Health Research in Portland, Oregon. During Phase I, 1,685 participants participated in a behavioral weight loss program. Individuals who successfully lost > 4 kg (n=1032, 63%) were randomized to one of three Phase II weight loss maintenance conditions: (1) a Personal Contact (PC) intervention providing monthly counseling primarily by telephone; (2) an Interactive Technology (IT) intervention providing frequent contacts through an interactive web-based program, or (3) a Self-Directed (SD) control group. Phase II weight regain was less in PC than SD, but, although there was an early difference between IT and SD, this difference was not significant at 30 months post randomization into Phase II. Importantly, 42% of all participants were maintaining at least 4 kg of weight loss at 30 months post randomization.

Predictors of success include maintaining healthy eating, attendance at face to face meetings, older age, higher perceived mental health, greater initial weight loss, frequent weighting and physical activity but predictors vary by gender and race. To examine extended treatment effects, a final 30-month phase (Phase III) randomized PC participants to continued PC intervention (PC-Active) or discontinuation (PC-Control) and the IT intervention was stopped. Five-year follow-up data have just been completed for SD, IT, PC-Active, and PC-Control. Recent funding will allow for further analyses that will isolate the most successful components of the interventions such that more powerful intervention can be developed for a future trial.

Bariatric Surgery Follow-up. Louisiana ranks among the top six states in terms of obesity related expenditures. This study examined weight, health outcomes, and medical and pharmacy costs for 33 severely obese adults who received bariatric surgery in 2004 as part of a pilot project sponsored by the Office of Group Benefits, a health



Error bars indicate 95% confidence intervals.

insurance option for employees of the state of Louisiana and their dependents. The surgical costs were approximately \$25,000 per procedure. Pre-surgical weight averaged 134.49 kg and the average weight loss at 4 years was 44 kg. Follow-up measures of health outcomes and quality of life ratings were encouraging. Cost savings, considering the cost of surgery, began emerging four years post surgery.

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



Corby K. Martin, Ph.D.
Assistant Professor

Faculty:

Corby K. Martin, Ph.D.

Research Team:

Anastasia Chellino, B.S., John Correa, B.S., Gina Pennington, B.S., L.D.N., R.D., Desti Shepard, M.S., Heather Walden, M.S.

Focus: To understand the regulation of food intake and appetite; to develop and test the efficacy of interventions to reduce food intake and promote weight loss; and to develop and validate methods to measure food intake in laboratory and free-living conditions.

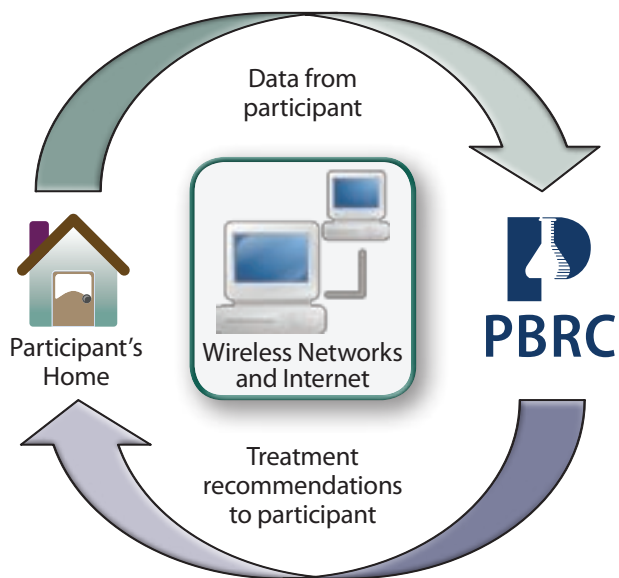
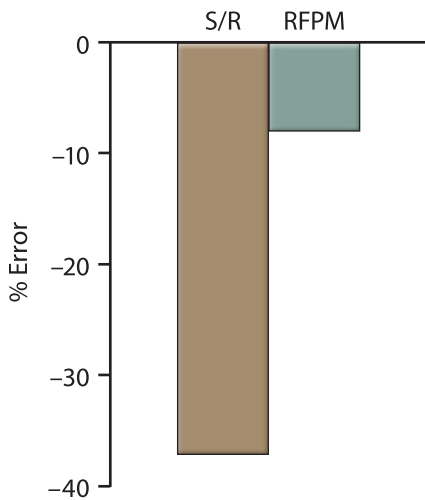
The Ingestive Behavior Laboratory (IBL) empirically tests the effect of pharmacological, herbal, and behavioral interventions on food intake, which is measured objectively in controlled laboratory conditions. The IBL also evaluates the effect of environmental stimuli, e.g., television viewing, on food intake, and we determine if individual characteristics, such as distractibility, interact with environmental stimuli to affect food intake.

In addition to measuring food intake in laboratory conditions, we developed a method called the Remote Food Photography Method (Martin et al., 2009) to measure food intake in free-living conditions. When using this method, participants use a camera-enabled Smartphone to take photographs of their food selection and plate waste while they live in their natural environment. These photographs are sent to the researchers via a wireless network in near real-time, and energy (kilocalories) and macronutrient intake is estimated by Registered Dietitians using a customized computer application. We also created a second computer application to

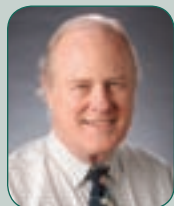
monitor data quality and organize incoming photographs for analysis. Initial tests indicate that the method underestimates food intake in free-living conditions by only 6% to 9%, which is a dramatic improvement upon existing methods. For example, self-report methods underestimate food intake by 37% or more. These results are illustrated in the left panel of the figure.

Following the validation of the Remote Food Photography Method, the laboratory developed an e-Health weight loss intervention that collects objective food intake, exercise, and body weight data from participants while they live in their home environment. These three types of data are transmitted to our laboratory via wireless networks and the internet with very little participant burden. These data are then evaluated and personalized treatment recommendations are sent to the participant via the Smartphone every one to three days. This process is illustrated in the right panel of the figure. The e-Health application is grounded in behavioral theory, which posits that behavior change is fostered by participants receiving timely feedback that is based on objective data. The efficacy of the e-Health intervention is currently being tested in a randomized controlled trial.

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



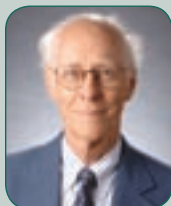
In the left panel, the error in estimating food intake with self-report (S/R) methods and the Remote Food Photography Method (RFPM) are depicted. The panel on the right provides a schematic of the e-Health application.



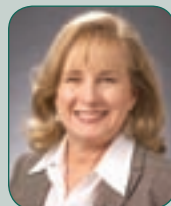
Frank Greenway, M.D.
Professor



Alok Gupta, M.D.
Assistant Professor



George A. Bray, M.D.
Boyd Professor



Donna Ryan, M.D.
Professor

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, tested in obese people and has now completed the clinical trials needed to submit for FDA approval (figure 1).

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.

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 can be a greater risk 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 partially explain the increased risk for heart attacks in this condition. It is hoped that altering the time blood pressure medication is taken may reduce these risks and blood pressure fluctuations 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 injected into lipomas causes them to get smaller. Lipomas are non-cancerous tumors composed of fat cells, and the present treatment for lipomas is surgery.

Faculty:

Frank Greenway, M.D.; Alok Gupta, M.D., George A. Bray, M.D., Donna Ryan, M.D.

Adjunct Faculty:

Drake Bellanger, M.D.; Thomas Guillot, M.D.; Mark Hausmann, M.D.; Larry Hebert, M.D.; Karl LeBlanc, M.D.; Zhijun Liu, Ph.D.; John Paige, M.D.; William Raum, Ph.D., M.D.; Brooke Whisenhunt, Ph.D.; Marney White, Ph.D.; Eugene Woltering, M.D.

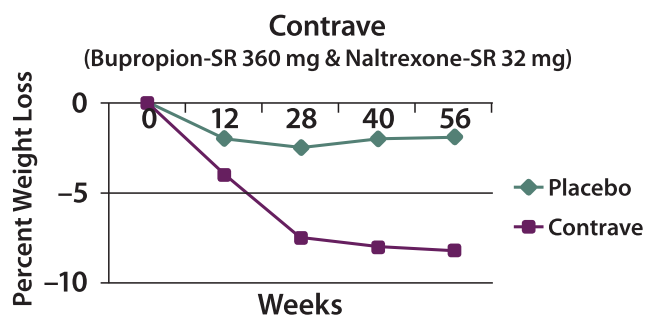
Research Team:

Mandy Shipp, LDN, RD (Clinic Administrator); Yolanda Robertson-Hill, N.P.; Jennifer Arceneaux, RN; Karen Boley, LDN, RD; Mary Beth Burnett; Lauren Cox, B.S.; Mavis Crow, LPN; Amber Dragg, LDN, RD; Chrystal Duncan, LPN; Angela Eldredge, B.S.; Janet Fahr, B.S.; Linda Guy; Lauren Harrington, RN; Claire Hazlett, RPh; Frances Hutchinson, B.S.; Jana Ihrig, RN; Carolyn Johnson, LPN; Pamela Jolivet, B.A.; Stacie La Prarie, RN; Melissa Lingle, B.S.; Susan Mancuso, RN; Kimberly Marcell; Sarah Masters, B.S.; Jennifer Perrault; Dawn Rachal, B.S.; Vimala Rajapho, LDN, RD; Lura Reed; Charles Sides, RPh; Marisa Smith, B.S.; Allison Strate, RN; Katie Tomayko, LDN, RD; Aimee Yoches, LPN; Ying Yu

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.

Figure 1





Paula J. Geiselman, Ph.D.
Associate Professor

Faculty:

Paula J. Geiselman, Ph.D.

Research Team:

Megan Apperson, M.A., Amanda Manning, M.A., Whitney Jenkins, B.S., Sean Morrison, B.A., Tara LaVigne, Rekeesha Greenwood, Mallory McGuffey, Megan Lipe, Y'annika Edwards, and Amy Teddler.

Focus: The objective of this laboratory is to study the role of fat and other macronutrient intake and fat preferences in the control of food intake and body weight.

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

It was recently reported in the literature that chewing gum produced a significant decrease in subsequent food intake, in comparison with intake in a control condition. We, therefore, designed a study to assess specific macronutrient intake and total caloric intake after having chewed gum. This approach was taken as some foods, based at least partially on their macronutrient content, are more effective in suppression of food intake; whereas, other foods have been associated with hyperphagia. Further, dietary fat and

sweets are both highly palatable to humans; and palatability is also a major determinant of food intake. After consuming a standard lunch, subjects chewed gum for 15 minutes hourly for 3 hours and then were tested with the use of our MSSP and FPQ. Results showed that, in the gum condition, subjects significantly decreased their total caloric intake, in comparison with their intake in the no-gum condition. The decreased caloric intake was due to a specific decrease in intake of high-sugar foods in the gum condition. Results also revealed that the subjects perceived high-sugar foods as less palatable in the gum condition, in comparison to their perceived palatability of these foods in the no-gum condition. Further, participants had to ingest significantly more kcals from the high-sugar foods in the no-gum condition to achieve the same degree of satiation that was produced by significantly smaller amounts of high-sugar foods (and less total kcals) in the gum condition. These results consistently demonstrate that chewing gum may be effective in the suppression of perceived palatability and intake of high-sugar foods, thereby producing a significant decrease in total caloric intake.

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

Research in this laboratory is supported by grants from the Wrigley Science Institute. The development of the MSSP and the FPQ was funded by the U.S. Department of Agriculture.



Conrad Earnest, Ph.D.
Assistant Professor



Tim Church, M.D., M.P.H., Ph.D.
Professor



Tuomo Rankinen, Ph.D.
Associate Professor

Faculty:

Conrad Earnest, Ph.D., Tim Church, M.D., M.P.H., Ph.D., Tuomo Rankinen, Ph.D.

Research Team:

Neil Johannsen, Ph.D.; Exercise Testing Core - Melissa Lupo, B.S.; Fitness Center - Ben Butitta, B.S. Laura Esposito, B.S., Melissa Nauta, B.S., Sarah Dicharry, B.S.

Focus: To understand the metabolic effects of exercise and nutrition on metabolism, obesity, and fatigue as it relates to physical performance and recovery.

Exercise is a well-established means of improving health and attenuating the effects of many diseases including obesity, diabetes, cardiovascular disease, cancer and depression. Fundamental to these observations is the underlying fact that exercise positively affects a constellation of mechanisms within the body. In essence, exercise is one of the few interventions related to health that can improve multiple cellular, circulatory, musculoskeletal and physiological systems simultaneously. We are currently initiating two trials examining the influence of varied doses of exercise (intensity and duration) in populations with pre-diabetes and also exploring the use of herbal extracts that may enhance fat metabolism during exercise.

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. Though typically associated as an exercise training technique for athletes, a recent report demonstrated that interval training was a more effective training method than traditional aerobic training in

75-year-old patients with stable heart disease, peripheral artery disease, intermittent claudication, coronary artery disease, congestive heart failure, asthma, or COPD without adverse medical side effects or complications. In our ongoing study, **The Insulin Sensitivity using Aerobic Interval Conditioning (ISAIC)**, we examine the role of interval training compared to “regular” aerobic training in participants who are at risk for developing diabetes.

In another study, we are examining the role of plant carotenoids as a means of improving fat metabolism during exercise. Emerging data suggests that certain plant carotenoids improve fat metabolism in mice. However, few studies have examined the role of these carotenoids in humans. We are investigating the role of carotenoids in exercising humans following 28 days of supplementation. Finally, we have begun a series of data extraction efforts from several previous studies to examine the underlying components of exercise testing performance to examine the question, “is maximal aerobic capacity the gold standard of determining exercise performance adaptation?” We feel this is an important area of research as little exploration into the “sub-maximal” components of exercise has been explored or applied to more clinical populations. However, it is quite conceivable that certain markers may show the potential for determining the efficacy of exercise training when the gold standard does not.

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



Marc Hamilton, Ph.D.
Professor

Faculty:

Marc Hamilton, Ph.D.

Research Team:

S.Y. Park, Ph.D.

Adjunct Collaborators:

T.W. Zderic, Ph.D., D.G. Hamilton, B.S.N., M.S.

Focus: To understand the role of sedentary behaviors (sitting too much) on metabolic and cardiovascular disease processes.

Inactivity physiology is an emerging new area of medical research. Inactivity physiology is a novel way of thinking about the medical consequences of a “sedentary lifestyle”. Decades of exercise physiology research has provided convincing evidence to recommend that people should perform sustained moderate-to vigorous-intensity physical activity (aerobic exercise) because exercise has an established preventive role in premature mortality, cardiovascular disease, type 2 diabetes, obesity, and some cancers. However, the paradigm of inactivity physiology argues that too much inactivity (primarily sitting) has deleterious effects on health independent of whether people meet the current exercise guidelines, and that physical inactivity is not the biological equivalent of too little exercise. The dire concern for the future may rest with growing numbers of people unaware of the potential insidious dangers of sitting too much.

Although only a minority of people exercise regularly, sedentary behaviors are ubiquitous and sitting time may increase with further seductive innovations in sedentary promoting technologies. However, scientists currently know much more about the effects of 2-3 hours of weekly exercise than how sitting for 70 or more hours per week impacts human physiology.

My laboratory focuses on inactivity physiology. We began by identifying molecular mechanisms at the level of how genes are switched on or off when rats and humans reduced the time spent standing. We have also been studying how cholesterol regulation and insulin sensitivity (the key determinant for healthy glucose utilization) can be profoundly impaired during physical inactivity, and why exercise is not necessarily the antidote. We have used radioactive tracers and other techniques to identify key metabolic steps. We have identified the most

potent cellular signals currently known to regulate the enzyme (lipoprotein lipase) that functions as the rate-limiting step for vacuuming fat (triglyceride) out of the bloodstream. We also have shown that inactivity very quickly (within hours) changes the fate of the fat in the bloodstream; instead of fat being utilized for fuel in leg skeletal muscles during standing or light movements, it is instead misdirected elsewhere in the body during inactivity. We have even learned that a pharmaceutical used in treating atherogenic dyslipidemia does not work the same during inactivity as during standing/light ambulation. As part of the testing of the inactivity physiology paradigm, we have not only gained new insights about the biology of “sitting too much”, but also have begun several fruitful translational collaborations identifying pragmatic lifestyle changes for how to best prevent the health hazards caused by inactivity in homes, schools, and workplaces.

My laboratory will continue to focus on testing the tenets of the inactivity paradigm using multidisciplinary approaches ranging from molecular biology and genetics to changing human behavior.

Research in this laboratory is supported by grants from the National Institutes of Health, the American Heart Association, and various pharmaceutical corporations.



None of the time subjects actually exercised or participated in sporting activity. But notice that despite not exercising, the leg muscles specialized for standing and light activity were “turned-on” as evidenced by the EMG signals (analogous to the EKG signal for the heart but in skeletal muscles). Not also that when sitting, the same leg muscles were turned-off and thus metabolically inactive.



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



Conrad Earnest, Ph.D.
Assistant Professor

Faculty:

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

Research Team:

Neil Johannsen, Ph.D., Ronald Monce, PA-C, Kimberly Kramer, M.P.H., Ruben Rodarte, M.S., Stephanie Abshire B.S., Rebecca Ardoin, B.S., Markee Baltazar, B.S., Nathan Britt, N.P., Ben Butitta, B.S., Amy Clemons, B.S., Shannon Cocreham, B.S., Sarah Dicharry, B.S., Sheletta Donatto, RD, CDE, Laura Esposito B.S., Nicole Guidry, B.S., Melissa Lupo, B.S., Melissa Nauta, B.S.

Focus: To understand the role of physical activity and weight loss in the prevention and treatment of chronic diseases such as diabetes, cancer and heart disease as well explore strategies to promote healthy aging.

The primary activity of the Preventive Medicine Laboratory has been conducting 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 A1c 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 HbA1c. HbA1c is assessed before and after 9 months of intervention along with a variety of other outcomes. To date we have enrolled over 250 individuals into the study, and participant compliance/retention is excellent. The intervention component of the study will end in mid-2010.

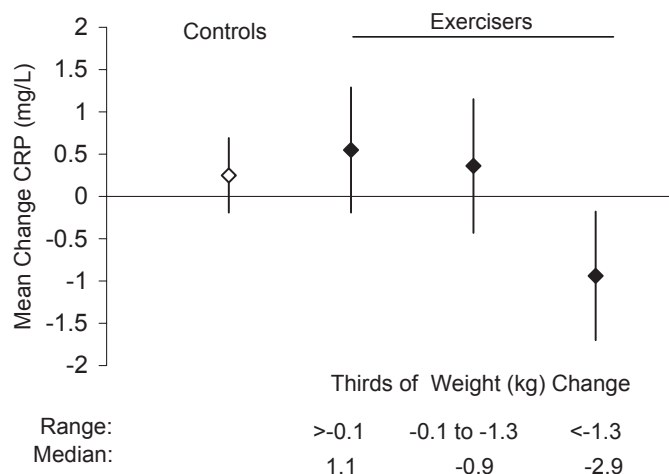
We submitted for publication the results of the Inflammation and Exercise trial (INFLAME), which examined the effect of exercise on the inflammatory marker C-reactive protein (CRP). Although there is no medication currently approved to reduce CRP, there continues to be increased significance placed on CRP as a risk factor for heart disease. Thus INFLAME will provide valuable insight into the therapeutic role of exercise and weight loss in improving CRP.

Numerous studies have reported overweight breast cancers survivors to have an increased risk of cancer reoccurrence compared to normal weight survivors. Recently, a large epidemiological study reported that breast cancer survivors who are regularly active have a 50% reduced risk of reoccurrence compared with those who remained inactive post-treatment. The role of exercise and weight

loss in breast cancer survivorship has never been tested in a large clinical trial which is unfortunate given the potential benefits. CASTLE is a pilot study designed to examine the effectiveness, feasibility and acceptability of combining motivational interviewing with physical activity and dietary restrictions in breast cancer survivors to promote weight loss. We have enrolled 60 overweight women from local cancer centers to participate. This study will provide us with valuable experience working with breast cancer survivors as well as help us create working relationships with people and institutions in the Baton Rouge cancer community.

Other plans for future work include examining the role of weight loss in reducing inflammation as well as examining if large doses of exercise promotes overeating and if so what are the mechanisms.

Research in this laboratory is supported by grants from the National Institutes of Health the Coypu Foundation, the Edward G. Schlieder Foundation and the Pennington Medical Foundation.



Results from INFLAME demonstrating the interaction of weekly exercise and weight loss in reducing systemic inflammation as measured by C-reactive protein (CRP)



Eric Ravussin, Ph.D.
*Professor, Douglas L. Gordon
Chair in Diabetes and Metabolism*



Yourka Tchoukalova, M.D.
Instructor



Leanne M. Redman, Ph.D.
Instructor



Darcy L. Johanssen, Ph.D.
Instructor

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.

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 are conducting an 8-week 40% overfeeding study in lean and overweight participants who have similar total body fat but hypertrophic or hyperplastic adipocytes. 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

Faculty:

Eric Ravussin, Ph.D., Yourka Tchoukalova, M.D., Ph.D.,
Leanne M. Redman, Ph.D., Darcy L. Johanssen, Ph.D.

in collaboration with Washington University and Tufts University. 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.

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. Dr. Redman was recently awarded a 5-year career development grant K-99 to conduct such studies.

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

POPULATION SCIENCE

POPULATION SCIENCE





Peter T. Katzmarzyk, Ph.D.
Associate Executive Director for Population Science
LPFA Chair in Nutrition

Background

The establishment of Population Science as a research component was a priority in the Center's five-year strategic plan, Vision 2010. This goal was realized in August of 2007 when the position of Associate Executive Director for Population Science was created. In the last two years, we have added four new population science laboratories at the Center in addition to three existing ones to complement our research strengths in basic and clinical science.

Current Status

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

In addition to our research efforts, over the last two years the Population Science unit has developed two initiatives in education and scientific advocacy. First, the Center organizes an annual public health conference on the topic of childhood obesity. Childhood obesity is fast becoming the greatest public health challenge facing America. During the last three decades, the number of overweight and obese children has skyrocketed, resulting in a growing number

of children facing health consequences that were traditionally only experienced by adults. This annual public health conference brings together local, national and international experts on the topic of childhood obesity, with a focus on prevention. The major goal of this annual conference is to develop public health strategies that can be employed to tackle the growing problem of childhood obesity.

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

The Future

According to the World Health Organization, about 80% of all deaths worldwide are the result of chronic diseases. The situation is even more acute in North America. An aging population, coupled with an increasing prevalence of obesity, does not portend well for the health of the population. In addition to individual-level behavior changes, large scale population shifts in normative behavior are required to see real improvements in population health. The population scientists at the Pennington Biomedical Research Center are well positioned to make major contributions to seeing these much-needed health improvements through to fruition.

Population Science Research lies within two program areas.

Epidemiology and Prevention

Chronic Disease Epidemiology

G. Hu

Contextual Risk Factors

S. Broyles

Health Behaviors and Chronic Disease

D. Harsha

Health Economics

A. Gandjour

Nutritional Epidemiology

C. Champagne, D. Harsha, B. Kennedy

Physical Activity Epidemiology

P. Katzmarzyk

Health Psychology

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

Physical Activity and Health

Physical Activity and Ethnic Minority Health

R. Newton

Walking Behavior

C. Tudor-Locke



Gang Hu, M.D., M.P.H., Ph.D.
Assistant Professor

Faculty:

Gang Hu, M.D., M.P.H., Ph.D.

Research Team:

Yujie Wang, MSc.

Focus: To assess the role of lifestyle and other risk factors and their interactions on the risk of several chronic diseases, including coronary heart disease, stroke, heart failure, diabetes, cancer and Parkinson's disease.

The Chronic Disease Epidemiology Laboratory is collaborating with several large-scale epidemiological studies and clinical trials, including the FINRISK (also called FINMONICA) Study, Tianjin Gestational Diabetes Prevention Project, Tianjin Children Obesity Study, and Tianjin 3 Million Rural Population Health Status Study.

The FINRISK (FINMONICA) Study

The FINRISK Study is one of the largest prospective epidemiological studies of chronic disease risk factors in the world. The total sample consists of 62,013 individuals from Finland (30,031 men and 31,982 women) aged 25-74 years. The follow-up is virtually complete through the nationwide register linkages including the Causes of Death Registry, the National Hospital Discharge Registry, the National Social Insurance Institution's Drug register, and the National Cancer Registry. Follow-up databases have been recently updated and outcome data are available until the end of 2006. At the moment, over 13 000 deaths and almost 6000 coronary heart disease and 4000 stroke cases, over 3500 heart failure cases, over 800 Parkinson's disease and over 6500 cancer cases are ascertained during the mean 20 years of follow-up. We are currently assessing the role of lifestyle factors and classical chronic disease risk factors on the risks of stroke, heart failure, cancer and Parkinson's disease.

Tianjin Gestational Diabetes Prevention Project

Tianjin Gestational Diabetes Prevention Project is a trial conducted at the Tianjin Women and Children's Health Center, Tianjin, China. It is an ongoing three-year lifestyle intervention

program among 1,000 Chinese women with gestational diabetes mellitus (GDM). The main objective of this trial is to obtain new information on the interaction between lifestyle and genetic factors on the risk of type 2 diabetes (T2D) in Tianjin women with GDM after at least 1-year delivery. The specific aims are: (i) to implement and evaluate a lifestyle intervention program (including dietary practice and physical activity pattern) to prevent T2D among high-risk women with GDM after delivery; (ii) to assess the efficacy of the lifestyle intervention program to reduce the prevalence of the metabolic syndrome among high-risk women with GDM after delivery; and (iii) to test gene-intervention interaction through diabetes genetic loci identified by genome-wide association study (GWAS).

Tianjin Children Obesity Study, and Tianjin 3 Million Rural Population Health Status Study

Tianjin Children Obesity Study, and Tianjin 3 Million Rural Population Health Status Study are two cross-sectional studies, which were carried out in 2004 and 2005 in Tianjin, China. We currently investigate the prevalence of overweight/obesity and hyperglycemia and their determinants in these populations.

Research in this laboratory is funded by the Finnish Cancer Foundation, Finnish Heart Association, Merck, and European Foundation for the Study of Diabetes (EFSD)/Chinese Diabetes Society (CDS)/Lilly Programme for Collaborative Research between China and Europe.



Stephanie Broyles, Ph.D.
Assistant Professor

Faculty:
Stephanie Broyles, Ph.D.

Focus: To understand how the different contexts in which we live – e.g., neighborhoods, schools, work, parks, social networks – shape our disease risks and health outcomes.

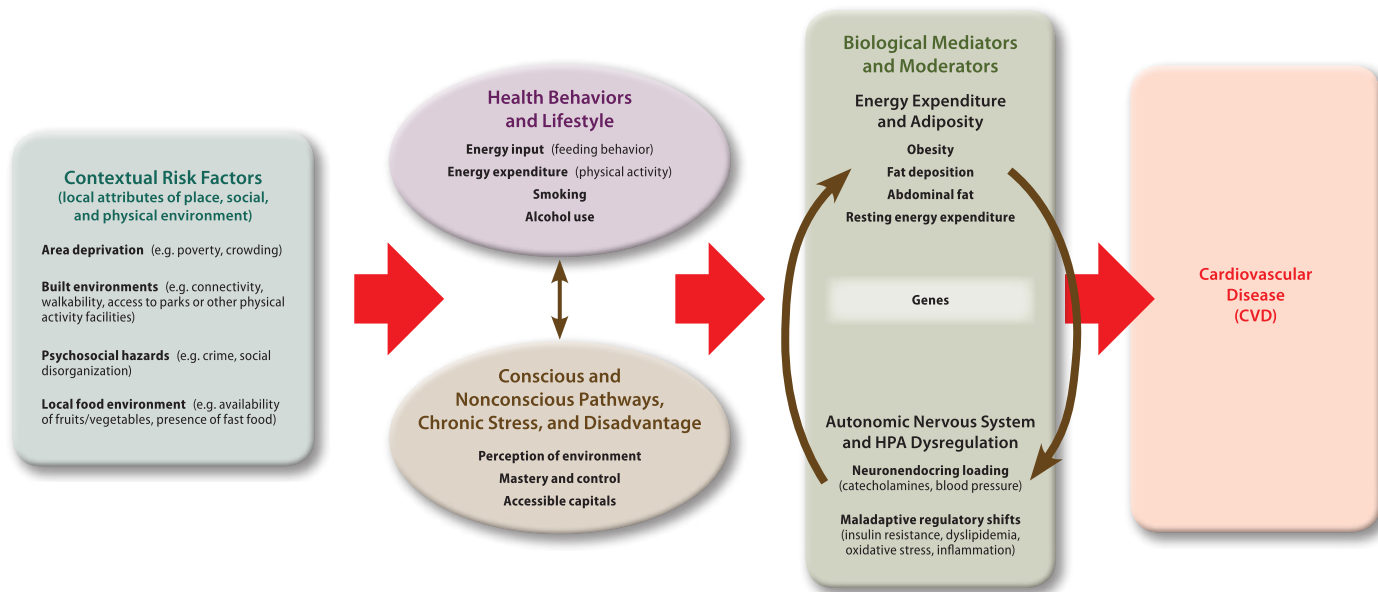
In recent years, a new epidemiological research paradigm has emerged that recognizes that the traditional risk factors like smoking, poor diet, physical inactivity, and obesity are themselves shaped by the social and physical environments in which we live.

The goal of the Contextual Risk Factors laboratory is to identify modifiable aspects of the social, physical, and policy environments that are linked with individual health risk factors or behaviors. Currently, we are focusing on risk factors and behaviors in the broad areas of cardiovascular disease and obesity. One example of current research includes studying the role that neighborhood parks play in fostering “social capital” among park users, which we hypothesize will in turn promote higher levels of park use, physical activity within parks, and social support among park users. This line of research is part of a collaboration led by a colleague in the LSUHSC School of Public Health in New Orleans.

Another project involves studying the biological pathways through which a child’s neighborhood contributes to development

of early markers of cardiovascular disease (CVD), including obesity and diabetes. The framework for this research is shown in the accompanying figure. One aspect of this research uses national survey data to study the independent contributions of diet, physical activity, and stress associated with poverty or living in unsafe neighborhoods on levels of biomarkers for CVD. Another aspect of this research focuses a little closer to home and studies aspects of the neighborhood environments of 400 children taking part in a current Pennington-LSUHSC study. This project involves linking neighborhood characteristics like food retail outlets, opportunities for physical activity, and neighborhood safety and disorder to cutting-edge biological measures that indicate early CVD risk. Results from this research will shed light on specific pathways linking the neighborhood environment to development of CVD risk during a critical time period, thus providing tools for improved disease screening, an impetus for targeted environmental and policy change, and a basis for future preventive efforts.

Research in this laboratory is supported by the Centers for Disease Control and Prevention and the Pennington Biomedical Research Foundation.



Conceptual framework that illustrates how contextual risk factors shape individual risk factors, which ultimately give rise to disease. Adapted from Daniel et al. (Health & Place, 2008) and Glass & McAtee (Soc. Sci. Med., 2006)



David Harsha, Ph.D.
Associate Professor

Faculty:

David Harsha, Ph.D.

Focus: To develop information on the relationships between behaviors, biomedical traits, and chronic disease risk in children and adults.

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

The US Army, cognizant of the degree to which obesity might impact society in general and its own recruitment base in particular, has funded research into the roots of the development throughout childhood and into early adulthood. This is the TRIM (Troop Recruit Improvement) Study, a multi-center effort which will extensively examine the interactions of body composition, physiological, genetic, social, psychological, and economic factors relating to the development of obesity in children, adolescents,

and young adults. Pennington center is one of four clinical sites gathering data to clarify these relationships. Currently in Phase I (pilot) data on smaller samples of children and adolescent are being gathered in 2009 to finalize data collection protocols and set the stage for the full study to begin in 2010.

Phase II will begin the intensive examination of approximately 2000 youths from 4 states. These participants will be followed annually for up to 4 years submitting data in the areas outlined above. Information collected will not only characterize individual children and youths, but will also yield information on the social and economic environments in which they reside and include less commonly examined issues such as food security and availability and seasonal/cyclical factors related to growth, development, and body weight. Data on neighborhood, school, and community characteristics will also be gathered.

The result will be the most extensive picture of the development of overweight yet undertaken and will be invaluable in informing interventions and preventive programs aimed at reducing the public health burden of overweight currently affecting society.

Research in this laboratory is supported by grants from the U.S. Department of Defense.



Afschin Gandjour, M.D., Ph.D., M.A.
Associate Professor

Faculty:

Afschin Gandjour, M.D., Ph.D., M.A.

Focus: (1) to save lives and improve health through resource allocation and (2) to develop methodologies to improve the allocation process.

In the current reform debate on how to reduce healthcare expenditures, three strategies have received particular attention: prevention, comparative effectiveness research, and information technology. The health economics lab analyzes the savings potential of prevention and in particular of physical activity and dietary interventions for obesity and related disorders. It takes a novel approach by considering the cost consequences of i) a postponement of the expensive last year of life and ii) future technological advancements for treating disease.

In addition, the health economics lab develops new methodologies to make cost-effectiveness analysis (CEA) easier, more valid, and more acceptable to the public. Current CEA standards require complex modeling of long-run costs and effects

while, on the other hand, resources in terms of researchers and time are limited. This makes it difficult to substantially increase the number of CEAs. Furthermore, existing CEAs show limited comparability as they have often used different methodologies. For example, CEAs differ on whether they have accounted for health expenditures during years of life gained by the intervention. Finally, CEA is often perceived as a tool for cost cutting and ethically controversial. The health economics lab will address the above shortcomings, by developing a less complex CEA method which does not attribute life extensions costs to the individual intervention. Furthermore, the lab will develop cost-effectiveness outcome measures which focus on lives saved as opposed to life years or quality-adjusted life years gained.



Catherine M. Champagne, Ph.D.
Professor



David W. Harsha, Ph.D.
Associate Professor



Betty M. Kennedy, Ph.D.
Instructor

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

The Delta Obesity Prevention Research Unit (OPRU) – Summer Day Camp Project in Rural Phillips County Arkansas

As part of an ongoing collaborative, multi-year research effort to design, carry out, and evaluate nutrition interventions directed at improving the nutrition in the impoverished and disadvantaged Lower Delta region of Arkansas, Louisiana, and Mississippi have been collecting dietary intake information in rural Arkansas since the summer of 2007.

Partnering with the Delta OPRU colleagues in Little Rock, AR, and with the National Center for Toxicological Research in Jefferson, AR, we have collected dietary intakes prior to the start and upon completion of the summer camp. The camp provides lunch and snacks for the students aged 6 through 13 years and includes nutrition education lessons. Data on dietary intakes will be used to determine the success of these intervention efforts. This is expected to be an ongoing activity for several years.

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. The POUNDS LOST

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 Moran, RD, LDN, Katherine Lastor, RD, LDN, Erma Levy, MPH, RD, LDN, Dawn Turner, B.S.

trial utilized four different diet treatments varying in protein and fat to scientifically test these diets for weight loss effects. Subjects were asked to follow structured meal plans or exchange options in order to adhere to the dietary targets. The laboratory research dietitians/interventionists played a key role in working with these participants by conducting both group and individual sessions utilizing nutrition information and behavior change messages.

Soldier Nutritional Epidemiology

Since 1996, nine studies have been supported in collaboration with USARIEM. No studies have been conducted between 2002 and 2008, due to the war in Iraq. However, two studies will be conducted beginning in August 2009. Camp Mackall, North Carolina will be the site for a special forces study entitled “Energy Expenditure & Physiological Strain in Special Forces Candidates and Cadre.” In September 2009, Fort Bragg, North Carolina will initiate a study in their dining facilities entitled “Testing the Efficacy of Modifying Serving Practices in Military Dining Facilities to Enhance Healthy Nutrition in Soldiers.” Staff from the Nutritional Epidemiology section will support these studies.

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



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

Faculty:

Peter T. Katzmarzyk, Ph.D., FACS

Research Team:

Sarah Camhi, Ph.D., Emily Mire, M.S., Samaah Sullivan, M.P.H.

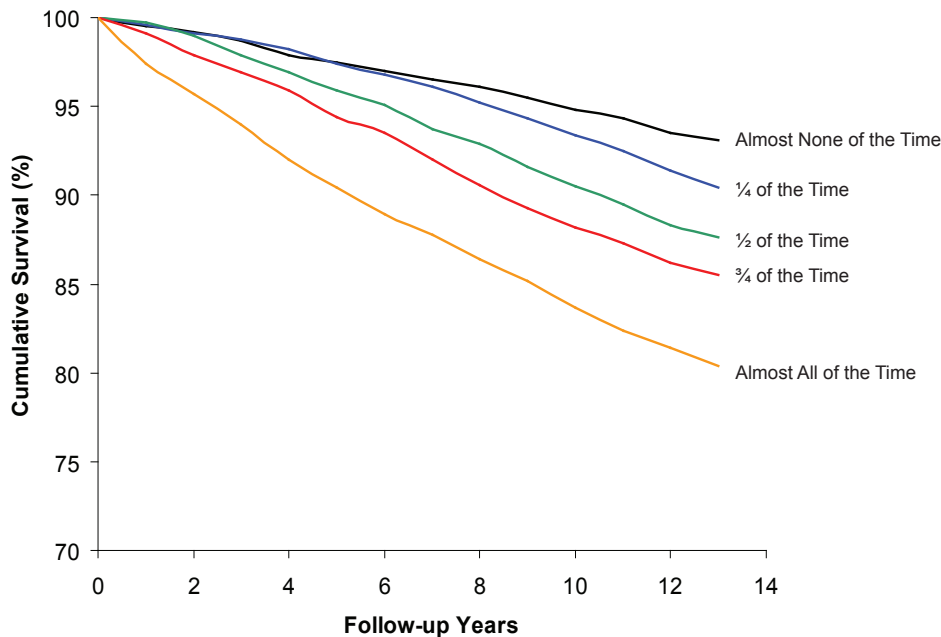
Focus: To investigate the effects of physical activity, fitness and obesity on morbidity and mortality, and to quantify their impact on population health.

It is clear that physical activity is associated with numerous health benefits. However, questions still remain about the shape of the dose-response relationship between physical activity and health, how physical activity interacts with obesity and other risk factors in predicting health outcomes, the role of sedentary behaviors such as sitting and watching television versus undertaking moderate or vigorous physical activity on health, and how much and which types of physical activity should be recommended for optimal health benefits. Beyond these basic questions, we have much to learn about how to motivate individuals and communities to adopt physically active lifestyles which will in turn result in a healthier population.

We are actively collaborating on several projects that are designed to unlock answers to the questions above, including the Canadian Physical Activity Longitudinal Study (PALS), the

Bogalusa Heart Study, InSight, and the National Health and Nutrition Examination Survey. Further, we are developing a cohort of volunteers who have participated in clinical studies at the Pennington Biomedical Research Center in order to better characterize the health of the population and to follow them over time for the development of a variety of health problems. This cohort, the Pennington Center Longitudinal Study (PCLS), holds the promise of providing important information on the role of physical activity, nutrition, obesity and other lifestyle behaviors on the future health of the population, particularly in Louisiana.

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



This figure is from a mortality study, and it shows the cumulative survival, or the probability of surviving over time across different levels of sitting during the day. Note that people who spend almost all of their day sitting have a much lower chance of being alive after 13 years compared to people that spend very little time sitting during their day.



Donald Williamson, Ph.D.
John Stauffer McIlhenny
Professor of Nutrition



Robert Newton, Jr., Ph.D.
Assistant Professor



Tiffany Stewart, Ph.D.
Instructor

Focus: The Health Psychology 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 involves collaboration between the Louisiana Public School System, the Louisiana Board of Regents, and the Pennington Biomedical Research Center to address the childhood obesity problem. Data collection for this three-year study ended in May 2009. This cluster randomized controlled trial tested the efficacy of two school-based prevention programs (combination of primary and secondary prevention and primary prevention alone) that were 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.

Military Health Behaviors: Promotion of Healthy Weight and Fitness in Career Personnel: Initiated in May 2003 and completed in July 2009, this study has two primary aims: (1) development of an environmental/internet-based intervention to promote healthy

Faculty:

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

Research Team:

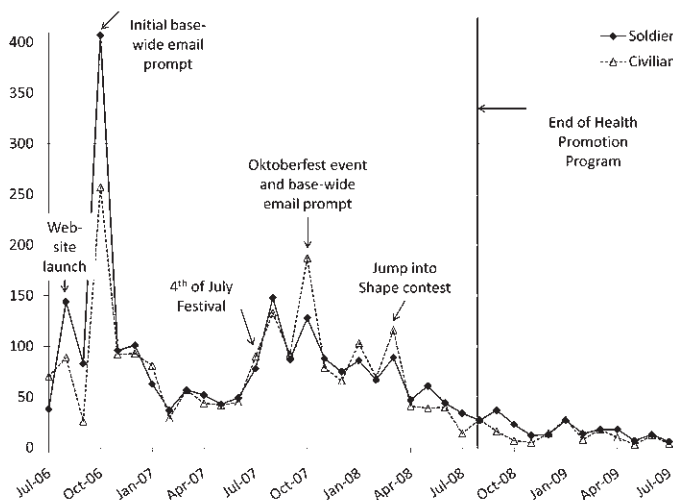
Allison Davis, M.A., Shelly Duhé, M.S., LDN, RD, Jeanne Gabriele, Ph.D., Helen Guay, M.A., RD, John Lambert, A.S., David McGucken, M.S., Kristi Rau, B.S., Melanie Spinks, B.A., Phi Truong, B.S., Heather Walden, M.S., Jeffrey Wiggins

weight and physical fitness, and (2) testing the efficacy for weight management and consumer satisfaction with the environmental/internet-based intervention in a single population, i.e., soldiers at Fort Bragg, NC. Figure 1 illustrates the utilization of the internet-based program over a three-year period. This figure shows that during the initial two-years of the project, utilization of the website systematically increased as a function of conducting a variety of health promotion events. Once the health promotion program ended, utilization was reduced, but was maintained at a lower level.

Weight Measurements and Standards for Soldiers: This study is being 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. This study will end in July 2010.

Weight Measurements and Standards for Soldiers Phase 2: This five-year study is a continuation of the Fort Bragg and New England studies and is being conducted with the Louisiana National Guard. Using a cluster randomized controlled trial this project will test the efficacy of the environmental/internet-based intervention tested at Fort Bragg and in New England using a controlled research design. This study will begin in early 2010.

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



Utilization of the internet-based program over a three-year period at Fort Bragg.



Robert Newton, Ph.D.
Professor

Faculty:
Robert Newton, Ph.D.

Focus: To study the impact of physical activity on the health of ethnic minority populations. This is accomplished by assessing the relationship between physical activity and health, as well as through interventions designed to increase physical activity in ethnic minority populations.

African Americans suffer disproportionately from various health conditions, including obesity, hypertension, and diabetes. Lack of regular physical activity has been shown to be an independent risk factor for cardiovascular disease risk and the development of cardiovascular diseases. It has been shown that African Americans spend less time in physical activity compared to other ethnic groups. Thus, African American adults are prime targets for studying the relationship between physical activity and cardiovascular disease. Furthermore, they are ideal targets for interventions designed to increase physical activity.

The lab is currently focused on studying sedentary behavior. Our initial efforts are designed to develop thresholds for sedentary behavior using accelerometers. Accelerometers are motion sensors that are lightweight and worn on the waist. Participants in the study wore the accelerometers while engaging in several different activities that would be considered sedentary. They also engaged in light and moderately intensity activities. Our data show that the threshold is similar to other thresholds developed. The participants in the study also wore the accelerometers in free-living conditions. The data from this study show that the participants spent less than the recommended 30 minutes per day in moderate intensity physical activity. The data also showed that approximately 55-60% of their waking hours were spent engaged in sedentary behavior.

The next phase of the study is to study the relationship between objectively measured sedentary behavior and risk factors for cardiovascular disease. For this study, we will utilize existing data from the Jackson Heart Study. This is an epidemiological study of cardiovascular disease risk in African American participants. A subset of these participants wore accelerometers while being assessed for cardiovascular disease risk factors. This will allow us to assess the association between physical activity and sedentary behavior with cardiovascular risk factors. In the long-run, we will be able to assess the relationship between these measures and actual cardiovascular disease occurrence.

The ultimate goal of the lab is to find effective behavioral strategies to increase physical activity and decrease sedentary behavior in ethnic minorities. One project is a physical activity promotion program for African American males. Most of the research that has been conducted with African Americans has been conducted with females. This means that there is a need for more research on this population, as they suffer from disproportionately high rates of hypertension and cardiovascular disease mortality. In addition, we are seeking to develop novel components that can be used to decrease sedentary behavior in children.

Research in the lab is supported by grants from the National Institutes of Health and PBRC's Clinical Nutrition Research Unit.



Catrine Tudor-Locke, Ph.D.
Assistant Professor

Faculty:

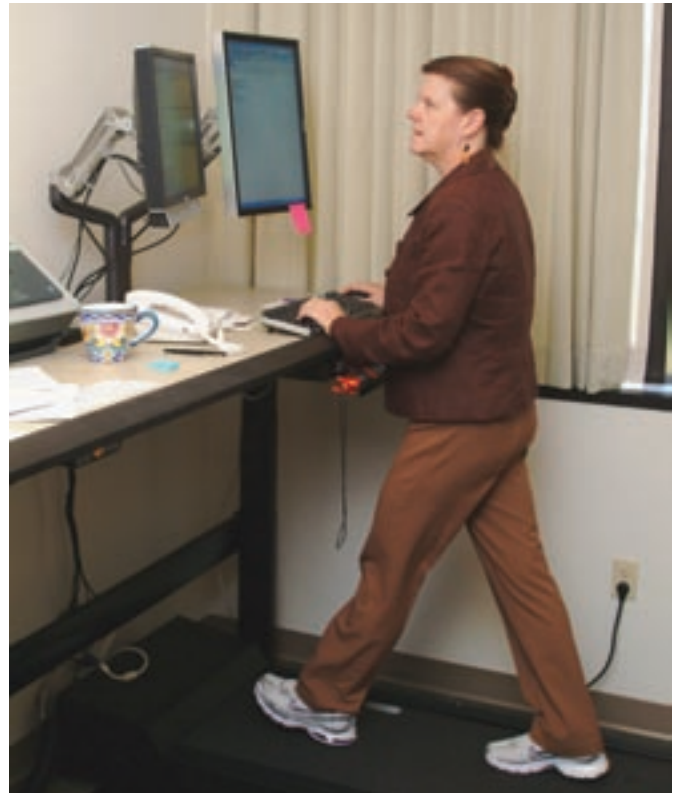
Catrine Tudor-Locke, Ph.D.

Focus: To study the measurement and motivation of walking behaviors in relation to important health outcomes, including changes in body weight.

To achieve this mission, this lab employs a broad range of quantitative and qualitative methods, taps into existing data sets, and actively seeks funding to support original research studies.

Walking, regardless of form or purpose, is considered to be of substantial importance to public health, and of special relevance in the continuing battle against the creeping obesity epidemic. Walking is the most commonly reported leisure time exercise and is a functional part of daily life. Specifically, walking undertaken during the course of the day in transportation, occupation, shopping, chores, walking a dog, and during leisure-time (for non-exercise purposes) can add up and affect weight change in a positive manner (i.e., promoting weight loss or weight stability). Simply put, every step counts in terms of energy balance. In contrast, sitting behaviors may counteract these effects and the WBL is interested in also quantifying and manipulating excessive sitting behaviors. Ultimately, the WBL is interested in teasing apart the effects of walking and sitting to evaluate independent influences of these two behaviors on weight change.

Secondary data analysis projects are focused on accelerometer data collected through the National Health and Nutrition Examination Survey (NHANES) and detailed time diaries collected by the American Time Use Survey (ATUS). Using the NHANES we are able to describe a robust physical activity/sedentary behavior profile, accounting for each minute of the day, from objectively monitored data. The data include step (walking) variables as well as time in sedentary behaviors. We are currently examining these data by body weight indicators. The ATUS also provides another way to capture walking and sedentary behaviors (as well as other behaviors), again accounting for each minute of the day. The ATUS has recently included body weight as data point, facilitating analyses congruent with the focus of the WBL.



Dr. Tudor-Locke on her “treadmill desk,” where she can evaluate the benefits of this method of introducing activity into a routine office environment.

New studies include Training Reduced Activity Individuals to Step Far Above Normative Amounts (TRANSFORM) and Energy Expenditure of Physical Activity Levels (EEPAL). TRANSFORM is designed to evaluate the impact of progressively higher volumes of pedometer-determined physical activity on weight change in originally sedentary individuals. EEPAL is designed to develop a better method of estimating individuals’ real world energy expenditure from accelerometers, particularly those most frequently used in research and currently used in national surveillance of physical activity and sedentary behaviors.



Phillip Brantley, Ph.D.
Division Chief, Education

The mission of the Pennington Biomedical Research Center (PBRC) encompasses education as well as research. The Division of Education serves as the catalyst for the Center's educational initiatives which focus on three major areas: (1) training the next generation of scientists, (2) planning and coordinating meetings and symposia that attract world-renowned scientists to our center and (3) sponsoring professional and community education programs to engage the citizens of Louisiana and the state's medical community and to provide educational outreach.

Institutional Postdoctoral Training Programs

The Division coordinates many of the activities mandated by the Center's Institutional Postdoctoral Training Grants from the National Institutes of Health. These programs are designed to train postdoctoral fellows to become productive research scientists capable of establishing independent scientific careers in biomedical research. One of these grants is funded by the National Institute of Diabetes and Digestive and Kidney Diseases and trains fellows to conduct studies that investigate genetic, molecular, behavioral and population aspects of obesity. The other training grant from the National Center of Complementary and Alternative Medicine focuses on identifying new plant compounds that may aid in the prevention or treatment of metabolic syndrome and its related disorders such as diabetes. 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 thirty 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 web site and in scientific journals. Recent topics have included: Circadian Biology and Sleep: Missing Links in Obesity and Metabolism (April 26-28, 2009); Adaptive Thermogenesis and Human Obesity (December 7-9, 2008); Neuro-Immune Signaling and Inflammation (December 2-5, 2007); Epigenetic Mechanisms in Obesity: Research and Public Health Implications (May 20-23, 2007); and Diabetes Complications (January 29-30, 2007).

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 Pennington Conference Center. We have partnered with Blue Cross Blue Shield to provide Louisiana citizens with a web based health program entitled "The Louisiana 2 Step" designed to promote healthy eating and physical activity. Also, under the coordination of Patti Boyd, the Center offers "Take 5 for Diabetes" an American Diabetes Association recognized program in diabetes prevention and management for community adults.

LSU Agricultural Center

The Division continues its successful partnership with the LSU Agricultural Center and its Division of Education, the Louisiana Cooperative Extension Service. The objective of the partnership is to provide an effective, efficient means of disseminating information and advice to the people of Louisiana. Dr. Heli Roy who holds joint appointments at the LSU Ag Center and PBRC coordinates this effort. Much of the information collected now comprises the "Pennington Nutrition Series," a downloadable collection of health and nutrition materials that can be found on the LSU Ag Center and Pennington Biomedical Research Center Web sites.

Wellness Day for Women

Dr. Catherine Champagne is the coordinator of the Wellness Day for Women, an education and outreach program that specifically targets women's health issues. The Wellness Day for Women attracts more than 500 women, and consists of educational seminars on current issues, health-related exhibits, cooking demonstrations, and other feature presentations.

Future Goals

We would like to increase the number of postdoctoral fellows at the center from its current level of 40 to a total of 75. We plan to develop new coursework in botanicals research as well as a survey course in the field of complementary and alternative medicine for postdocs recruited to our recently acquired training grant focusing on the role of botanicals in combating metabolic syndrome. Efforts will be made to identify an underwriter and namesake for our scientific symposia series. A stable source of funding would allow for long term planning and expanded scientific programs. Finally we plan to continue our community and professional outreach.

Basic Science Cores

- Animal Metabolism and Behavior
- Cell Biology and Cell Imaging
- Cell Culture
- Comparative Biology
- Genomics
- Proteomics and Metabolomics
- Transgenics



Donald K. Ingram, Ph.D.
Professor

Director:
Donald K. Ingram, Ph.D.

Faculty:
Paul Pistell, Ph.D.

Staff:
Armand Cassani, B.S.



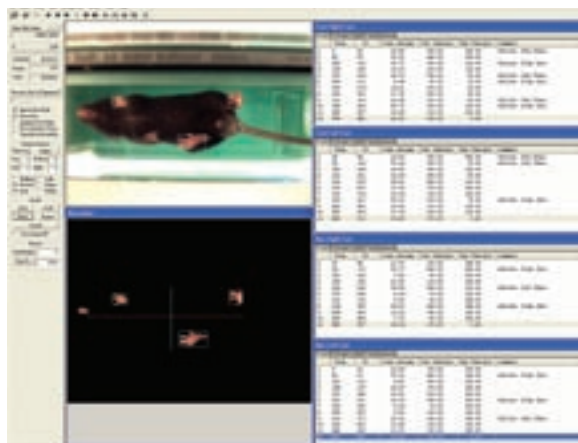
David Burk, Ph.D.
Instructor

Director:
David Burk, Ph.D.

Staff:
Courtney Cain, B.S.

Mission: To support the mission of the center by facilitating the assessment of metabolism and behavior in rodent models.

This Core provides the tools and support for investigators to assess a wide range of metabolic and behavioral characteristics of laboratory rodents. For measuring metabolism, highly specialized equipment provides continuous monitoring of exchange of oxygen and carbon dioxide to generate estimates of energy expenditure and respiratory quotient (carbohydrate versus fat metabolism) over time as well as locomotor activity, food and water intake. Using other apparatus, feeding behavior can be measured to estimate meal size and feeding bout frequency across daily periods (circadian rhythms). Body composition (fat and lean content) can be measured noninvasively using a NMR machine designed for small animals. The Core also has a telemetry system for monitoring blood pressure and body temperature via implantable radio frequency transmitters. A battery of behavioral tests is also available using specially designed equipment. Measures of motor performance include locomotion, balance, gait, and endurance. Motivational measures include hunger, thirst, and anxiety. Specialized apparatus for measuring cognition include various mazes for assessing spatial learning and memory, classical (Pavlovian) conditioning, and operant conditioning (Skinner boxes). Core staff assists investigators in designing experiments and analyzing data as well as providing training in using the equipment.



(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).

Mission: To provide access to state-of-the-art bioimaging, analytical, histological, and flow cytometry related instrumentation and technical support to facilitate data collection and analysis by current and future Pennington PIs and their staff.

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

The histology/specimen preparation section of the core houses all the necessary equipment for tissue processing, sectioning, and staining PBRC researchers may need. The core provides access to an automated tissue processor, four cryostats, three rotary microtomes, a sliding microtome, a vibratome, and autostainers for both traditional stains as well as immunohistochemical stains. In addition, the core provides access to a laser microdissection system for the precise collection of single cells or whole tissues from sectioned materials. This platform provides materials that can be further analyzed for either genomic or proteomic methods in nearby core facilities.

The analytical/flow cytometry section includes a fluorometric plate reader equipped with a robotic fluidic system for advanced kinetic studies in multi-well plate formats, an analytical flow cytometer and a new high speed cell sorter (iCyt Reflection) housed in a BSLII lamellar flow hood capable of sorting live animal and human cells at high purity for downstream applications.

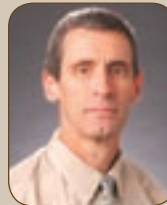
Training is available on almost all of the platforms within the CBBC and staff are available for assistance in the development of experimental protocols, data collection, analysis, and interpretation.



Jeffrey M. Gimble, M.D., Ph.D.
Professor

Director:
Jeffrey M. Gimble M.D., Ph.D.

Staff:
Gang Yu, M.S., Katie Hamel



Barry Robert, D.V.M., Ph.D., DACLAM
Associate Professor

Director:
Barry Robert, D.V.M., Ph.D., DACLAM

Assistant Director:
Cindy Kloster, B.S., RVT, RLATG, CPM

Mission: To provide cell culture facilities, equipment, and expertise to investigators requiring such services.

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

Staff:

Cynthia Angelloz, ALAT, Tracy Brown, Linda Chase, LAT, Michelle Dry, Paula Grymes, Darryl Howard, Frank Hsu, Faye Louviere ALAT, Deborah Minor, LAT, Suna Ozoral, Sarah Payne BS, Monique Simmons, Shannon Sterba, Sherman Wells, Daleveckio Wyre.

Mission: To provide the highest quality animal housing space, animal husbandry and veterinary care, training, and technical support for scientists using animal models at the Center.

CBC is a 38,000-square-foot centralized service unit that provides laboratory animal housing, receiving and quarantine facilities, animal procedural, behavioral testing and surgical laboratories, and a diet preparatory area for use by scientists at PBRC.

The Core is 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, highlighting the Center’s commitment to the highest quality laboratory animal program. CBC fully 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. These documents define our responsibility for the proper care and use of laboratory animals. 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 laboratory animals.

We are dedicated to providing on-going training opportunities for the research and Core staff. All new employees who will work with laboratory animals must attend an animal care and use orientation program. Specific technical training in laboratory animal biotechnology for the scientific staff is available and on-going training of the laboratory animal care technicians includes weekly lectures based on the American Association of Laboratory Animal Science Laboratory Animal Technician series. This training ensures that our staff provides the highest quality of care to our laboratory animals and remains current on all applicable laws and regulations.

Genomics Core Facility



Leslie P. Kozak, Ph.D.
Professor

Director:
Leslie Kozak, Ph.D.

Co-Director:
Robert Koza, Ph.D.

Staff:
Susan Newman, B.S., Jana Smith, B.S.,
Diana Holmes, M.S.

Proteomics and Metabolomics Core Facility



Indu Kheterpal, Ph.D.
Assistant Professor

Director:
Indu Kheterpal, Ph.D.

Staff:
Ginger Ku, M.S., Liana Coleman, B.S.,
Carmen Ruiz, B.S., and Kelsey Hundley

Mission: To provide next-generation sequencing for RNA and DNA analysis, DNA sequencing, DNA fragment analysis, qualitative and quantitative analysis of DNA, protein, and RNA samples, quantitative PCR, microarray services, robotics, and bioinformatics services. The Genomics Core Facility (GCF) provides training and consultation for sequence analysis, real-time PCR, and microarray analysis.

The Genomics Core Facility seeks to achieve high quality and cost effective research data production by providing research services, sharing instrumentation, and providing the expertise of facility personnel to the research community. The laboratory provides next-generation sequencing services including resequencing, gene expression, small RNA, methylation, and ChIP analysis using Life Technologies SOLiD sequencer and DNA sequencing and fragment analysis with two 3130XL sixteen capillary genetic analyzers. Next-generation data storage and analysis is provided through a contract with Geospiza. Four Applied Biosystems 7900HT Sequence Detection Systems equipped with 96 well, 384 well, and low density array blocks perform quantitative PCR. Microarray service is provided using the Illumina Beadarray scanner. Spotfire software is 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 and a Qubit fluorometer are 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 available. Three computer workstations are provided for sequence analysis and alignment, PCR primer design, and RT-PCR data analysis.

Mission: To provide scientific knowledge, technical expertise and laboratory resources for state-of-the-art proteomics and metabolomics studies that will foster new research and contribute to the ongoing research at the Center.

The Proteomics and Metabolomics Core Facility provides a variety of technical services for targeted and global proteomics and metabolomics studies. The facility supports activities ranging from detailed characterization of a single peptide, protein or metabolite to global, unbiased analysis of thousands of proteins or metabolites in one experiment. **The proteomics** capabilities of the facility include: identification and quantification of proteins within cells, secreted media, subcellular fractions, tissue or biological fluids; protein modification analysis; characterization of protein complexes and identification of protein interaction partners; and protein structure determination. **The metabolomics** capabilities of the facility include: identification, quantification and characterization of small molecules such as lipids, fatty acids and amino acids present in tissues and biological fluids.

The facility utilizes powerful separation technologies such as two-dimensional gel electrophoresis and multi-dimensional liquid chromatography in conjunction with mass spectrometric detection techniques to analyze proteins and metabolites. A high resolution and high mass accuracy quadrupole time-of-flight instrument (Q-TOF) is interfaced with a nano-ultra performance liquid chromatography (UPLC) system for proteomics applications. This Q-TOF is also interfaced with an UPLC system for metabolomic profiling and metabolite identification and structural characterization. A tandem quadrupole mass spectrometer is interfaced with an UPLC system for targeted metabolite profiling and quantification. The facility is also equipped with a 3-color fluorescence scanner, robotic workstations for excising gel bands and protein digestion and a MALDI-TOF mass spectrometer. The core facility has recently received NIH funding to acquire a hybrid linear ion trap and triple quadrupole mass spectrometer interfaced with two LC systems for biomarker verification, validation and quantification. The facility also maintains a variety of software packages to provide bioinformatics support for proteomics and metabolomics applications.



Randall Mynatt Ph.D.
Assistant Professor

Director:
Randall Mynatt Ph.D.

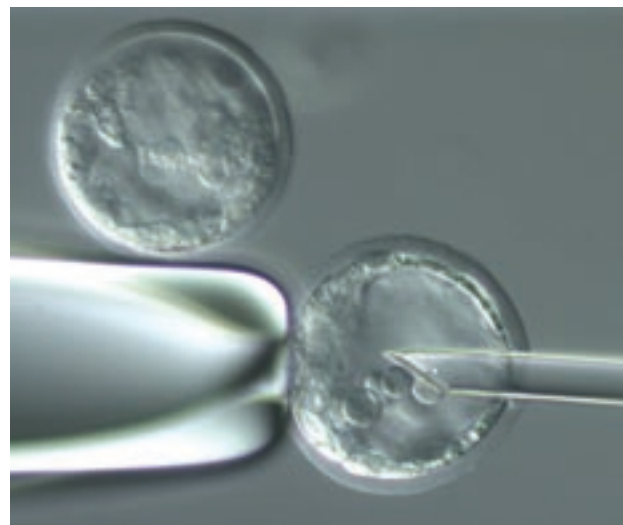
Staff:
Jingying Zhang, Ph.D., Christina Crane, B.S., Steven Bond, B.S., Dieyun Ding, B.S.

Mission: To provide controlled manipulation of gene expression and to facilitate investigators in understanding gene function. The transgenic core currently produces mice for the Center faculty and investigators at other institutions. The transgenic core uses pronuclear microinjection and embryonic stem cell technology to control gene expression in mice.

The transgenic core currently produces mice for faculty at Pennington Biomedical Research Center as well as investigators at other institutions. The transgenic core utilizes pronuclear microinjection and embryonic stem cell technologies to control gene expression in mice. The mission of the core is to establish a service at PBRC that will allow for the controlled manipulation of gene expression and facilitate investigators in understanding gene function. The core strives to provide services at prices that are below those that are commercially available. The unique feature that we offer over most other cores is a “turn key” service for generating knockout mice at a price well below commercial cost. By having a full time person devoted to the design and construction of the targeting vector, we have created an efficient, money saving service for PBRC investigators

Facilities

Pennington Biomedical Research Center has an AALAC approved animal facility capable of housing and providing care for the number of mice necessary for transgenic work. The barrier portion of animal facility has 3,000 sq. ft. for transgenic use capable of housing 6,000 mice. There is a 400 sq. ft. wet lab within the barrier for embryo manipulation.



Microinjection of mutant mouse embryonic stem cells into mouse blastocysts

Clinical Research Cores

- Clinical Chemistry
- Dietary Assessment
- Exercise Testing
- Imaging / MRS
- In-patient Clinic Unit
- Library and Information Center
- Mass Spectrometry
- Metabolic Chambers
- Outpatient Clinic
- Recruitment
- Research Kitchen

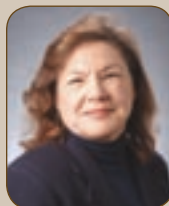
Population Sciences Core

- Biostatistics and Data Management



Director:
Jennifer C. Rood, Ph.D., DABCC, FACB

Jennifer C. Rood, Ph.D.
Professor



Director:
Catherine M. Champagne, Ph.D., R.D.
Faculty:
H. Raymond Allen, Ph.D.

Staff:
Dawn R. Turner, B.S., Mary Marlene Afton

Catherine M. Champagne, Ph.D., RD
Professor

Staff:

Stacey Roussel, M.T. (ASCP), Stephen Lee, M.T. (ASCP), Carla Kimmel, M.T. (ASCP), Margaret Graves, M.T. (ASCP), Jamie Tuminello, M.T. (ASCP), Bridget Conner, M.T. (ASCP), Laura Holloway, M.T. (ASCP), Amanda Lyons, B.S., April Clark, B.S., Steven Naremore, B.S., Patrick Cotogno, 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 Clinical Chemistry Core offers a comprehensive test menu ranging from routine screening assays to highly complex esoteric tests. The Core provides services in the following areas: phlebotomy, accessioning, chemistry, hematology, urinalysis, special chemistry, and point-of-care testing. The Laboratory also provides long-term specimen storage and maintains a comprehensive management system of specimens and data. During the past year, over 6000 venipunctures and 250,000 assays were performed. The Core performs more than 275 different clinical assays to support clinical trials, basic research, the U.S. Army Institute of Environmental Medicine, and contracting clients.

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.

The laboratory continues to provide method development for novel biomarkers. New assays developed during 2008-2009 include the following: glucose, lactate, glycerol, and ethanol in microdialysis fluids, cholecystokinin and pancreatic polypeptide in serum, brain derived neurotrophic factor in serum and saliva, and testosterone and neuropeptide Y in saliva.

Mission: The mission of the Dietary Assessment Core is to provide accurate information on dietary intakes of research study participants who keep food records, food frequency questionnaires, and/or dietary recalls. This Core also designs menus meeting specific nutrient targets which can be used by either study participants or metabolic kitchen staff.

The current version of Moore's Extended Nutrient Database (MENU) is MENU 6. This version is currently in the process of being updated. Primary datasets used are from USDA. The total count of foods and recipes contained within the MENU food composition files numbers 21,934, from the following data 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) which is used to conduct the U.S. Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD) and U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics (Hyattsville, MD). What We Eat in America, NHANES 2003-2004 Documentation: Dietary Interview - Individual Foods -- First Day (DR1IFF_C). (2006, September). Available from: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/dr1iff_c.pdf
- Supplementary information from the scientific literature or other reliable food composition tables.
- User defined foods, allowing the input of nutrient data for foods needed in menus or recipes for which an appropriate food match cannot be found otherwise.
- Recipes input by users of the system at PBRC, using a 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 individuals in research studies. Since 2007, more than 10,000 lines of data on dietary intake were processed.

Food Frequencies. In association with most major research projects involving collection of dietary intake data by food records, a number of studies also include the administration of food frequency questionnaires to capture intakes over a longer period of time. Currently converted to a scannable questionnaire, the Block Food Frequency Questionnaire (1992) is being used with results exported as an electronic file; approximately 740 food frequencies were processed during the last two years.



Conrad Earnest, Ph.D.
Assistant Professor

Director:
Conrad Earnest, Ph.D.

Staff:
Melissa Lupo, B.S.,
Rosemary Biehl, B.S.



Steven R. Smith, M.D.
Professor

Director:
Steven R. Smith, M.D.

Staff:
Kori Murray, M.S., Bradley
Newcomer, Ph.D., Julia St.
Amant, ARRT R.T. (R), Denise
Jarreau, M.S., Kimberly Landry,
R.C.T., Randell Deen, R.T. (R)

Mission: The primary mission of the Exercise Testing Core is to provide consistent, valid and reliable assessment of physiologic, cardiorespiratory and muscular strength parameters of exercise performance. The primary aim of the Fitness Center is to provide accurate exercise monitoring for studies requiring specific exercise interventions and to the exercise portion of our Corporate Wellness Program for Pennington employees.

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 Core is equipped with a Parvomedics True One™ metabolic cart for the performance of VO2max testing, a custom Lode Valiant Treadmill™ with a “double-wide” (105 cm; 41 inches) and extra long (200 cm; 78.7 inches) treadmill running surface and a Lode Excalibur Sport™ bicycle ergometer. The Core also includes a Biodex™ isokinetic strength dynamometer to perform constant velocity strength testing

Our Valiant Treadmill has a zero starting speed and acceleration capabilities ranging from 0.2 - 40 km/h (0.125-25Mph) and is capable of imposing both positive (+25%) and negative/downhill (-10%) running grades, while accommodating patient weights up to 340kg (750lbs.) The Lode Excalibur Sport ergometer is capable of singular wattage increments ranging from 0-1000 W. The Biodex system interfaces with computer microprocessors to measure torque, power, and endurance for resistance throughout a joint’s range of motion of most musculoskeletal joint areas. In 2009, we added the ability to perform muscle biopsy’s in association with exercise testing and exercise performance.

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.

The core also includes 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 (in collaboration with Bradley Newcomer, Ph.D., University of Alabama, Birmingham)
- Phosphorus spectroscopy – to measure post-ischemic and exercise phosphocreatine recovery rates (resting and maximal ATP synthesis; in collaboration with Dr. Kevin Conley, Seattle, WA) The measurement of resting ATP turnover rates is complimented by a new tool in the lab called optical spectroscopy. This technique allows researchers to directly measure oxygen consumption in skeletal muscle. When combined with resting ATP turnover rates the mitochondrial coupling ratio or P/O can be directly measured for the first time in intact muscle.

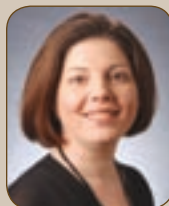
In-patient Unit



Director:
Steven R. Smith, M.D.

Steven R. Smith, M.D.
Professor

Library and Information Center



Director:
Lori Steib, B.A., MLIS, AHIP

Staff:
Marilyn Hammond, B.A.

Lori Steib, B.A., MLIS, AHIP
Director

Staff:

Crystal Traylor, R.N., W.H.N.P., Amy Braymer, L.P.N., Kim Crotwell, L.P.N., Lisa Dalfrey, L.P.N., Lorraine Eames, L.P.N., Rhonda Hilliard, L.P.N., Karen Jones, Project Manager, Katrina Prescott, L.P.N., Stephanie Tatum, R.N., Bridget Taylor, L.P.N., Susan Thomas, R.N., F.N.P., Valerie Toups, L.P.N., Celeste Waguespack, R.N., Onolee Thomas, R.N., Erin Wimberly, Administrative Assistant, Olga Sereda, Research Associate, Gloria Jones, Medical Assistant, Linda Stockton, Medical Assistant

The inpatient unit serves the needs of clinical investigators for the conduct of advanced clinical endpoints in studies of obesity, diabetes and metabolism. The unit consists of:

- Seven rooms, with two beds each, for overnight clinical stays and procedures. These rooms have been recently renovated and are comfortably furnished with large windows, private bath facilities, and telephones.
- two 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 while in protocols
- a large nursing station that includes a remote pharmacy, internet/intranet access and work table
- a psychology data collection area for questionnaire completion on PCs
- immediately adjacent facilities: DEXA, echocardiography, ultrasound, 3T MRI/MRS and pulmonary function and exercise testing units

The unit is staffed 24 hours, 7 days a week except major holidays.

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

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.



Jennifer C. Rood, Ph.D.
Professor

Director:
Jennifer C. Rood, Ph.D., DABCC, FACB

Staff:
Bruce Toth, M.A., Evest Broussard, M.S., Paige McCown, B.S., Feng Xu, Ph.D., Valery Hymel, B.S., Megan Smith



Lilian de Jonge, Ph.D.
Instructor

Director:
Lilian de Jonge, Ph.D.

Research Associates:
Cullen Whittaker B.E., Jonathan Simmons B.S., Tiffany Friedland B.S., Elizabeth Frost, Jeffrey Thompson, Katie Veron

Mission: The mission of the Mass Spectrometry Laboratory is to provide scientific expertise and resources for the analysis of stable isotopes.

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. The instruments are also used to measure total body water (Oxygen-18 and Hydrogen-2) and whole body glycolysis (Hydrogne-2). In addition, the Laboratory has three Agilent gas chromatgraphs with mass spectrometry detectors. These instruments are used to measure stably labeled carbohydrates and amino acids. This technology is currently being used to measure 6,6 D2 glucose to determine hepatic glucose output during hyperinsulinemic, euglycemic clamps. It is also used to measure labeled amino acids to examine protein turnover. These techniques allow researchers to explore glucose, amino acid and fatty acid metabolism in studies of obesity, diabetes and other conditions.

Mission: The mission of the metabolic chambers core is to perform and provide reliable and reproducible assessments of energy expenditure and substrate oxidation in humans.

Two types of equipment for these measurements are available. Metabolic carts (Deltatrac II metabolic monitors) are used for measurements under resting conditions. The Pennington Biomedical Research Center (PBRC) has eight of those devices, which are used 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.

For the measurements of energy expenditure and substrate oxidation on a 24H basis whole room indirect calorimeters are used. PBRC has two of these rooms which each measure 10x10x8 ft and were designed to 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 by using a gas mixture, 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 8, 1993, and July 1, 2009 researchers used the metabolic chambers for 3121 subjects days over 28 clinical studies.

Outpatient Clinic



Frank Greenway, M.D.
Professor

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

Recruiting Core



Timothy Church, M.D. Ph.D., M.P.A.
Professor

Faculty:
Timothy Church, M.D. Ph.D., M.P.A.

Staff:
Ruben Rodarte, M.S., Ami Parks B.S., Brenda Dahmer, B.S., Grace Bella, B.S., Jessica Beech, B.S., James Edmonds, B.S., Latrica Peters, B.S., Maria Sanchez, B.S.

Adjunct Faculty:

Drake Bellanger, M.D., Thomas Guillot, M.D., Mark Hausmann, M.D., Larry Hebert, M.D., Karl LeBlanc, M.D., Zhijun Liu, Ph.D., John Paige, M.D., William Raum, Ph.D., M.D., Brooke Whisenhunt, Ph.D., Marney White, Ph.D., Eugene Woltering, M.D.

Staff:

Mandy Shipp, LDN, RD (Clinic Administrator), Yolanda Robertson-Hill, N.P., Jennifer Arceneaux, RN, Karen Boley, LDN, RD, Mary Beth Burnett, Lauren Cox, B.S., Mavis Crow, LPN, Amber Dragg, LDN, RD, Chrystal Duncan, LPN, Angela Eldredge, B.S., Janet Fahr, B.S., Linda Guy, Lauren Harrington, RN, Claire Hazlett, RPh, Frances Hutchinson, B.S., Jana Ihrig, RN, Carolyn Johnson, LPN, Pamela Jolivet, B.A., Stacie La Prarie, RN, Melissa Lingle, B.S., Susan Mancuso, RN, Kimberly Marcell, Sarah Masters, B.S., Jennifer Perrault, Dawn Rachal, B.S., Vimala Rajapho, LDN, RD, Lura Reed, Charles Sides, RPh, Marisa Smith, B.S., Allison Strate, RN, Katie Tomayko, LDN, RD, Aimee Yoches, LPN, Ying Yu, MS.

Mission: The Outpatient Clinic Core supports clinical trials by screening volunteers and collecting research data. Screening involves visits in the clinic for those that pass the initial telephone screening by the recruiting core.

The Outpatient Clinical Core is on the first floor of the clinical research building which occupies 16,485 square feet of space, 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 testing laboratory, and a vascular ultrasound lab.

The Outpatient Clinic employs 35 people: A clinic administrator, two physicians, a nurse practitioner, ten nurse coordinators, six study coordinators, four dietitians, one project coordinator, a medical record librarian with two assistants, four secretarial personnel, a data entry supervisor and two part-time pharmacists.

During 2008 there were 16,876 telephone screenings, 2199 screening visits and 1556 subjects randomized into clinical trials. There were 29 new clinical trials directed by 10 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. A new clinical facility is under construction and will allow elimination of the trailers and growth of the clinic.

Mission: To provide recruitment services for clinical trials to accelerate participant accrual rates.

The recruiting core is dedicated to promoting clinical trials to the public. Since the formalization of the core in 2007, much advancement has taken place to improve the efficacy and efficiency of recruiting. The Core has developed an on-line system to help investigators determine budgeting needs for the study's recruitment effort. Our goal is to accelerate recruitment by establishing innovative methods of advertisement, increasing available resources, and developing tools to streamline the accrual process. Traditional advertisement mediums that are utilized include newspaper, radio, television, and direct mailing. Meanwhile more novel methods have been employed including online advertisement and email advertisement. An advertisement tracking system provides the necessary metrics to measure efficacy and facilitate market testing. The Core is equipped with a Uniform Call Distributor (UCD) enabled call center and is operated by a team of six full time recruiters. A UCD system expands the capability of a traditional phone system by processing large volumes of phone calls and distributing them evenly across available recruiters. During periods when the volume of calls exceeds the number of available recruiters, callers are directed to a voicemail system. That information is subsequently inputted into an electronic message tracking application, developed to expedite and track follow-up. One of the tools developed to enhance the recruiting process was the electronic phone screen system. The electronic phone screen allows recruiters to screen potential participants while seamlessly matching them to alternative clinical trials in an event they do not meet the criteria for the study for which they originally called.



Courtney Brock, RD, LDN
Director

Director:
Courtney Brock RD, LDN

Staff:
Marlene Afton, B.S., Kelly Atteberry, R.D., L.D.N., Ellen Broussard, Betty Fisher, Mandi Harvill, B.S., Mallory Purvis, B.S., Renee Puyau, B.S., R.D., Rachel Romaine, B.S., Nutritional Manager and Dawn Turner, B.S.



William D. Johnson, Ph.D.
Professor

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

Mission: To support nutritional research as an integrated component of the Pennington Biomedical Research Center by designing, preparing, and serving meals to meet study-specific criteria and produce valid scientific results.

The Research Kitchen is located on the second floor of the Clinical Research Building. It is a state-of-the-art facility that is equipped to provide quality service and is ideal for conducting simultaneous study protocols. Approximately 225 meals per day can be prepared in the facility. The Research Kitchen’s RDs use a nutritional analysis program to precisely plan menus and recipes to meet the requirements of each study protocol. The Research Kitchen is integrated into the clinic scheduling system of the Pennington Biomedical Research Center and the Research Kitchen’s RDs work directly with Principle Investigators as they plan research and design study protocols. The Research Kitchen works closely with the Inpatient Unit and Ingestive Behavior Laboratory, providing meals to these entities and collecting food intake data by weighing food provision and plate waste, and entering these data into the Center’s Central Database.

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

Biostatistics Staff:
Hongmei Han, M.S., Claudia Leonardi, Ph.D., Meghan McGlone, M.P.H.

Data Management Staff:
Connie Murla, B.S., Jessica Arnold, M.S., John Ruth, B.S., Carl Scogland, B.S., Aimee’ Stewart, M.S.

Mission: To provide biostatistics and data management expertise and resources to enhance reliable and objective research at Pennington Biomedical Research Center.

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

The Biostatistics faculty offers expertise to ensure rigorous statistical integrity of research in the basic, population and clinical sciences. The faculty is strongly encouraged to maintain current expertise through continuing education and to pursue independent research in statistical theory and methods relevant to the 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.



Ralph Underwood

Associate Executive Director for Administration & Finance

Despite the challenging economic times we face, the Pennington Biomedical Research Center maintains the capability of expanding and growing its scientific, clinical, and population science research efforts. The Center hopes to continue in its role as a leader in research and a source of economic development.

Among the factors that give the Center stability is the fact that its funding comes from a variety of sources—from federal grants and cooperative agreements, private grants and contracts, state research grants, and an annual appropriation from the State of Louisiana. Additionally, two foundations—the Pennington Biomedical Research Foundation and the Pennington Medical Foundation—provide funding for periodic capital projects and ongoing operations. With such diversified funding sources, the Pennington Biomedical Research Center has been able to maintain a high level of productivity and research activity in spite of the difficult economic environment.

Federal Grants and Cooperative Agreements

The Pennington Biomedical Research Center continues to be a success story in attaining federal research funding. Federal research funding increased by 13% to \$23 million as of the end of fiscal year 2008-09. A large portion of this federal funding comes from the National Institutes of Health (NIH). These grants result from a highly competitive review process, and it is gratifying to note that the Center's research scientists are very successful in competing with top researchers across the country.

The Department of Defense continues its long-standing research relationship with the Pennington Biomedical Research Center. Through the years, this research has delved into a number of facets of military nutrition and fitness, and this relationship continues to be very important to the growth and success of the Center.

The USDA has been a long-time supporter of research at the Pennington Center as well. It has helped in launching ambitious longitudinal research projects studying the factors, both physiological and behavioral, that make people susceptible to unhealthy weight gain.

The National Science Foundation has provided research funding to the Center as well during the past fiscal year.

Private Research Grants and Contracts

The Pennington Biomedical Research Center has long been recognized by private industry as a premier clinical and basic research institute. Private grants and contracts come from pharmaceutical

companies, the food industry, non-profit health organizations such as the American Diabetes Association, the American Heart Association and the American Cancer Society, and various other businesses and not-for-profit entities. Given the current economic environment, it is not surprising that private grants and contracts have leveled off this year. It should be noted that some of that may be attributable to the fact that the clinical research units have been operating at full capacity the past two years, a situation that should be remedied with the completion of the new clinical research building in the summer of 2010 that will triple available clinical research space.

State Appropriations

As is the case with almost all of the state governments, the economic downturn has impacted the coffers of the State of Louisiana as well. The Center's most recent state appropriation for the 2009-10 fiscal year decreased by almost 10% compared to the previous year. In our most recent fiscal year, state appropriations comprised 26% of the Pennington Biomedical Research Center's operating budget. Unrestricted state dollars are used to fund pilot studies that result in new grants and contracts and as seed money to recruit new research faculty and build new research programs at the Center. In return for its investment, the state receives an inflow of research dollars from sources outside of the state, creating new jobs and new wealth in Louisiana.

Other Revenues

State research grants decreased by approximately \$600,000 in the past fiscal year, from \$1.26M to approximately \$660,000. Indirect cost recoveries increased by \$800,000, from \$5.8M to \$6.6M due to the increase in federal research grants.

Summary

While some revenues have increased and others have decreased, overall funding of the Pennington Biomedical Research Center has grown in spite of recent difficult economic conditions worldwide. The diversity of the Center's funding has proven its value. The Center's researchers continue to be very productive, we are eager to fill the new clinical research building with more productive scientists, and we look forward to a bright future.



Glen Duncan
Director

Glen Duncan, B.S., M.J., M.S., APR
 Alan Pesch, B.G.S.
 Tim Nguyen, B.A.
 Keller Hill

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.



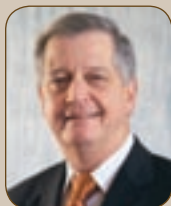
Guy LaVergne
Director

Guy LaVergne, B.S., CCNP, Cherie Gravois, B.S., B.A., M.B.A., Ray Allen, Ph.D., Barry Buchanan, CNE, Claire Lassalle, B.S., Andrew Russell, B.S., Daniel Turner, B.S., Archana Acharya, M.S., Stephen Acosta, B.S., Jason Brakel, B.S., Spencer Burt, B.S., Kavitha Challa, M.S., Clint Duffy, B.A., Michael Gelpi, B.S., Jeff Hannaman, B.S., Diana Holmes, B.A., M.S., John Kelly, B.S., M.C.S., Justin Landry, B.S., Eric LeBlanc, B.S., Jennifer Parfait, B.S., Sanjana Singh, B.S., Ying Wu, Ph.D., Terrell Carter, Shawn LeBlanc, Hailong Shen

Mission: To provide exceptional technical support in cutting edge technologies, collaborative tools and customized application development.

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

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



Jerry Blanchard
Director

Jerry Blanchard, B. ARCH., RA, NCARB, Bob McNeese, B.I.E. (retired September 2009), Marilyn Hughes, B.A.S., Walter Legett, B. ARCH., RA, A.I.A., Darryl Lejeune, B.S., Robin McDonald, B.A., Arthur Broussard, Wendy Brown, Barbara Corkern, Walter Farr, Adam Fauchaux, Jerrol Jackson, Clinton Jarrett, Cornelius Johnson, Paul Johnson, Bryan Marks, James Palmer, Brett Saurage, Charles Smith and Ken Wesley.



Mark Alise
Director

Mark Alise, M.B.A., Ph.D., Thomas Blalock, B.S., Joey Cyrus, B.S., Pam Fisher, B.S., Steve Kelly, M.S., Ph.D. (Cand.), Charlie Mackles, B.S., Monica Mougeot, M.S., CPA, Matt Zyllicz, M.S., Annette Potter, Mary Simpson, Yvette Stokes, Juanita Westly, and Diane Lowrey.

Facilities Management provides operation and maintenance services to support the mission of the Pennington Biomedical Research 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 acquisition funded by the Pennington Medical Foundation. Presently, department personnel are administering and supervising the design and implementation of more than 50 million dollars of Capital Outlay construction projects which include a new Clinic Building, new Imaging Center, renovations & upgrades to the existing Administration Building and Basic Science Laboratory Building, new Utilities and Medical Records Storage Facility, and the renovations to the existing Clinic Building.

Receiving Department

Dwayne Lambert, Barrett Mabile, Dennis Dahmer

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. This information is entered 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.

Security Department

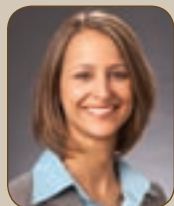
Scott Bertrand, Karen Quebedeaux, Jennifer Heckert, Steven Kirby, La Keisha Borel, Lionel Smith and Rhea Franklin.

The Security Department was reorganized in July of 2005 when control was transferred from the LSU Police Department to PBRC. Security officers are responsible for the safety and well being of employees, visitors and the protection of property. Officers are responsible for providing coverage on a twenty four hour basis throughout the year. The Security Department issues employee identification badges, parking tags and regulates and issues temporary cards for contractors, outside technicians, third party vendors, as well as special guests of the center. Officers are also responsible for monitoring critical plant equipment and recording temperatures of numerous ultra low freezers ensuring that they are in the proper temperature range. Officer's duties also include providing parking assistance and security for special events and responding to all emergencies at the Center.

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.

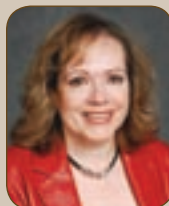
The management services provided by Fiscal Operations include payroll, purchasing, processing vendor invoices for payment, sponsored projects accounting, contracts audit, budget preparation and monitoring, travel reimbursement audit, collection of university revenues, in addition to assisting in portions 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.



Winona Ward
Director

Winona Ward, B.A, CRA
Katherine Granier, M.P.A.
Danielle Johnson, B.A.
Katie Thudium, B.A.



Anne Jarrett
Director

Anne Jarrett, Ph.D., J.D., L.L.M., M.B.A., M.P.H.
Anita Patin
Betty Rushing
Janice Warren, B.S.

Sponsored Projects provides advice and support to the Center in the acquisition and administration of externally funded projects in the furtherance of our research mission. Sponsored Projects is responsible for the pre-award and non-financial post award management of sponsored research and clinical trials. We strive to enhance the competitiveness of our researchers by providing customer service-oriented assistance, and maintaining current information on sponsor requirements, and state and federal regulations.

The services provided by Sponsored Projects include proposal review, budget development, contract preparation, training, reporting, subrecipient monitoring, negotiation of award terms and conditions, post award modifications and interpretation of regulations and sponsor requirements. We also assist faculty with locating funding opportunities, preparing and processing proposal information, and administering awarded projects. Sponsored Projects is dedicated to providing information, advice, and assistance to faculty and staff, and continually seeks ways to improve our services toward the advancement of research at the Center.

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. The IPLRA Office serves as a portal for the business community to identify areas of research and to ensure that interested parties are put in touch with the proper PBRC laboratories and researchers.

Economic Development and Commercialization

The economic development mission of the Office of IPLRA is to commercialize PBRC's intellectual property – new inventions and discoveries, such as patents and copyrights and to license these technologies and develop business partnerships in the U.S. and worldwide. These activities help to improve the lives of individuals and encourage economic development.

The most recent commercialization successes include a \$9 million license 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 several researchers at other LSU campuses, figured prominently in this cancer research discovery and its development. This unique, targeted anticancer fusion protein is selectively toxic to cancer cells. Initial studies show regression of well-established cancer, and *Esperance* is currently conducting proof of concept human trials.

NuPotential, LLC, founded by PBRC researcher Kenneth Eilertsen, PhD, received \$3 million in new venture capital funding from Louisiana investors. *NuPotential* is advancing cell therapy technologies to quickly and precisely develop new regenerative medicines for diseases such as Alzheimer's, diabetes, and others.

A recent discovery has uncovered a novel peptide to improve insulin sensitivity and reverse certain metabolic syndromes linked to obesity and diabetes. A multi-year research project conducted by Dr. Andrew Butler was funded by an American biotech company. PBRC is finalizing the license terms with the company for the technology.

The Director of IPLRA is working with the Pennington Biomedical Research Foundation and the Pennington Medical Foundation to implement a new technology development and commercialization funding program called CATALyst (Commercialization and Technology Accelerator). CATALyst focuses on providing critical resources to PBRC researchers between the time of an initial discovery and the availability of equity investment capital.

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.



Gena Doucet
Director

Gena Doucet, B.S., M.B.A.
Adrienne Davis, B.S., M.B.A.
Becky Guillot
Sharon Hebert, B.A.
Betty Rushing
Jason Hymel, B.S.



Ricky Caro
Director

Richard Caro Jr, B.S.
Errol Broussard, B.S.
Rodney Bynum
Brad Guidry, B.S.

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.

Pennington Stores is a full-service storeroom that offers research, medical, and office supplies to Pennington Biomedical Research Center employees. Products not in stock can be special ordered. Pennington Stores main objective is to support the PBRC faculty and staff by offering a convenient place to purchase all types of supplies and equipment. Our staff has the ability to purchase scientific and research supplies and equipment up to \$25,000 on our LSU Procurement Card, usually within 24hrs of the receipt of order. A significant function of Stores is the placing and tracking of supply and equipment orders for the researchers. Stores recently acquired a 24-hr stocking cabinet which allows researchers access to supplies outside of our normal business hours. The cabinet is housed on the 4th floor of the new research building. Stores is also responsible for the storage and distribution of gas cylinders used throughout the facility as well as maintaining liquid nitrogen levels in numerous long-term storage vessels. On a weekly basis, Stores also distributes copy paper to the community copiers/printers to make sure that there is always a supply of paper for the users. All of the radioactive materials ordered for researchers are housed and distributed through Stores upon their arrival to PBRC. The team in Stores is committed to providing the PBRC community with quick and accurate service, along with excellent customer service.

Adjunct Employee	PBRC Title	Education Level	Institution
Aguilera, Miguel	Instructor	M.D.	LSU Health Science Center
Argyropoulos, George	Associate Professor	Ph.D.	Weis Center for Research
Baker, David	Professor	Ph.D.	LSU Veterinary Medicine
Basso, Brandi	Instructor	M.D.	Lake Primary Care Physicians
Bazzano, Lydia	Assistant Professor	Ph.D.	Tulane University School of Public Health and Tropical Medicine - Dept. of Epidemiology
Bellanger, Eric D.	Instructor	M.D.	Vista Surgical Hospital, Perkins Rd. Baton Rouge, LA
Bennett, Peter H.	Professor	MB, FRCP	NIDDK, NIH
Berenson, Gerald	Professor	M.D.	Tulane University
Blair, Steven	Professor	PED	Arnorld School of Public Health at the University of South Carolina
Bombet, Leon	Instructor	M.D.	The Baton Rouge Clinic, Pediatrics
Brown, Sandra	Professor	Ph.D.	Southern University Professor of Grad. Nursing Program
Bunnell, Bruce	Professor	Ph.D.	Tulane University, Department of Pharmacology
Burris, Thomas	Professor	Ph.D.	Scripps Research
Caffery, Terrell	Instructor	M.D.	Earl K. Long Medical Center
Caprio, John T.	Professor	Ph.D.	LSU Department of Biological Science
Cassidy, William	Assistant Professor	M.D.	LSU Health Science Center
Chalew, Stuart	Professor	M.D.	LSU Health Sciences Center and Children's Hospital of New Orleans
Chen, Wei	Associate Professor	M.D., Ph.D.	Tulane University; Department of Epidemiology
Civitarese, Anthony	Assistant Professor	Ph.D.	Arizona State University; Center for Metabolic Biology
Clisham, Paul Ronald	Assistant Professor	M.D.	Tulane University School of Medicine
Coe, Ronald	Instructor	M.D.	Livingston Parish Coroner and St. Francis Cabrini Medical Center
Cohen, Deborah A	Professor	M.D., MPH	Rand Corporation, Santa Monica, CA
Colvin, Lisa A.	Professor	Ph. D., FACSM	ULM Monroe , Professor , Department of Kinesiology
Copeland, Amy	Associate Professor	Ph.D.	Louisiana State University - Department of Psychology
Do, Thuytien	Instructor	M.D.	St. Elizabeth Hospital
Elkind-Hirsch, Karen	Associate Professor	Ph.D.	Research Dir., Reproductive Med. Women's Research Inst.
Finley, John W.	Professor	Ph.D.	Professor - Food Science; LSU Ag Center
Fonseca Vivian	Professor	Ph.D., MBBS	Tulane University, Armed Forces Medical College
Garitty, Earl James	Instructor	MD.	LSU Department of Otolaryngology; Earl K. Long Hospital
George, Julia	Instructor	J.D.	Attorney 3 Dept. of Culture, Recreation and Tourism, Office of the Secretary, Deputy General Counsel
Glancy, David	Professor	M.D.	LSU Health Science Center
Gordon, Stewart	Assistant Professor	M.D.	LSU Health Science Center, Earl K. Long Department of Pediatrics
Guidry, Jimmy	Assistant Professor	M.D.	LA Dept of Health & Hospitals
Guillot, Thomas	Assistant Professor	M.D.	Our Lady of the Lake; Plastic Surgery
Hasek, Barbera	Instructor	Ph.D.	Baton Rouge Community College
Hausmann, Mark	Associate Professor	M.D.	The Surgeons Group of Baton Rouge
Howell, Michael	Instructor	M.D.	Howell Healthcare, LLC
Hulver, Matthew	Assistant Professor	Ph.D.	Virginia Polytechnic Institute and State University

Adjunct Employee	PBRC Title	Education Level	Institution
Jazwinski, S. Michal	Professor	Ph.D	Tulane University Health Sciences Center
Johnson, Jolene	Assistant Professor	M.D.	LSU Health Science Center & Earl K. Long, Department of Internal Medicine
Johnson, Sterling	Associate Professor	Ph.D.	William S. Middleton Memorial Veterans Hospital, Geriatric Resaerch-Madison, WI
Jones, Glen	Associate Professor	Ph.D.	Adult Psychology & Center for Primary Care Reseearch, EKL Medical Center
Keenan, Michael	Associate Professor	Ph.D.	Associate Professor-Human Nutrition and Food/School of Human Ecology
Lammi-Keefe, Carol	Professor	Ph.D.	LSU School of Human Ecology
LeBlanc, Karl	Professor	M.D.	The Surgeons Group of Baton Rouge
LeBlanc, Monique M.	Instructor	Ph.D.	LA GEAR UP, Baton Rouge
Lefevre, Michael	Professor	Ph.D.	Center for Advanced Nutrition; Utah State University
Lenard, Natalie	Instructor	Ph.D.	Our Lady of the Lake College
Liu, Zhijun	Professor	Ph.D	Prinicpal Investigator of the Medicinal Plants Lab LSU - Ag Center
Lopez, Mandi	Associate Professor	D.V.M., Ph.D.	LSU School of Veterinary Medicine
Lovejoy, Jennifer	Professor	Ph.D	Free and Clear, Inc.
Luftig, Ronald	Professor	Ph.D.	LSU Health Science Center
Markward, Nathan	Assistant Professor	Ph.D.	Blue Cross/Blue Shield of Louisiana
Martin, Pamela	Assistant Professor	Ph.D.	Louisiana Department of Social Services
McLaughlin, Leslie	Assistant Professor	D.VM	LSU Department of Veterinary Medicine
Newcomer, Bradley	Associate Professor	Ph.D.	University of Alabama Birmingham
Ochoa, Augusto	Associate Professor	Ph.D.	LSU Health Science Center
O'Patry, Sean	Instructor	M.D.	Earl K. Long Medical Center
Paige, John T.	Assistant Professor	M.D.	LSU Health Science Center
Petty, Paul	Instructor	M.D.	Earl K. Long Medical Center
Phifer, Curtis	Professor	Ph.D.	Northwestern State University
Quintana, Humberto	Professor	M.D.	LSU Health Science Center
Raskin, Ilya	Professor	Ph.D.	Biotech Center, Cook College Rutgers University
Raum, William	Professor	M.D., Ph.D	LSU Health Science Center
Ribnicky, David	Professor	Ph.D.	Biotech Center, Cook College Rutgers University
Richards III, Edward	Professor	J.D. M.P.H.	LSU Paul M. Hebert Law Center
Rodriguez, Paulo	Instructor	Ph.D.	LSU Health Science Center
Sjostrom, Lars	Professor	Ph.D	Gothenburg University
Sothorn, Melinda	Associate Professor	Ph.D.	LSU Health Science Center
Srinivasan, Sathanur	Professor	Ph.D.	Tulane University Department of Epidemiology and Biochemistry
Stephens, Jacqueline	Professor	Ph.D	LSU Department of Biological Sciences
Stewart, Laura K.	Assistant Professor	Ph.D.	LSU Department of Exercise Physiology
Volaufova, Julia	Professor	Ph.D	LSU Health Science Center
Whisenhut, Brooke	Assistant Professor	Ph.D.	Missouri State University Department of Psychology
White, Marney	Assistant Professor	Ph.D.	LSU Department of Psychology
Woltering, Eugene	Professor	M.D.	LSU Health Science Center

In cooperation with the Louisiana State University Health Science Center, the Pennington Biomedical Research Center has granted the Honoris Causa Doctorate to three world class scientists who have made seminal contributions in fields related to the mission of the Center.



Douglas Coleman, Ph.D. (2005)

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 Honoris Cause Doctorate 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 40 years ago provided the foundation for the understanding of how our brain interacts with peripheral tissues in order to maintain energy balance.



Albert J. Stunkard, M.D. (2006)

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.



Howard Green, M.D. (2008)

Howard Green received his Doctorate in Medicine at the University of Toronto. He began his independent scientific work at New York University School of Medicine, where he ultimately became Professor and Chairman of the Department of Cell Biology.

From 1970-1980 he was Professor of Cell Biology at Massachusetts Institute of Technology. He came to Harvard Medical School in 1980 and served as Chairman of the Department of Cellular and Molecular Physiology from then until 1993. Since then he has been George Higginson Professor in the Department of Cell Biology.

While at MIT and Harvard Medical School, he developed the first therapeutic use of cultured cells – the use of keratinocytes for the regeneration of epidermis on severely burned patients. The first large-scale, life-saving use of this procedure was demonstrated with cells grown in his laboratory on the 6th floor of Building C2, where his lab is still located. Dr. Green also developed adipocyte (fat cell) lines that are used around the world in the study of adipocyte differentiation and adipose tissue biology.

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Dear Friends,

This annual report marks the closing of an era. For the last ten years we have had the pleasure of working with Dr. Claude Bouchard both as a member of our Board of Trustees and as Executive Director of the Pennington Biomedical Research Center. Dr. Bouchard will be returning to the laboratory to resume his research career. During the ten years of Dr. Bouchard's leadership, the Medical Foundation constructed the new 187,000 sq. ft. Basic Science Building, the 14,000 sq. ft. Population Research Building, and provided \$2.5 million in seed funding for the new Clinical Research Building. It has been an era of major expansion, fueled by the funds provided by my grandparents and nurtured by the Pennington Medical Foundation Board of Trustees.

Since our last annual report, we have had some changes in our board membership. Two of our staunchest members, Mr. John Barton and Dr. Allen Copping decided to step down from active membership and assume emeritus status. Both of these gentlemen have been associated with the Pennington Medical Foundation and the Center from their inception. Their devotion to the Center, their leadership, vision, and dedication have contributed to the success of the Foundation and Center. We hope that we can continue to benefit from their wisdom for many years to come.



The resignations of Mr. Barton and Dr. Copping created an opportunity to add new Trustees to the board. We were extremely fortunate to find two outstanding individuals who were willing to devote their time and expertise to promote the mission of the Medical Foundation in its support of the Center. Mr. Charles Lamar and Mr. Richard Lipsey are now members of the foundation Board of Trustees. We look forward to their sage advice and business acumen.

During the past two years, the Medical Foundation provided the Pennington Biomedical Research Center with over \$9,000,000 in support for the Center. These funds included debt service on facilities, funds to recruit new faculty, supplemental support for the Executive Director, and seed funds for various Center initiatives. The Medical Foundation also provided administrative and startup funds for the CATALyst program, a new pre-angle capital program designed to stimulate economic development.

As one era ends with the regret of losing the administrative skills of a preeminent leader, a new one begins with the excitement of finding a new leader to build on the successes of Dr. George Bray and Dr. Claude Bouchard. The Medical Foundation stands ready to assist our new leader to build on the success of the past and identify new goals and opportunities for the Center.

Sincerely,

A handwritten signature in cursive script that reads "Paula Pennington de la Bretonne".

Paula Pennington de la Bretonne

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Dear Friends,

I am honored to assume the chairmanship of the Pennington Biomedical Research Foundation in 2009. I continue to appreciate the national and international significance of the lifesaving and impactful research conducted at the Pennington Biomedical Research Center. Together, we are working diligently to advance the Center, its scientists, and most importantly the research, to reach their full potential.

Today, the research of PBRC is more important than ever. The Center has earned a worldwide reputation as a leader in finding ways to prevent today's most serious diseases: diabetes, obesity, heart disease, cancer and dementia. Private philanthropy plays a critical role in supporting the Center's research programs.

In January 2009, the Center broke ground for a new Clinical Research Building, an important advancement that will pave the way for significantly increasing the Center's ability to translate discoveries from the laboratory to individuals. However, this will only become a reality if we can fill this new space with more researchers and expanded clinical programs.



Gifts to the Pennington Biomedical Research Foundation help in so many ways...seed funding for emerging research projects, the most advanced instrumentation and equipment, recruiting and retaining the best and brightest scientists, and underwriting vital community education programs that apply the advancements made at the Center.

I hope you'll agree that we cannot pause for a moment, despite the challenging economic climate. To the contrary, we have to seize this moment and opportunity to advance PBRC to the greatest degree possible. Our health, and the health of future generations, is dependent upon our success in doing so. For it is medical research, that provides the hope that we can enjoy healthier lives. On the following pages, you'll see the many individuals, corporations and foundations that have answered this call in a significant way. Thank you for your generosity and ongoing commitment to making this hope become a reality.

Sincerely,

A handwritten signature in black ink, appearing to read "Tim Barfield". The signature is fluid and cursive, with a large initial "T" and "B".

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Douglas L. Manship Professorship in Diabetes <i>William Cefalu, M.D.</i>	Douglas L. Manship, Sr.	1992
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Honoring Lifetime Giving

With sincere gratitude, the Pennington Biomedical Research Foundation thanks and recognizes the donors whose lifetime giving is \$5,000 and above. The individuals, corporations, and foundations listed have shown their firm and steadfast commitment to our mission throughout the history of our organization. Members of The Legacy Society are also listed and include those individuals who have made a planned gift to the Pennington Biomedical Research Foundation or have notified the Foundation of their intention to do so.

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