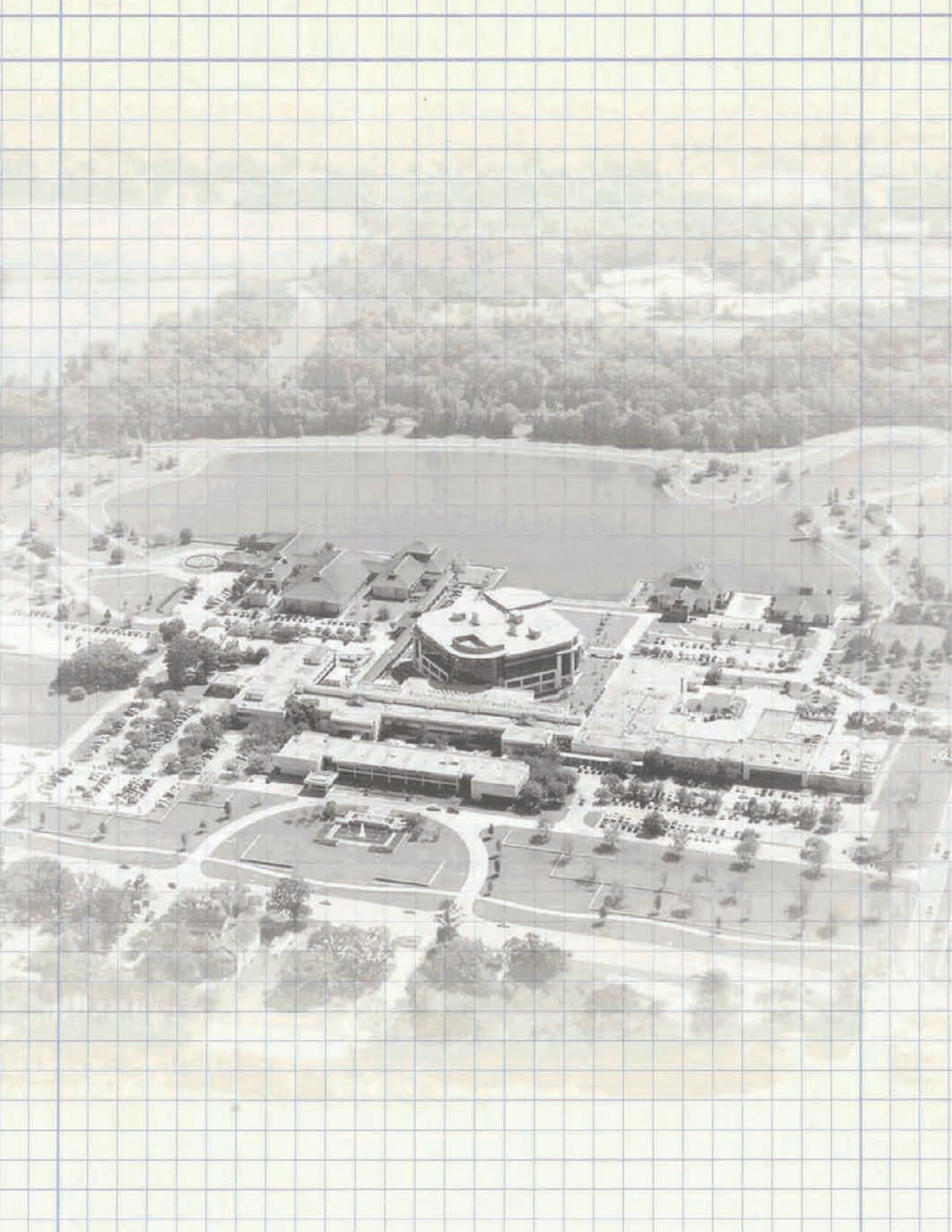
PENNINGTON BIOMEDICAL RESEARCH CENTER

SCIENTIFIC REPORT 2004–2005

LOUISIANA STATE UNIVERSITY SYSTEM

PENNINGTON BIOMEDICAL RESEARCH CENTER



PENNINGTON BIOMEDICAL RESEARCH CENTER

LOUISIANA STATE UNIVERSITY SYSTEM

SCIENTIFIC REPORT

2004–2005

The accomplishments of the Center from January 2004 through December 2005

Respectfully Submitted to:

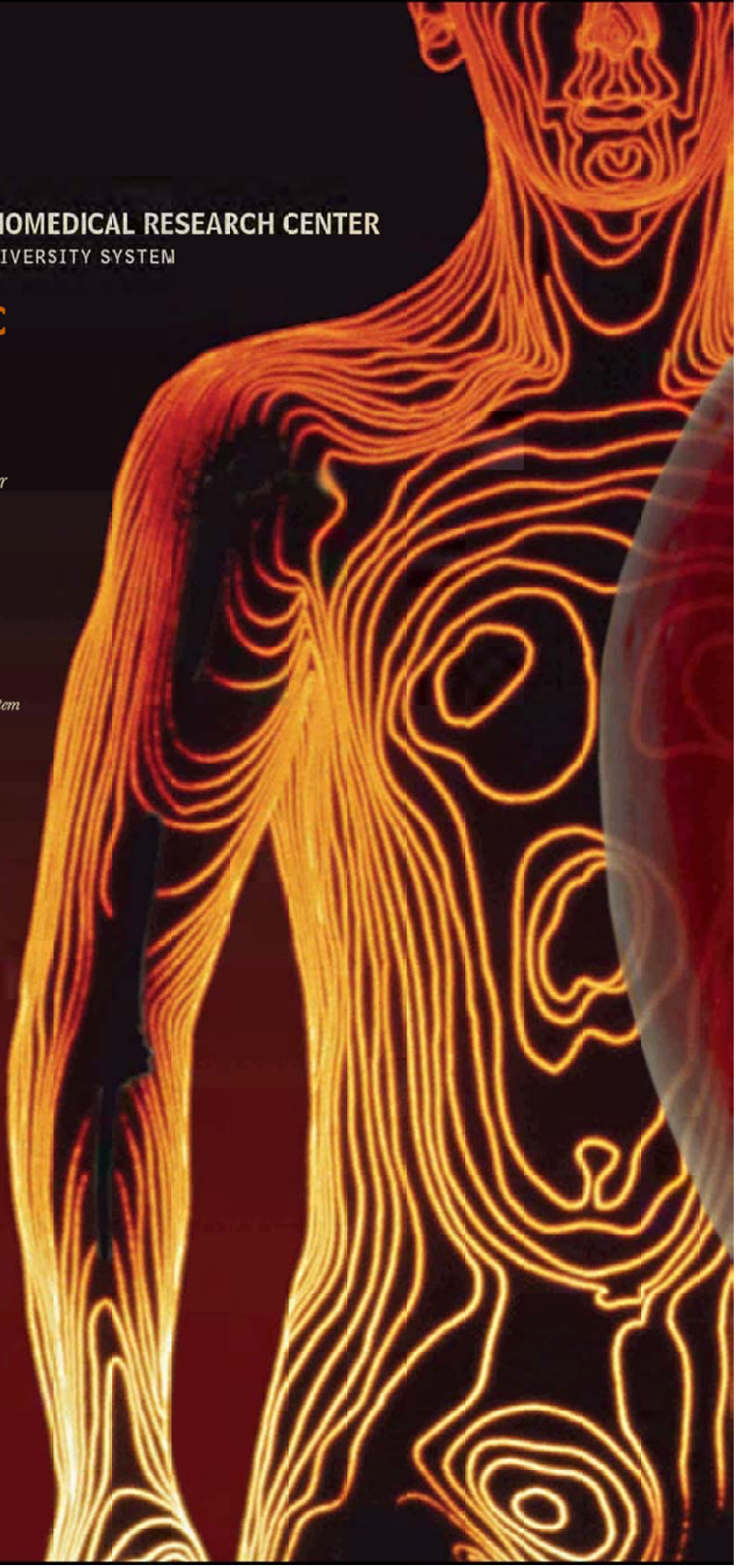
Dr. William Jenkins
President of the Louisiana State University System

Mr. Roderick K. West
Chair of the LSU System Board of Supervisors

Mrs. Paula Pennington de la Bretonne
Chair of the Pennington Medical Foundation

Mr. John Noland
Chair of the Pennington Biomedical Research Foundation

Members of the LSU System Board of Supervisors



cose 6-phosphatefructose 6-phosphatefructose1,6-diphosphatedihydroxyacetone phosphate carcinoembryonic antigen fibroblast growth factor 23 (FGF-23) assay carbohydrate sulfotransferase-6 (CHST6) gene assay Provitamin D2 = ergosta-5,7,22-trien-3-ol HER-2/neu (369) assay microdissection genotyping assay for follicular-derived thyroid Unlocking Phosphorylation with enzyme phosphofructokinase (PFK) / fructose 6-phosphate phosphorylation fructose1,6-diphosphate retinol = 2,6,6-trimethyl-1-hydroxy-3',7'dimethylnona-1',3',5',7'-tetraenyl cyclohex-1-ene vitamins the Apple = 16 kcal = 0.055g (protein) 0.100g (fat) 4.31g (CHO) 2.05mg (Ca) 0.05 g (Fe) 0.005mg (B1) 0.004mg (B2) 0.09g (fiber) mg (chol) secrets metabolism of glucose molecule = $C_6H_{12}O_6$ + 6 O_2 = 6 CO_2 + 6 H_2O 689 kcal mol-1 of glucoseglucose 6-phosphatefructose 6-phosphatefructose1,6-diphosphatedihydroxyacetone phosphate myeloid-related protein 8/14 (MRP-8/14) nutrition citric acid = 2-Hydroxypropane-1,2,3-tricarboxylic acid Glucose + 2P_i + 2ADP + 2NAD+ = 2 Pyruvate + 2ATP + 2NADH + 2 H_2O Vitamin D2 =(5Z, 7E, 22E)-(3S)-9,10-secoergosta-5,7,10(19),22-tetraen-3-ol RQ for carbohydrate = RQ =6 CO_2 / 6 O_2 = 1.00 Vitamin D2 =(5Z, 7E, 22E)-(3S)-9,10-secoergosta-5,7,10(19),22-tetraen-3-ol glucoseglucose 6-phosphatefructose 6-phosphatefructose1,6-diphosphatedihydroxyacetone phosphate carcinoembryonic antigen fibroblast growth factor 23 (FGF-23) assay carbo-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Foreword

We are indebted to LSU System President William Jenkins, Ph.D., and Mr. William Silvia, Executive Vice-President, other vice-presidents of the LSU System and members of the LSU Board of Supervisors (past Chairs, Mr. Stewart Slack and Mr. Bernard Boudreaux, and current Chair, Mr. Roderick K. West) for supporting the mission and encouraging the growth of the Pennington Biomedical Research Center.

An extremely important asset in our effort to build a world class research center is the Office of the Governor (Kathleen Babineaux-Blanco, Governor) and the Louisiana State Legislature. I would like to express our gratitude to the Governor, the President of the Senate, Dr. Donald Hines, and the Speaker of the House, Mr. Joe Salter, for their support, particularly during the challenging times the State of Louisiana has experienced in the last quarter of 2005. I am thankful to the Commissioner of Administration, Mr. Jerry Luke LeBlanc. We are also grateful to the Louisiana Board of Regents (Current Chair, Roland Toups) and to the Commissioner of Higher Education, Dr. T. Joseph Savoie, for the confidence they have expressed in the future of the Pennington Biomedical Research Center.

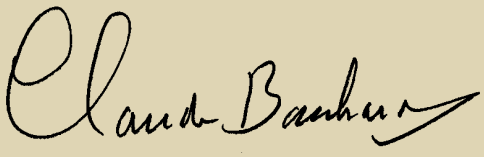
Our deepest gratitude goes to the men and women who serve on the boards of our two supporting foundations: the Pennington Medical Foundation and the Pennington Biomedical Research Foundation. Mrs. Paula Pennington de la Bretonne, chair of the Pennington Medical Foundation, leads a group of professionals whose management skills have resulted in the growth of our endowment. They have made it possible for the Pennington Biomedical Research Center to break ground on new facilities and to acquire sophisticated equipment and technologies on a regular basis. Likewise, Mr. John Noland, Chairman of the Board, and Ms. Jennifer Winstead, President and CEO of the Pennington Biomedical Research Foundation, and their fellow board members are fully engaged in the task of creating endowed chairs and professorships and raising unrestricted funds as well. We are all extremely grateful for their dedication and hard work on our behalf. To all the donors who are so generous in their response to the requests from the Pennington Biomedical Research Foundation, goes our heartfelt gratitude and thanks.

CLAUDE BOUCHARD, PH.D.
Executive Director
George A. Bray, Jr. Chair in Nutrition

The exciting progress we have made during the last two years would not have been possible without the dedication of our faculty, staff and management team. Their devotion to improving lives and commitment to their work make the Pennington Biomedical Research Center an inspiring place to work.

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

Our mission remains: **to promote healthier lives through research and education in nutrition and preventive medicine.**
What has changed, significantly, is the breadth and depth with which we are achieving our mission. As you go through this report, you will discover a spectrum of research projects, discoveries and related publications about which we could only dream a decade ago. To find more about the Pennington Biomedical Research Center and its ongoing activities, please visit **www.pbrc.edu**. If you want to learn more about the mechanisms available to support the mission of the Pennington Biomedical Research Foundation at: **www.penningtonfoundation.org.**



Claude Bouchard, Ph.D.
Executive Director

A Message from Our Executive Director...

The close of 2005 marked the Pennington Biomedical Research Center's 17th year of operation. We have grown from a handful of skilled men and women in large but nearly vacant laboratories to a campus teeming with nearly 600 scientists, technicians and support staff. In terms of number of faculty, publications, size, and scope, we have achieved the status of the largest academically-based nutrition research center in the world, with the unique distinction of having the highest number of researchers dedicated to obesity.

During the period covered by the present report, 2004-2005, the Pennington Biomedical Research Center assumed control of the multifunctional conference facility located on our campus and previously owned and operated by our two supporting foundations. This conference facility was used extensively by various organizations in the community for about ten years. The Center is converting some of the space available in the conference building to a Population and Prevention Study facility.

Among the most important developments that have occurred during this period, one needs to mention the two large center grants that we were awarded by the National Institutes of Health. The first to be funded was a Center of Excellence in Botanicals and Metabolic Syndrome (Dr. William Cefalu as the leading scientist). The main objective of this grant is to identify and test botanical compounds (plant extracts, for example) for their potential application in the prevention or treatment of insulin resistance, metabolic syndrome features or diabetes. More recently, we obtained funding for a Clinical Nutrition Research Unit (Dr. Eric Ravussin as the leading scientist) from the National Institutes of Health. This unit seeks to identify fundamental biological phenomena that occur *in utero* which modify the risk profile for obesity and associated chronic diseases. The environment of the womb, including prenatal nutrition, appears to have a profound effect on long-term development, particularly on the modulation of metabolic risk factors for diseases. This new unit at the Center will focus on several facets of this fascinating field of research.

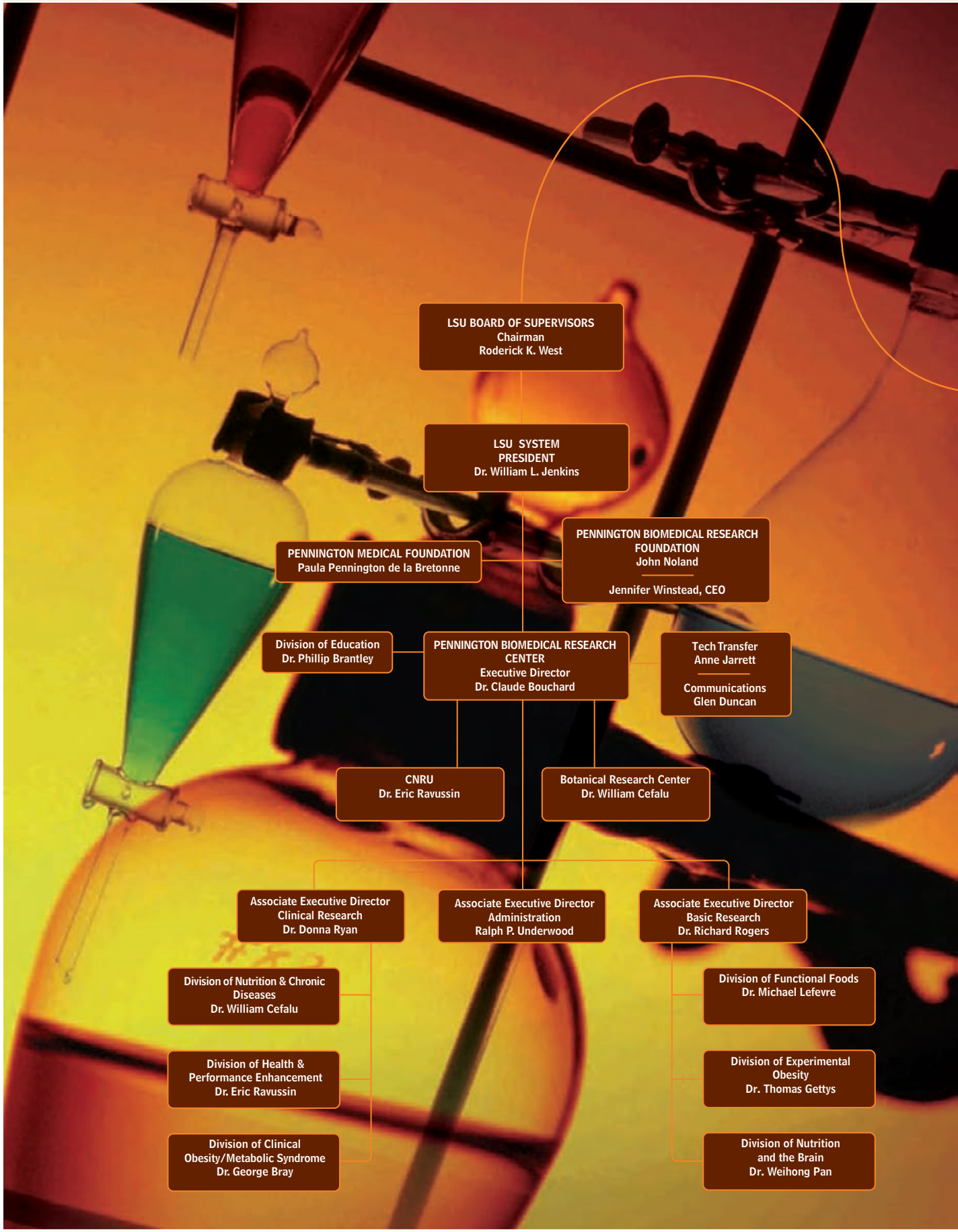
Thanks to the help of the Pennington Biomedical Research Foundation and the generous support of citizens and not-for-profit organizations, we have also designated two named laboratories in 2005: The William Hansel Laboratory for Cancer Prevention and the John S. McIlhenny Laboratory of Botanical Research.

In 2005, we reached another milestone. It has been a long-standing goal of PBRC to recognize esteemed and accomplished scientists from around the world. In collaboration with the Chancellor of the LSU Health Sciences Center, Dr. John Rock, and with the support of the LSU System, we jointly conferred an Honoris Causa Doctorate on Douglas Coleman, Ph.D., retired scientist from the Jackson Laboratory in Maine. Dr. Coleman's research focused on mechanisms responsible for diabetes and obesity that, according to the 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"

Dr. Samuel McCann, holder of the United Companies/Harris J. Chustz Endowed Chair in Diabetes and one of the most highly cited scientists in the biomedical literature, recently retired and was awarded the title of Professor Emeritus by the Board of Supervisors of the LSU A&M System. Dr. McCann was an exceptional scientist and his departure left a great void in our faculty. We wish him the happiest and healthiest retirement.

As a result of the devastation caused by Hurricane Katrina in south Louisiana, the facilities and programs of the LSU Health Sciences Center in New Orleans were dramatically compromised. The academic year of nearly 600 medical, nursing, dental, and allied health students, as well as the research activities of hundreds of faculty and staff, was in jeopardy. The Pennington Biomedical Research Center was able to assist our colleagues from New Orleans by providing teaching space, offices, and research space. We intend to continue to support them until they can return home.

Among other important developments that have occurred in the recent past, one should note the recent acquisition of a 3.0 Tesla Magnetic Resonance Spectroscopy unit and the renovation of existing space in the Clinical Research building in order to accommodate this equipment. The MRS unit was acquired through a major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Administration
Ralph P. Underwood
Associate Executive Director
Basic Research
Dr. Richard Rogers
Division of Nutrition & Chronic Diseases
Dr. William Cefalu
Division of Health & Performance Enhancement
Dr. Eric Ravussin
Division of Clinical Obesity/Metabolic Syndrome
Dr. George Bray
Division of Functional Foods
Dr. Michael Lefevre
Division of Experimental Obesity
Dr. Thomas Gettys
Division of Nutrition and the Brain
Dr. Weihong Pan

financial contribution from the Department of Defense and the space renovation was underwritten by the Pennington Medical Foundation. This new facility will have a strong impact on our ability to conduct sophisticated *in vivo* metabolic studies in people. Additionally, thanks to a special grant from the National Institutes of Health, we were able to add housing space in our Comparative Biology core facility.

Organizational Structure

By the end of 2005, the Pennington Biomedical Research Center employed about 600 people, including 70 faculty and more than 40 post-doctoral fellows. The faculty are grouped into six research divisions, each defining a major field of interest in nutrition and preventive medicine. Moreover, the Center operates a Division of Education. The scientists and their support staffs each belong to one of 13 large research laboratories, 9 in the basic science area and 4 in clinical research. This research enterprise at the Center is supported by the expertise and physical resources of 16 core facilities.

Our current organizational chart *(Left)* shows that the Executive Director of the Center reports directly to the President of the Louisiana State University System. Three Associate Executive Directors with the following responsibilities report to the Executive Director. Dr. Donna Ryan oversees the clinical research programs and the activities of the Nutrition and Chronic Disease, Clinical Obesity and Metabolic Syndrome, and Health and Performance Enhancement Divisions. Dr. Richard Rogers supervises the basic research programs and the operations of the Experimental Obesity, Nutrition and the Brain, and Functional Foods Divisions.

Mr. Ralph Underwood is responsible for the administration and finance areas. He oversees the activities of computer services, facilities management, human resources management, fiscal operations, sponsored projects, central stores, property control and receiving, and security.

The chart also indicates that the two new units created with funding from the National Institutes of Health, i.e. the Clinical Nutrition Research Unit and the Botanical Research Center, report directly to the Executive Director. Additionally, the Division of Education, the Office of Intellectual Property, Legal and Regulatory Affairs, and the Office of Communications also report to the Executive Director. Finally, the Center is supported by two foundations, the Pennington Medical Foundation and the Pennington Biomedical Research Foundation. All these units are defined in greater detail in the present Scientific Report.

Scientific Impact on Our Community

The development of significant and life-improving findings is the hallmark of the Pennington Biomedical Research Center and its researchers. We achieve this, in part, through aggressive recruitment of leading researchers and a competitive tenure policy that ensures dedication to innovative research. In addition, the Pennington Biomedical Research Center offers first-class research facilities in an

environment that is completely conducive to free thought and collaborative research. The result is a most productive senior faculty in terms of acquired funding, successful publication, and numerous citations of their work in the scientific literature.

Collectively, the faculty has published approximately 7,500 peer-reviewed papers in their careers or about 107 per faculty member. These papers have been cited more than 176,000 times, a frequency that is highly reflective of a core of productive and influential scientists.

An important indicator of the performance of the Center's scientists is the list of accomplishments resulting from the research undertaken at PBRC. These advances are quite numerous and cannot be fully enumerated here. However, an abbreviated list focusing on the major advances is presented *(below)* to provide some indication of the nature of those accomplishments in basic and clinical research.

Although we constantly seek advice from external reviewers and experts, and although the work of our scientists is constantly examined by panels of experts reviewing grant applications and scientific publications, we feel the need to obtain advice from individuals who are engaged in science in elite institutions around the world. Every two years, we bring in panels of three or four external reviewers to examine the science and the performance in each of our six research divisions. In alternate years, we convene an External Advisory Board. This Board is asked to scrutinize from a global perspective the status of the whole research enterprise of the Center and to give us its view on the competitiveness of our science, priority areas, and opportunities for growth. This External Advisory Board was last convened in April, 2004. *(See chart on right.)*

Basic Research	Clinical Research
Identification of a specific ion channel responding to dietary fat	Investigation of a lifestyle program reducing the risk of type 2 diabetes by almost 60%.
A new lytic peptide approach to treating certain cancers	A diet rich in fruits, vegetables and low-fat dairy products which can reduce blood pressure and hypertension medications.
Identification of genes for abdominal obesity	Prevention of kidney stones and bone loss during prolonged space travel.
Identification of genes for the response to exercise	Augmentation by physical activity of the ability to adapt to dietary fat increases.
Identification of a peptide regulating dietary fat ingestion	Definition of warfighter energy and water requirements.
Definition of afferent neural signals from the gastrointestinal track on feeding behavior	Improvements in operational rations and in nutritional intake of recruits in basic combat training.
Molecular genetics of thermogenesis in brown fat	Demonstration that agouti protein promotes adipogenesis

External Advisory Board - 2004

Scott M. Grundy, M.D., Ph.D. Chair	Director, Center for Human Nutrition Department of Internal Medicine University of Texas Southwestern Medical Center, Dallas
Richard Havel, M.D.	Cardiovascular Research Institute University of California, San Francisco
Steven N. Blair, P.E.D.	President and CEO Cooper Institute
Barbara C. Hansen, Ph.D.	Professor of Physiology and Director, Obesity and Diabetes Research Center School of Medicine University of Maryland
Dennis M. Bier, M.D.	Director, USDA/ARS Children's Nutrition Research Center Baylor College of Medicine, Houston
Allen S. Levine, Ph.D.	Research Service Director, Minnesota Obesity Center at the VA Medical Center, Minneapolis
Norman Hollenberg, M.D., Ph.D.	Brigham and Women's Hospital Director of Physiological Research, Department of Radiology, Harvard Medical School, Boston
Edward S. Horton, M.D.	Vice President and Director of Clinical Research Joslin Diabetes Center Harvard Medical School, Boston
Robert Jeffery, Ph.D.	Division of Epidemiology University of Minnesota, Minneapolis
Mitchell Lazar, M.D. Ph.D.	Sylvan H. Eisman Professor of Medicine Chief, Division of Endocrinology, Diabetes, and Metabolism Director, Penn Diabetes Center University of Pennsylvania School of Medicine
Alan Tall, M.D.	Tilden Weger Bieler Professor of Medicine College of Physicians and Surgeons Department of Medicine Division of Molecular Medicine Columbia University, NY

Economic Impact of the Center

As described in the report prepared by Mr. Ralph Underwood, Associate Executive Director for Administration and Finance, Pennington Biomedical Research Center has a real economic impact on the community as well. The Center's funding comes from federal grants and cooperative agreements, unrestricted funding through an annual appropriation from the State of Louisiana, private grants and contracts, state research grants, and indirect cost recoveries. During the two years covered by this scientific report, revenues have increased by 40%. It should not be surprising, given the rate of growth and the surge in technology transfer activities, that we make it part of our mission, vision, and strategic plan to create a positive economic impact on our city, state, and region.

In that context, we are pleased that the Baton Rouge Area Chamber has recognized the Center's economic contribution by making it a priority to increase both our stature in the legislature and financial support from the state.

Endowed Chairs and Professorships

Our long term goals can only be met with the dedication, insight and innovative research of a globally-recognized faculty. To compete for the highest quality candidates, we offer not only a superb setting but also colleagues with demonstrated accomplishments. In addition, we rely on the resources of endowed chairs and professorships, which confer recognition of achievement as well as some financial support to supplement grantsmanship.

By the end of 2005, there were five occupied endowed chairs and three endowed professorships at the Pennington Biomedical Research Center. The full list of chairs and professorships is provided in the table *(below)*.

Chair or Professorship	Holder
Hibernia National Bank/ Edward G. Schlieder Chair (1995)	David York
Claude Bernard Pennington Chair (1998)	Leslie Kozak
George A. Bray, Jr. Chair in Nutrition (1999)	Claude Bouchard
Douglas L. Gordon Chair in Diabetes and Metabolism (2002)	Eric Ravussin
United Companies/Harris J. Chustz Chair in Diabetes (2004)	Abba Kastin
Louisiana Public Facilities Authority Chair in Nutrition	TBA
John S. McIlhenny Endowed Chair in Health Wisdom	TBA
Marie Edana Corcoran Endowed Chair in Pediatric Obesity and Diabetes	TBA
Peggy M. Pennington Cole Endowed Chair in Maternal Biology & the Risk of Obesity	TBA
John W. Barton, Sr. Endowed Chair in Genetics & Nutrition	TBA
Douglas L. Manship, Sr. Professorship in Diabetes (2003)	William Cefalu
George H. Bray Professorship (2001)	Hans Berthoud
John Stauffer McIlhenny Professorship in Nutrition (2003)	Donald Williamson

Strategic Plan 2005-2010

In January 2005, the Center launched its second five-year strategic plan, ***Vision 2010,*** with a bold, challenging new vision statement:

"By the year 2010, the Pennington Biomedical Research Center will be the leading nutrition and preventive medicine research center recognized for the outstanding quality of its research, its contribution to scientific discovery, and its commitment to professional and public education initiatives."

This vision statement raises our sights without altering our goals. The Center continues to be guided by 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

The driving force of ***Vision 2010*** is a set of ten specific priorities supported by a business plan that depends largely on a successful public and private partnership. These ten priorities are defined below with a comment on what has been achieved during the first year of the 2005-2010 plan.

Priority 1 - Establish a Division of Nutrition and the Brain.

The Center has done this, grouping nearly a dozen neurobiologists and neuroscientists into this division and naming Weihong Pan, M.D., Chief of the Division.

Priority 2 - Expand Comparative Biology and Enhance the Transgenic Animal Core.

The Center has secured funding from NIH to expand the comparative biology facility in a first phase of construction of 4,000 square feet. It is expected to be operational in April, 2006. The ultimate goal is an expansion of 25,000 sq. ft., and we continue to search for funding to complete it.

Priority 3 - Increase Expertise in Developmental Biology and Genetic Epidemiology.

One faculty was recently added in the field of genetic epidemiology (Dr. Nathan Markward) and recruitment is under way for the endowed chair position in developmental biology.

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

A phase 1 construction project is dedicated to our Population and Prevention Science program. Currently underway, it is renovating approximately 21,000 sq. ft. of the Conference Center and adding 15,000 sq. ft. of new office and work space to house the growing faculty and staff in this important research area.

However, support for a significant increase in Clinical Research programs requires a new facility. Our goal is to secure funding for a four-floor research building of approximately 80,000 sq. ft. This is a $25 million project that we hope to have underway soon.

Finally, we have renovated a portion of our clinical research space to house a Magnetic Resonance Spectroscopy (MRS) unit. The renovation was funded by the Pennington Medical Foundation. The MRS equipment was purchased with the support from the Department of Defense and became operational in February 2006. This technology will allow our scientists to undertake non-invasive studies of molecular and cellular functions in health and disease conditions.

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

Several new faculty in these area joined the ranks of PBRC late in 2005 and others are being recruited for 2006.

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

We have achieved a significant portion of this priority with the recent acquisition two center grants. William Cefalu, M.D., and his team were able to secure NIH funding for a Center of Excellence in Botanicals and Metabolic Syndrome. In partnership with Rutgers University, the center will focus on molecules that may have benefits for the prevention and treatment of diabetes and metabolic syndrome. Likewise, Eric Ravussin, Ph.D., and a group of PBRC faculty were awarded a Clinical Nutrition Research Unit grant focusing on “Nutritional Programming: Environmental and Molecular Interactions”.

More information on these centers is included in separate reports later in this document.

Priority 7 - Expand the post-doctoral program.

The faculty is currently examining the postdoctoral and mentoring programs with the aim to strengthen and improve them. Specific goals of the Division of Education include the submission of a new post-doctoral training grant application to NIH to increase the scope of the current T 32 NRSA, conducting seminars on grantwriting and career development, and enrichment of the mentoring programs.

Priority 8 - Expand Community and Professional Education Efforts.

The Division of Education has expanded its Community and Professional Education Efforts by developing a website based collection of nutrition educational materials currently being used by parish extension agents and school teachers conducting nutrition and health education seminars throughout Louisiana. This collection is called the "Pennington Nutrition Series" and can be found on the Pennington Biomedical Research Center and LSU Ag Center web sites. Dr. Heli Roy of the PBRC Division of Education and a faculty at the LSU Ag Center has spearheaded this project. Along with this effort, PBRC has hosted two Scientific Symposia this year that have attracted international scientists to Baton Rouge. The themes of these meetings, by invitation only, were: Prevention of Weight Gain and Weight Regain; and Physiological and Biological Properties of the AgRP-MCR Pathway. Finally, the Division hosted a four-day course in "Statistical Applications for Genetic Epidemiology" taught by Dr. Robert Elston and Dr. Courtney Gray-McGuire from Case Western and designed to train scientists to conduct population based genetic research.

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

We have identified strategic partners and have completed a feasibility and marketing study in collaboration with consultants. This planning effort will soon tell us whether establishing such a center could be workable and self-sustaining as well as whether it would significantly enhance our research. Indeed, while serving the community, the facility should align with the Center's research mission, particularly in providing new research opportunities for the Clinical Research and the Population and Prevention Science programs of PBRC.

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

We continue our efforts to ensure our scientists have the support necessary to conduct their research, manage their resources, and continue to apply successfully for research grants.

Vision 2010 estimates that the five-year plan will necessitate expenditures totaling $350 million. It anticipates growth in overall operational revenue from about

$45 million in 2005 to $65 million per year by 2010; a growth in faculty from 70 to 100, and a growth in total employment from 600 to 950. The plan calls for an increased state allocation - an additional $3 million per year. This $15 million increase in state appropriation would be matched by an additional $60 million in revenues generated by PBRC from a number of sources outside the State of Louisiana.

Facing Unforseen Challenges

By a number of indicators, our first Strategic Plan covering the period 2000-2005 was a success. We anticipate that the ongoing planning effort covering the period from 2005-2010 will be characterized by a series of important advances. The latter plan was, however, developed many months prior to the devastating effects of the hurricanes Katrina and Rita that hit the State of Louisiana so hard. The Center must now operate under the constant threat of state budget cuts or, at best, zero-growth budgets. Moreover, our scientists must compete for funding in an environment defined as the worst in 36 years in a recent American Association for the Advancement of Science assessment of the fiscal year 2006 NIH budget.

Nonetheless, we believe that the future of the Pennington Biomedical Research Center continues to look bright for a number of reasons. We have been able to recruit several distinguished and productive faculty over the last two years. Our six Research Divisions and our Division of Education are doing quite well. The two NIH five-year center grants that we secured in 2005 will contribute enormously to the quality of our infrastructure and the productivity of our science. They will also support our efforts to maintain a constant dialogue between the basic science and human-based research. We have at our disposal five endowed chairs that are not filled at this time. This constitutes an important asset in our efforts to recruit competent and productive scientists. Our scientists publish regularly in key journals and their research enjoys a high rate of citations on the part of colleagues in the scientific community around the world. During the period covered by this report, i.e. the years 2004 and 2005, the operating budget of the Center increased by 40%, a clear indication that we are on a growth path.

PBRC will face serious challenges in the coming years, particularly in the context of the budgetary constraints of the State of Louisiana. However, with the support of the dedicated board members of the Pennington Medical Foundation and the Pennington Biomedical Research Foundation, the local business and philanthropic communities, and our corporate partners at the national level, we are confident that we will be able to surmount these challenges and actually thrive. To this end, a focus on the pursuit of excellence will continue to be the key to our success.

RICHARD ROGERS, PH.D.
Associate Executive Director
of Basic Research

DOUGLAS BRAYMER, PH.D.
Professor

DAVID YORK, PH.D.
Boyd Professor

Status of the Basic Research Programs

The Center's Basic Research programs were led by Dr. David York for most of this reporting period. In July, 2005, Douglas Braymer, Ph.D., assumed the position of acting director. In February, 2006, Richard Rogers, Ph.D., assumed the role of Associate Executive Director for Basic Research.

Organizational Growth – The last two years have been an eventful and successful time for the Center's Basic Science area. We have continued to grow with a faculty that now numbers 41 divided over three divisions. The divisions of Experimental Obesity, Functional Foods and the newly-created Nutrition and the Brain were all reviewed by external advisory panels this year. There are currently seven Research Cores: Cell Culture, Comparative Biology, Genomics, Microscopy, Animal Metabolic & Behavioral, Proteomics and Transgenics. These cores have increased the productiveness of the research programs by providing specialized equipment and technical assistance.

Funding Success – The Basic Science Area has received several new grants in the last year alone from a number of agencies including the National Institutes of Health, the National Science Foundation, the American Diabetes Association and the United States Department of Agriculture. PBRC has been successful in obtaining two Center grants: a Botanical Center grant and a Clinical Nutrition Research Unit grant. These two Center grants are primarily in the Clinical Area but they also benefit the research programs in Basic Science. The expansion of the containment areas of the Department of Comparative Biology was also funded by a National Institutes of Health grant. Funds provided through the Pennington Biomedical Research Foundation have resulted in the naming of the William Hansel Laboratory of Cancer Prevention and The John S. McIlhenny Laboratory for Botanical Research.

Cultivating the Future – Graduate training has been an increasing area of emphasis with a growing number of Postdoctoral Fellows. Some are supported

by the National Institutes of Health T-32 Training Grant which was obtained through the leadership of Dr. David York and Dr. Philip Brantley, and others are supported by individual research grants. Graduate student training, in cooperation with Louisiana State University, has resulted in the production of several doctoral degrees from research performed in the laboratories of the Pennington Center.

Broader Expertise – The Center has successfully recruited five outstanding scientists and an exceptional Director of Comparative Biology. Dr. Abba Kastin is a senior investigator who is internationally respected for his research on the blood brain barrier and also for his research on peptides with functions in the central nervous system. He is also the Editor of the journal, Peptides. Drs. Weihong Pan, Alberto Travagli and Kirsteen Browning have also joined the Nutrition and the Brain Division. Dr. Nikhil Dhurandhar has joined our faculty and will contribute to our knowledge of viral causes of obesity. All of these investigators are well-funded and bring new areas of expertise to the Center. The new Director of Comparative Biology, Dr. Barry Robert, has overseen the expansion of this department, as well as establishing his own research program on fibrosis of the peritoneal membrane caused by chronic peritoneal dialysis..

In the aftermath of Hurricane Katrina, this year has brought challenges to the Pennington Biomedical Research Center in our efforts to provide assistance and laboratory space to the displaced students and faculty of the LSU Health Sciences Center. This effort has created a silver lining by increasing collaborations between investigators of the two institutions. These collaborations have, in some cases, involved strengthening collaborations that were already in existence. In other instances, new interactions have been forged between labs that had not interacted before. It has been a true learning experience for all parties involved.

The Basic Science area has made good progress toward achieving the goals that are part of the Center's strategic plan, Vision 2010. The Division of Nutrition and the Brain has been established and the number of postdoctoral fellows has increased. The expansion of Comparative Biology is a goal that will hopefully be achieved in the next couple of years. New faculty coming on board in the next few months will allow us to achieve the goal of increased expertise in Genetic Epidemiology. Basic Science has accomplished many goals in the 17 years of its existence and has grown into one of the leaders in the area of nutrition research. The next few years will bring about even greater achievements.

Tom Gettys, Ph.D.
Division Chief
Experimental Obesity

Division of Experimental Obesity

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

Status Report

Obesity is most simply defined as excess accumulation of adipose tissue and it occurs when energy intake chronically exceeds

energy expenditure. Regulatory systems maintain energy balance by continuously modifying energy intake and expenditure relative to energy reserves. Dysregulation of this regulatory network compromises the ability to match energy intake and expenditure, and ultimately leads to excess accumulation of adipose tissue. The faculty of the Division are devoted to understanding the regulatory systems and communication networks which control energy balance.

A second unifying theme within our division is the use of genetically modified animal models to explore how specific genes affect the components of energy balance. These models include targeted gene disruption, transgenic overexpression, and naturally occurring mutations of specific genes. The common goal of these studies is to assess the role of specific genes in energy homeostasis and expand our understanding of how specific genes function to modify energy intake and/or expenditure. The reverse approach is also used in genetic mapping studies, where strain variation in specific components of energy balance are used to map the genetic basis for the phenotypic differences. With the recruitment of Dr. Nikhil Dhurander to the Pennington Biomedical Research Center this year, we have expanded the Division's perspective to include studies of the viral etiology of obesity. Dr. Dhurander makes a compelling case that infection with specific viruses facilitates the development of obesity by altering the adipogenic potential and endocrine function of adipocytes.

The creation of the Division of Nutrition and the Brain during the last year necessitated a redistribution of faculty between that division and the Division of Experimental Obesity. However, the study of obesity and energy balance are multidisciplinary by nature, so nearly all faculty within these two divisions are involved in collaborative studies that utilize the complementary expertise within each division. This has led to significant cross fertilization between the divisions with respect to ideas, experimental approaches, and technology. An important example is the development of a live cell imaging platform to study signaling events in cultured cells by Drs. Richard Rogers and Gettys. Collaborative studies between Drs. George Bray and Rogers have led to the development of methods to measure heat production from brown adipose tissue in living animals, and produced significant advances in our understanding of the central mechanisms regulating the process. A significant shared need is the recruitment of additional expertise in signal transduction and cellular signaling. This need was also identified as a priority in our recent center-wide strategic planning process.

The 14 faculty within the Division are supported by 25 extramural grants from the National Institutes of Health (NIH), U.S. Department of Agriculture, and the American Diabetes Association. Some of our junior faculty, who obtained their first independent funding in recent years, are approaching submission deadlines for competing renewals. Important divisional

goals for the upcoming year are to provide mentoring support for these renewal applications and assist our remaining unfunded junior faculty in obtaining initial independent support.

The Pennington Biomedical Research Center was awarded two NIH Center Grants during the past year, and faculty from the Division played essential roles in development of both successful applications (see center reports in this issue). The Center Grants are especially important to the Division in that they support and expand the capabilities of the Center's Genomic Core Facility and Transgenic Core Facility and will establish a Molecular Mechanisms/Cell Signaling Core facility. The Genomic Core provides essential support services to all faculty within the Division. One of the new center grants, an NIH Clinical Nutrition Research Unit (CNRU), provides support for the Transgenic Core to add additional staff with molecular biology expertise to assist faculty in developing and preparing constructs for pro-nuclear injection. As new discoveries are made and new target molecules are identified, the enhanced capabilities of the Transgenic Core will improve the ability of Divisional and Center faculty to develop new genetically modified animal models and test hypotheses concerning the in vivo function of their molecule. In addition, the support provided by the CNRU for establishment of the Molecular Mechanisms Core will expand the technical repertoire and associated questions faculty within the Division can address in their research programs.

The small animal phenotyping facilities located within the Comparative Biology Core provide important tools for faculty within the Division to study nutrient partitioning and energy balance in their various animal models. Use of these facilities has expanded over the last two years so that we are near capacity on certain components of the system. The consensus of faculty within the Division is to commit divisional resources to upgrading and expanding our phenotyping facilities to improve measurement of food consumption and provide the ability to measure heat production from specific organs using implantable miniaturized telemetry probes. These investments will enhance the ability of faculty within the Division to better understand how specific components of energy balance are being affected in the animal models that are central to the work in which each of us are engaged.

MICHAEL LEFEVRE, PH.D.
Division Chief
Functional Foods

Division of Functional Foods

Mission – *The application of cutting edge technologies to identify bioactive compounds that affect metabolic processes relevant to specific chronic diseases; discover the mechanistic basis of action for these compounds; and determine the health benefits of specific foods and food components in clinical studies.*

Status Report

Research interest and activities in "functional foods" - food items and their components which provide additional health benefits beyond that of meeting nutritional needs - continues to expand

nationally and internationally. Excitement in this research area is driven by desires to further understand the role that a healthy diet plays in the mitigation of chronic diseases including cardiovascular disease, obesity, diabetes, cancer, physical decline, and stress.

The Pennington Biomedical Research Center has established a strong research portfolio in the functional foods arena. This research portfolio is well balanced with respect to both discovery and mechanism oriented basic research and efficacy and application oriented clinical research.

Previous clinical studies have included those on the health promoting effects of individual fatty acids, plant sterols, a Mediterranean style diet, dairy products, rice bran oil, and nuts. Much of our recent clinical research activities have continued to build upon our established reputation to plan and conduct well-controlled feeding trials.

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

A strength of our clinical program is that it conducts high quality, hypothesis driven, industry sponsored trials. In support of new product development, controlled feeding trials have examined the effects of novel food processing methods or unique combinations of ingredients on cardiovascular disease-related endpoints. Other industry sponsored trials have examined the effects of herbs, herbal combinations, and/or novel food ingredients on features related to obesity. Indeed, the Center's reputation in the area of clinical obesity research continues to attract industry interest as companies seek to demonstrate the efficacy of weight loss or establish mechanisms of action for food products directed at weight management.

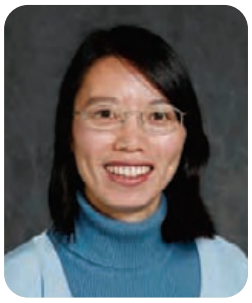
In 2005, the Division's basic science program was substantially expanded with the establishment of a NIH funded Botanical Research Center (see Centers of Excellence reports within this issue). This five-year program, which is shared with the Division of Nutrition and Chronic Disease, will pursue an integrated understanding of the molecular, cellular and physiological mechanisms by which select botanicals may prevent or reverse the development of insulin resistance. The Botanical Research Center consists of three separate research projects, a training component to develop new scientists in the area of functional foods, and a "discovery" component designed to identify new botanicals that may prove useful in the management of the metabolic syndrome. Importantly, the Botanical Research Center involves collaborations between Pennington Biomedical Research Center, Rutgers University, The Pennsylvania State University, and LSU Agricultural Center, which allows our Division scientists to directly interact and

work with leading scientists at other institutions.

As the Division looks to the future, it is important that it continues to build on its existing strengths in the areas of carbohydrate and lipid metabolism and energy and food intake regulation. Important in this process is the continuing development of functional foods related research in other research divisions at the Center. This is greatly facilitated by pilot and feasibility grants funded through both the Botanical Research Center and Pennington Biomedical Research Center institutional funds. In 2005, more than $150,000 was awarded to junior faculty to explore novel hypotheses or to generate important preliminary data in support of grant applications. Because of the modest size of this division, it will remain a goal for our division to continue to interact closely with the Center's other divisions on multiple research priorities through sharing expertise and technologies.

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

Richard Rogers, Ph.D.
Division Chief
Nutrition and the Brain
2005-2006



Weihong Pan, M.D., Ph.D.
Division Chief
Nutrition and the Brain
Appointed March 2006

Division of Nutrition and the Brain

Mission – *to become one of the world's finest, best respected and best recognized research programs dedicated to understanding the role of the nervous system in the control of energy balance in health and disease.*

Status Report

The Pennington Biomedical Research Center and the State of Louisiana have worked for more than ten years to recruit a faculty and construct facilities with a potential to achieve our mission. The latest development was the formal establishment in 2005 of the Division of Nutrition and the Brain, meeting one of the Center's strategic priorities.

The initial core of what could be called "neuroscience" at the Center consisted principally of Dr. George Bray, the first Executive Director of the Center (1989-1999), followed by David York, Ph.D. and Hans Berthoud, Ph.D. (arriving in 1991). It is almost impossible to write a paper dealing with autonomic involvement in energy homeostasis without citing work done by these Center scientists during the last ten years.

Our current faculty continues to build on this earlier research as well as venture into new areas of investigation. Richard Rogers, Ph.D. and Gerlinda Hermann, Ph.D., were recruited in 2002 to add

specialized in vivo physiological, and in vitro imaging expertise to the list of tools available to Center investigators. With the assistance of the Pennington Medical Foundation, they have firmly established in vitro live cell imaging as a technique used here by neuroscientists and cell biologists.

Roy Martin, Ph.D., also Chair of Human Ecology on the main Louisiana State University (LSU) Campus, arrived in 2002 to investigate nutrient detection mechanisms. Alberto Travagli, Ph.D. and Kristeen Browning, Ph.D. joined the Center in 2003 to provide a strong in vitro neurophysiological presence to the Division as well as to provide a basis for the study of Central Nervous System (CNS) control over pancreatic function. Greg Holmes, Ph.D., (2003) investigates the nature of spinal cord injury effects on autonomic control. Greg also manages the imaging and instrumentation core facilities for the Center. Chris Morrison, Ph.D. (recruited in 2003) has versatile training in histochemical methods for detecting transduction intermediates in hypothalamic circuits that regulate nutritional homeostasis. Drs. Weihong Pan and Abba Kastin arrived in 2004. Their seminal work on blood-brain-barrier physiology is directly applicable to questions of cytokine [leptin and TNF, for example] access to the brain. Answers to these questions bear directly on theories of the development of resistance to the action of cytokines. The faculty is also engaged in numerous "cross-division" collaborative relationships within the Center and also maintains sub-contracting relationships with investigators outside the Center.

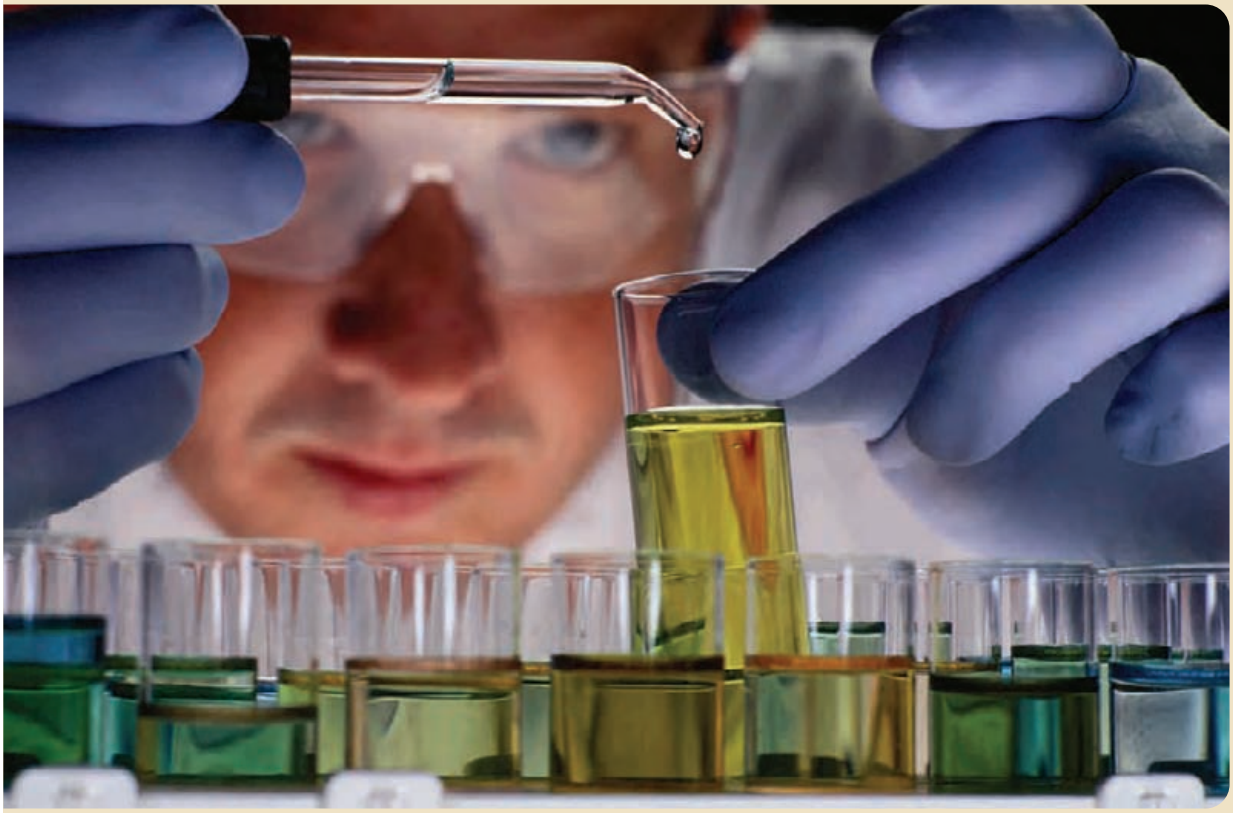
The eight laboratories in the Division occupy approximately 15,000 square feet of research space on campus. The Center has been generous in its start-up packages for faculty and has been successful in efforts to obtain core equipment from state and federal granting agencies. Major Core facilities include a two-photon confocal imaging system [Zeiss 510], a histological processing core, and a stable isotope [GCMS] core. The Comparative Biology Core facility houses laboratory animal care as well as most of the significant instrumentation required for behavioral and whole animal metabolic studies. Further, the Transgenic Core is contained within Comparative Biology. It is our belief that in combination with the resources of the Center's Core Services, the individual laboratories comprising the Division are very well equipped.

The faculty is reasonably well-acquainted with neuronal signal transduction mechanisms. It is clear that most of the initial advances made in unraveling signal transduction problems are made in cell culture models. We lack senior expertise in this area. It is very likely that mechanisms of agonist resistance and conditional reflex [and agonist] gating involve complex interactions between transduction mechanisms that will be solved initially in neuron cell culture. This is a priority recruitment target. On average, funding in the Division is good [approximately $3 million/yr],

though uneven. The senior faculty is, for the most part, very well funded. However, some of the junior faculty are not yet funded and as a result, not on track to become independent. As a means of achieving the full potential of our newest colleagues, the Center and its faculty are committed to a plan to emphasize mentoring relationships and to improve support to junior faculty.

Our facilities are near capacity. Although a major expansion of the current facility will take place shortly, it is clear that this, too, will be under pressure soon. Since practically all surgical, behavioral and metabolic procedures on chronic animal models are performed in this space, this situation represents a potentially serious obstruction to productivity in the Division.

Our neuroscientists have had a difficult time recruiting and retaining quality post-doctoral fellows. One of the reasons for this is that neuroscience in general and neurophysiology in particular often requires a detailed and well-integrated knowledge of complex instrumentation, surgical procedures, histochemical, molecular biological and behavioral methodologies. The research activities in the Division are strongly weighted toward the neurophysiological. Unless a candidate for post-doctoral training in our division already possesses a significant background in some aspect of neurophysiology, they will be ill prepared to work productively in many of the Division's laboratories. To help rectify this situation, Division faculty are crafting an application for an NIH [T32] fellowship training program.



Status of Clinical Research and Population Science Programs

Teamwork – Clinical research is a collective effort. The incredible productivity of the inpatient and outpatient units reflects the contribution of a multidisciplinary team, including physicians, scientists, psychologists, dietitians, kinesiologists, study coordinators, nurses, phlebotomists, clinical chemists, pharmacists and many more disciplines.

Our clinic operation is a well-oiled machine, and in the last year we housed more than 28 studies, of which 15 were newly initiated trials. Each day, on average, 85 volunteers come to the outpatient clinic for assessments and 40 volunteers per week are seen for intervention visits (Figures 1, 2). Our census on the inpatient unit averages 6 per night. The growth (our first clinical study was initiated in 1992) and success of this effort reflects the high regard in which the Center is held in the community (Figure 3).

Although our drawing area is comprised of only 450,000 people, our recruitment record is on a par with large cities with whom we collaborate on multicenter studies. Minority enrollment is also well-represented, an attribute of pride among our staff (Figure 4). All this reflects the esteem with which the Center is held in the community and endorses our commitment to ethical and highly proficient conduct of clinical research.

Scope – Our clinical research spans physiological studies, clinical trials with a focus on pharmacologic, dietary and behavioral interventions, and studies on populations, both epidemiologic assessments and interventions. This "spectrum" of research at the Center provides a rich academic environment and offers a great advantage - the opportunity to interact with scientists in different disciplines around a common theme.

Clinical research is not a stand-alone operation. Translating findings from the basic science laboratory into clinical applications and investigating clinical observations more thoroughly through animal and cell models in the basic laboratories is essential and our great strength at the Center. We have recently been awarded two center grants, the Botanical Research Center and the Clinical Nutrition Research Unit (CNRU), that reflect this strength. The theme of the Botanical Research Center focuses multidisciplinary efforts on how botanicals could effect the metabolic syndrome. Similarly, the theme of the CNRU, Nutritional Programming, engages both basic and clinical scientists.

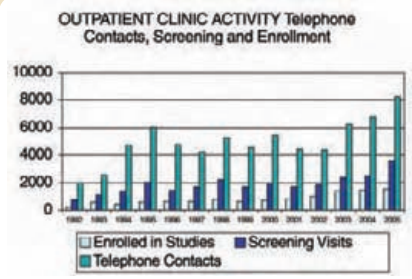


Figure 1

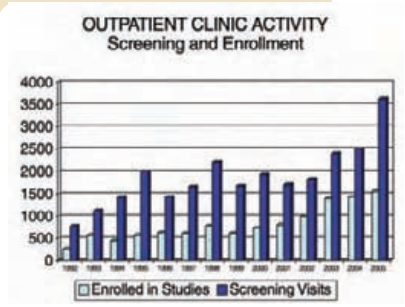


Figure 2

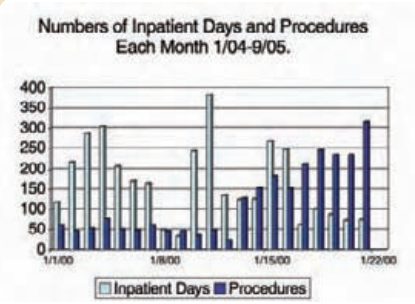


Figure 3

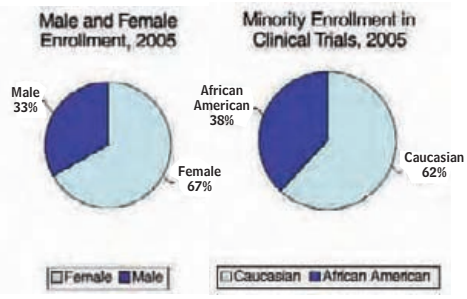


Figure 4

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

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

Facilities – Bursting at the seams, the clinical research efforts now spill over into 6 temporary units and are scheduled to occupy two additional trailers in 2006, bringing the total to 49 offices housed adjacent to our clinical unit. An addition to the existing clinical building has been planned that would double our current capacity to conduct clinical research studies. We are looking forward to consolidating our Population Science faculty and research staff in a new, 50-office wing to the Conference and Education Center. This facility will allow the recruitment of additional faculty in Population and Prevention Science, thus expanding the impact of this program. Another exciting expansion is the addition of Magnetic Resonance Spectroscopy (MRS) to our clinical facilities. We have always been proud of our superb facilities in assessment of energy balance and metabolism and our facilities for delivery of interventions; however, this new MRS technology will propel our research efforts enabling the study of in-vivo biochemistry and metabolism of muscle and liver.

Prognosis and plans for the future – We are well positioned for future success. Our chosen mission reflects the vision of our generous founder, Doc Pennington, but also addresses a great health need, for we are amidst a great epidemic of obesity. Diabetes and the nutritionally-related chronic diseases remain the leading causes of mortality in the developed world. Research in nutrition is a key to address these major public health problems. Clinical research is an essential component to address this need.

Nationwide, there is great concern regarding the future of clinical research. In academic health centers, the imperative of providing health service often overwhelms the role of clinical research. Clinical research is not an easy scientific path. At PBRC we are committed to assuring an academic home for this discipline. To that end, we are fortunate to have access to sister institutions in the LSU System. Our goal is to develop stronger ties to the LSU A&M Nutrition, Psychology and Kinesiology programs, and the LSU HSC Physiology and Medicine education programs. These alliances can be win-win opportunities for the partners, as the Center's research base can be used to mentor the clinical researchers of tomorrow.

Division of Clinical Obesity and Metabolic Syndrome

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

Status Report

The Division of Clinical Obesity and the Metabolic Syndrome was separated from the Division of Nutrition and Chronic Disease in 2002 to reflect the large program in clinical obesity, metabolism and behavioral medicine. Dr. Bray was named Chief of the Division and Dr. Donald Williamson the Deputy Chief. The faculty members assigned in part or wholly to the division include five Professors, five Associate Professors, five Assistant Professors and five Instructors. In most

cases, these individuals also participate in other divisions. A number of faculty members have moved to take other academic positions, reflecting the quality of the faculty and the enthusiasm with which they were recruited away. Among the faculty members, Donald Williamson, Ph.D., has been named John McIlhenny Professorship and Catherine Champagne, Ph.D., has been named to head the Center's Women's Nutrition Program. At the level of new facilities, construction has started on the Population and Prevention Science building and will be complete by the middle of 2006. A badly needed building for expansion of the clinical program has been put on hold. In the programmatic area, two new National Institutes of Health (NIH) center grants have been awarded to the Pennington Biomedical Research Center. The Clinical Nutrition Research Unit (CNRU), with Dr. Ravussin as the Principal Investigator, and a Botanical Research Center grant, funded to Dr. William Cefalu as principal investigator, have both begun operation (see center reports in this issue). The division is abundantly funded through a variety of external granting mechanisms. These include NIH funding of the following projects: 1) Diabetes Prevention Program Outcomes study (DPPOS); 2) Look AHEAD (Action for Health in Diabetics); 3) Weight Loss Maintenance Project (WLM); 4) Prevention of Obesity Using Novel Dietary Strategies (POUNDS Lost); 5) Healthy Transitions (Peri-menopausal study); 6) Prevention of Obesity after Smoking Cessation; 7) Health Improvement Program (HIP) for Teens; 8) Wise Mind; 9) CALERIE (Calorie Restriction); 10) a Clinical Nutrition Research Unit (CNRU).

The U.S. Department of Agriculture is funding studies on 1) Dietary Fat and Obesity; 2) The Delta Nutrition Intervention Research Initiative (DELTA NIRI); 3) Longitudinal Study of the predictors of obesity; and 4) Louisiana (LA) Health.

The State of Louisiana is funding the Louisiana Obese Subjects Study (LOSS), which is a study of the effectiveness of intensive medical management to promote significant weight loss in obese patients. And finally, the U.S. Department of Defense is funding two projects on weight control for active duty and reserve soldiers in the U.S. Army.

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

WILLIAM CEFALU, M.D.
Division Chief
Nutrition and Chronic Diseases

Division of Nutrition and Chronic Diseases

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

Status Report

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

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

The study of cancer in the Division has received national attention over the last several years because of the research from investigators in the William Hansel Cancer Prevention Laboratory. In a truly landmark study, this group has shown that conjugates of lytic peptides with a 15 - amino acid segment of the beta chain of CG or with LHRH are capable of targeting and destroying prostate, ovarian and breast cancer cells and their metastases, all of which express LH/CG and LHRH receptors in vitro and in vivo. This finding will have tremendous clinical applications and this novel treatment is now patented. Further, the National Cancer Institute (NCI) has accepted the work in its RAID (rapid advancement) program. NCI will manufacture greater quantities of the compound and will carry out many of the activities necessary to prepare application to the Food and Drug Administration (FDA) for human clinical trials.

The DNA Damage and Repair Laboratory continued its studies on the S3 protein that appears to interfere in the removal of highly mutagenic sites in DNA known to be involved in the onset of cancer. They have shown that S3 binds to DNA lesions with a very high affinity, and in doing so prevents access to DNA Repair enzymes. Through Hidden Markov modeling and SNP analysis, a putative DNA binding site was identified. Site-directed mutants of this site eliminated the binding to mutagenic sites in DNA. Notably, using iRNA technology, they found that "knockdowns" of S3 protected human cells from DNA damage.

Several programs in the Division, many of which have a special interest in gender and racial issues, are addressing cardiovascular disease and the associated risk factors. Investigators in the Division are concluding the analysis phase of the GET-READI (Gene-Environment Trial on Response in African-Americans to Dietary Intervention) for Heart Health trial. In the GET-READI trial, investigators are endeavoring to identify both genetic and non-genetic factors responsible for individual differences in heart disease risk factor responses to

recommended heart-healthy diets. Results from this study will allow for further researched focused on the goal of matching dietary interventions to underlying genetic makeup.

In addition to the GET-READI Trial, risk factors related to women's health are being addressed by investigators in the Division. The Women's Health Eating Behavior and Smoking Cessation Program is an NIH funded laboratory that has targeted a number of cancer and cardiovascular risk behaviors and other health-related factors that are particularly salient to women. These include smoking and smoking cessation, weight gain and obesity, fat and other specific macronutrient appetites and intake, female sex hormones, and menopause. This laboratory has developed and obtained a copyright for the Macronutrient Self-Selection Paradigm© (MSSP) and the Food Preference Questionnaire© (FPQ) for the accurate assessment of fat and other macronutrient intake and fat preference. Results from pre- and post-menopausal female smokers enrolled in the STOP Program (Smoking Treatment/Obesity Prevention) showed that both groups of women significantly increased their intake of high-fat, high-sugar foods following smoking cessation. Foods that are high in both fat and sugar content are most likely to be associated with hyperphagia and weight gain and therefore may significantly contribute to the weight gain that is often observed in women following smoking cessation.

In addition to the above, the Division continues an outstanding track record of funding and productivity in other related areas. The Epidemiology of Chronic Disease program has several federally funded initiatives involving areas encompassing Louisiana and the surrounding states whose focus is to identify nutritional health problems and to test interventions to remedy those problems. These include the Delta-NIRI study funded by the U.S. Dept. of Agriculture, which researches the nutrition and public health needs of the residents of the Lower Mississippi River Delta region, and The Louisiana Health Consortium, which promotes health delivery and appropriate lifestyle modification for residents of eastern and northern Louisiana parishes. Applications for extended funding to expand these programs is currently underway through the USDA and the US Dept. of Education.

Healthy lifestyle interventions also are currently underway. Building on the success of the earlier Dietary Approaches to Stop Hypertension (DASH and DASH-Sodium) as well as the Premier Lifestyle Interventions studies sponsored by NHLBI, our current Weight Loss Maintenance Study (WLM) seeks to determine effective means by which weight loss may be continued for extended periods. Funding for a continuation of this program is currently being sought through the NIH.

In recent years, there has been growing public interest in the use of stem cells for the repair and regeneration of failing tissues. The Stem Cell Laboratory has emerged to address the fundamental questions relating to adult or somatic stem cells isolated from a variety of organs and

ERIC RAVUSSIN, PH.D.
Division Chief
Health and Performance Enhancement

species. Five investigators have joined forces to focus their inter-related expertise on the isolation, characterization, and manipulation of adult stem cells. Independent studies are underway to identify novel mechanisms regulating the imprinting of genes in stem cells, the role of stem cells in wound healing, and the potential application of human adipose-derived stem cells for tissue engineering. The Stem Cell Laboratory is pursuing multiple funding mechanisms and initiating collaborations with other Divisions and external university and biotechnology partners.

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

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

Division of Health & Performance Enhancement (HaPE)

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

Status Report

The Division provides a vehicle for interactions between three areas of research: "Physiology and Metabolism", "Behavior and Population" and "Genetics and Molecular." Thirteen faculty members contributing to the major research themes of the Division.

The Division receives strong support from many of the core services available to Faculty and post-docs at the Pennington Biomedical Research Center. The following core services are particularly relevant to the research goals of our Division: biostatistics, clinical chemistry, dietary assessment, ingestive behavior and physical activity behavior, stable isotopes, energy metabolism, metabolic kitchen, outpatient unit, inpatient unit, imaging, comparative biology, genomics, microscopy, transgenic, proteomics, muscle phenotyping.

Rich faculty interaction within the Division has produced numerous productive projects, including the development and funding of a grant proposal in response to an RFA on the feasibility, safety and biology of long term caloric restriction in non obese humans. The grant was developed and written as a collaborative effort including many scientists from the Division. It was funded in 2002 for seven years. A second example is our successful attempt to secure a Clinical Nutrition Research Unit (CNRU) from the National Institutes of Health - NIDDK. During the past three years, we have also encouraged the development of our junior faculty and post-doctoral fellows through pilot and feasibility grants as well as travel awards designed to support attendance at meetings focused on a theme of interest to the mission of the Division.

Some of the ongoing research includes the investigation of the inter-individual variability in the adaptation to a high fat diet at the whole body level (physiology) as well as at the cellular level (molecular). Studies of calorie restriction in non-obese humans designed to look at biomarkers of aging are performed and involves an interdisciplinary approach among faculty from the division. Studies of the mechanisms of insulin resistance associated with obesity are investigating the interplay between the adipose tissue and the skeletal muscle both at the physiological and molecular level. Finally, intervention studies have been implemented in schools to prevent or delay the increasing prevalence of childhood obesity.

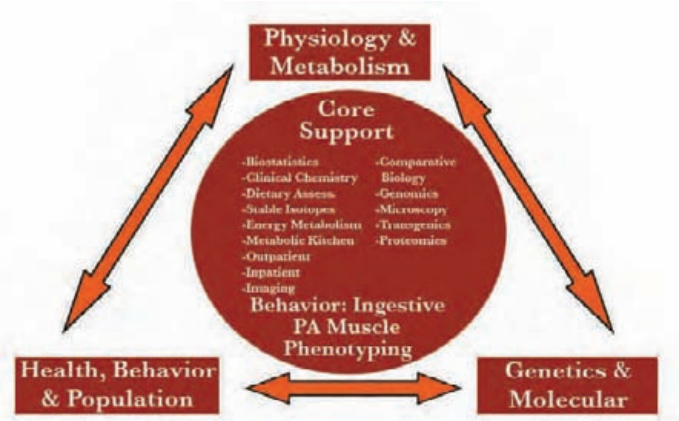


Figure 1 *The Division's research is on the interaction within and among three factors that affect health and obesity.*

Division of Education

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

Status Report

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

PHILLIP BRANTLEY, PH.D.
Division Chief Education

Institutional Postdoctoral Training Program – The Division coordinates many of the activities mandated by the center's Institutional Postdoctoral Training Grant from the National Institutes of Health. Directed by David York, Ph.D., and entitled "Obesity: From Genes to Man," the program supported by this grant is designed to train postdoctoral fellows to become productive research scientists capable of establishing scientific careers that further the understanding of complex interactions between genetic, molecular, physiological and behavioral aspects of obesity. 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 a post-doctoral journal club, ethics seminars and data presentation sessions.

HELI ROY, PH.D.
Associate Professor (adj)

Scientific Symposia Series – The Division continues to organize two 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. Some of our recent symposia are described below.

The fourth in our series of scientific symposia was held in May of 2004. Given the increasing prevalence of metabolic syndrome associated with an epidemic rise in obesity, William Cefalu, M.D., (Pennington Biomedical Research Center), together with D. Grahame Hardie, Ph.D., (University of Dundee), and Roger H. Unger, M.D., (UT Southwestern Medical Center, Dallas), co-chaired a symposium: "Pathogenesis of the Metabolic Syndrome".

The role of exercise in mood, behavior, cognitive function, and food intake was explored in a symposium "The Neurobiology of Exercise", held December 2004 and co-chaired by Hans Rudolf Berthoud, Ph.D. and David, A. York, Ph.D. (Pennington Biomedical Research Center), and Rod K. Dishman, Ph.D. (The University of Georgia).

Proteins that regulate metabolic processes in the hypothalamus and regulate feeding behavior and body weight were explored in a symposium "Physiological and Biological Properties of the AgRP-MCR Pathway", May 2005, co-chaired by George Argyropoulos, Ph.D., (Pennington Biomedical Research Center) and Gregory S. Barsh, M.D., Ph.D., (Stanford University).

Finally, in December of 2005 a symposium focused on the prevention of weight gain and weight regain. Co-chairs for this event were Phillip J. Brantley, Ph.D. and Donald Williamson, Ph.D. (Pennington Biomedical Research Center) and William H. Dietz, M.D. MPH (Centers for Disease Control and Prevention, Atlanta).

Professional Enrichment / Community Education – To update health professionals on contemporary issues, the Division of Education has sponsored several professional seminars. One such seminar was held in February 2004 entitled "The Genomics Revolution? Science, Law, and Policy," a collaboration among PBRC, the Paul M. Hebert Law Center (LSU), and the University of Montréal, Centre for Public Law Research. Program co-chairs were Michael J. Malinowski, Program in Law, Science, and Public Health, LSU Law Center, Dr. Bartha Maria Knoppers, Professor and Senior Researcher, Center for Public Law Research, University of Montreal, and Dr. Claude Bouchard, Executive Director, Pennington Biomedical Research Center.

To encourage and train research skills in graduate students and postdoctoral fellows at LSU, the Center sponsored the 2004 Annual Louisiana State University (LSU) Health Sciences Center Graduate Research Day. Attendees from New Orleans and Baton Rouge campuses met in April to present their research, receive feedback from LSU faculty, and compete for awards.

A recent seminar, held in August 2005, targeted new clinical researchers and provided them an "Introduction to Clinical Research." The purpose of this training program was to introduce newly recruited fellows and faculty to clinical research procedures and to provide general information relevant for preparing grants or initiating clinical research at the Center.

In December 2005, The Pennington Biomedical Research Center hosted a 4-day course in statistical applications in genetics. The course presented the software S.A.G.E. (Statistical Applications for Genetic Epidemiology) developed by the Human Genetic Analysis Resource (H.G.A.R.) in the Department of Epidemiology and Biostatistics, at Case Western Reserve University, Cleveland, Ohio. The development of the software is supported by the National Institutes of Health (NIH).The instructors for the S.A.G.E. course were Dr. Robert C. Elston and Dr. Courtney Gray-McGuire from the Case Western Reserve University, Cleveland, Ohio.

To foster community education and increase awareness of health concerns, the Division of Education has sponsored public events, focusing on educational outreach. An example is the Annual Men's Health Conference, held each spring at the Pennington Conference Center. In April of 2004, a conference was held to highlight worksite wellness programs in Louisiana and their impact on employee healthy and productivity, entitled "CEO's Who Care: Employee Wellness Programs."

In July of 2004 and 2005, high school students from around the country participating in the "National Youth Leadership Forum" met at the Center for a program highlighting careers in medical research.

LSU Agricultural Center – The Division continues to partner with the LSU Agricultural Center and its Division of Education, the Louisiana Cooperative Extension Service. The Extension Service

plays a unique role in both rural and urban parishes in Louisiana. It is an agency devoted to providing research-based outreach education. The objective of the partnership is to provide an effective, efficient means of disseminating information and advice to the people of Louisiana through parish extension agents. The partnership focuses on all aspects of the Pennington Biomedical Research Center's nutrition research findings by ensuring that the results of research are translated into practical recommendations that are made immediately available to the citizens of Louisiana. Dr. Heli Roy from the LSU Ag Center is the Outreach Coordinator and charged with providing culture-specific research information to Extension agents across Louisiana. Much of the information collected now comprises the "Pennington Nutrition Series," a collection of health and nutrition materials that can be found on the LSU Ag Center and Pennington Biomedical Research Center web sites. Materials developed to combat obesity, based on research conducted at the Center, have been made available to all 64 parishes in Louisiana and extension agents have been briefed on many of the latest nutrition related issues by Pennington Biomedical Research Center faculty. Another program launched here at the Center, but with statewide outreach, is "Louisiana On The Move." As part of this program, extension agents have been trained to conduct education sessions to promote physical activity among residents of Louisiana parishes.

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

Future Goals – The Division has plans underway to expand our current institutional postdoctoral training grant and to submit another postdoctoral training grant proposal in 2006. We would like to help increase the number of postdoctoral fellows at Pennington from the current 40 to 75 by 2010.

The Division of Education provided its grant preparation skills to assist the Center in acquiring its first two National Institutes of Health Center Grants in 2005, one designed to explore botanical compounds and one designed to investigate pre-natal casues of obesity (see Centers of Excellence reports in this issue). Staff from the Division wrote the training and

enrichment sections of these proposals, both of which received highly positive reviews. We plan to put these plans (i.e., faculty retreats, newsletters, training grants) into action during the next two years. We would like to continue holding two to three scientific symposia per year. Finding a permanent endowment for our symposium series would help guarantee that we could maintain this schedule. We have already begun work on our next series of symposia, one to be held in April/May 2006 on "Infection, Inflammation and Obesity" and one in October 2006 that will focus on "Botanicals and Cardiometabolic Risk." The Division intends to continue its efforts to provide up-to-date community education programs, directly with its participation in and sponsorship of health fairs and indirectly by its expanding collaboration with the LSU Agricultural Extension Service, to reach a wider audience in and around Louisiana. An educational program addressing the importance of prenatal nutrition to lessen chronic disease risk in adulthood will be developed and made available statewide. Finally, our division will pursue partnerships with outside organizations to explore the opportunity to establish a wellness center on our campus that would allow the Center to offer state-of-the-art wellness programs to the citizens of the Baton Rouge metropolitan area while maintaining a valuable scientific database for Center scientists.


RPE Sc
Very, very
Very light
Fairly light
Somewhat
Hard

ERIC RAVUSSIN, PH.D.
Principal Investigator

Clinical Nutrition Research Unit

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

Center for Research on Botanicals and Metabolic Syndrome

William Cefalu, M.D.
Principal Investigator

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

Center Mission and Goals

The scientific goal of the Botanical Research Center is the pursuit of an integrated understanding of the molecular, cellular and physiological mechanisms by which select botanicals may prevent or reverse the development of insulin resistance, the key pathophysiologic feature of the metabolic syndrome. The Botanical Research Center consists of three (3) specific research projects, an Animal Research Core, a Botanical Core and an Administrative Core. Each of the research projects will evaluate a specific botanical and will assess the effect on pathogenic mechanisms leading to the development of insulin resistance. Specifically, the botanicals chosen for initial study are *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 will be subjected to further studies through a high through-put screening system. Since these leads affect different mechanisms related to the development of insulin resistance and metabolic syndrome, they are very much central to the theme of the Center.

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

It is expected that during the next five years, the Botanical Research Center will promote a collaborative and interactive research environment to establish an internationally recognized center of excellence in the area of botanicals and mechanisms of metabolic disease. It will identify and further study botanicals with potential efficacy in metabolic syndrome, identify their bioactive constituents, standardize and optimize those botanicals, and provide necessary preclinical and mechanisms of action data. The long range goals are to translate the foregoing findings into clinical studies in humans. The center hopes to expand the critical mass of investigators addressing botanical research by identifying, recruiting and mentoring promising young investigators.

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

Basic Research Laboratory Reports

Basic Research at the Center is organized around nine areas, each of which has multiple investigators and laboratories. This section contains reports from each laboratory as outlined in the following list:

Stem Cell Biology

- Stem Cell Biology Laboratory
  J. Gimble, B. Floyd
- Epigenetics and Nuclear Reprogramming Laboratory
  K. Eilertsen
- Regenerative Biology Laboratory
  B. Kozak

Nutrient Sensing

- Adipocyte Signaling Laboratory
  T. Gettys
- Skeletal Muscle Metabolism Laboratory
  M. Hulver
- Endocrinology Laboratory
  S. Smith

Molecular Genetics

- Molecular Genetics and Thermogenesis Laboratory
  L. Kozak, R. Koza, J. Rim
- Taste Genetics Laboratory
  B. Smith-Richards
- Neuropeptides Laboratory
  A. Butler

Human Genomics

- Human Genomics Laboratory
  C. Bouchard, T. Rankinen, J. Brand
- Energy Balance Laboratory
  G. Argyropoulos

Neuroscience

- Neurobiology and Nutrition Laboratory I
  H. Berthoud, H. Zheng
- Neurobiology and Nutrition Laboratory II
  A. Travagli, K. Browning
- Neurobehavior Laboratory
  R. Martin
- Autonomic Neuroscience Laboratory
  R. Rogers, G. Hermann
- Blood Brain Barrier Laboratory I
  W. Pan
- Blood Brain Barrier Laboratory II
  A. Kastin, H. Tu
- Neutrorauma and Nutrition Laboratory
  G. Holmes

Cancer Laboratory

- The William Hansel Cancer Prevention Laboratory
  W. Hansel, C. Leuschner
- DNA Damage and Repair Laboratory
  W. Deutsch, V. Hegde

Experimental Obesity

- Experimental Obesity Laboratory
  D. York
- Dietary Obesity Laboratory
  G. Bray, D. Braymer
- Neurosignaling Laboratory
  C. Morrison
- Functional Genomics Laboratory
  A. Zuberi
- Infection and Obesity Laboratory
  N. Dhurandhar
- Agouti Research Laboratory
  R. Mynatt

Bioinformatics and Statistical Genetics

A. Ptitsyn

Diabetes

- Diabetes and Nutrition Laboratory
  W. Cefalu, Z. Wang
- Antioxidant and Gene Regulation Laboratory
  J. Ye, Z. Gao
- Mechanisms of Diabetes Complications Laboratory
  I. Obrosova

JEFF GIMBLE, M.D., PH.D.

STEM CELL BIOLOGY

Stem Cell Biology Laboratory

Faculty – Jeff Gimble, M.D. Ph.D., Beth Floyd Ph.D.

Research Team – Sanjin Zvonic, Ph.D., Gail Kilroy, Xiying Wu, M.D., Martin Vidal, D.V.M. , Ram Devireddy, Ph.D. (collaborator) , Mandi J. Lopez, D.V.M., Ph.D. (collaborator), Rustin Moore, D.V.M., Ph.D. (adjunct), Sreedhar Thirumala, M.E., Katherine Blalock, Brian Goh

FOCUS

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

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) 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 are conducted with investigators at the LSU School of Veterinary Medicine and the Department of Mechanical Engineering as well with biotechnology industry partners (Artecel Sciences, Cognate Therapeutics, Vet-Stem, Zen-Bio). Studies supported by NIH will determine whether 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.

(b) The characterization of the "proteome" of human ASCs. Proteomics represents the next wave 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. We have identified two major protein classes that are modulated as a function of differentiation. One is the heat shock protein/chaperone family that control protein folding and the ability of the cell to respond to oxidative stresses. The second is the class of secreted proteins known as serine protease inhibitors or serpins. The serpins are of particular interest since they have been implicated as "adipokines" or fat-derived growth factors that control insulin sensitivity.

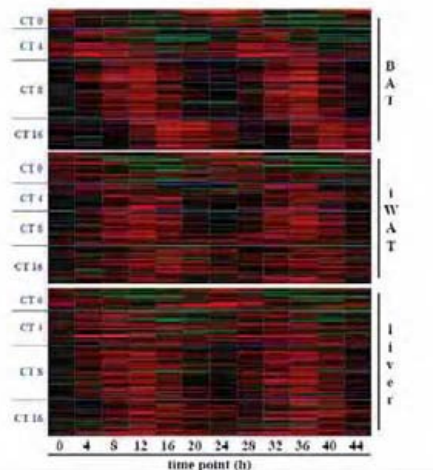
(c) The circadian biology of adipose tissue, bone, and other metabolically active peripheral tissues. Drs. Floyd, Gimble, Mynatt, and Zvonic, together with Dr. Ptitsyn in Bioinformatics, have demonstrated that the transcriptional machinery responsible for maintaining circadian rhythms in the brain exists within bone and fat. The studies are being conducted with NIH support with investigators at Duke University, LSUHSC-Shreveport, and Hebrew University. Studies by other laboratories have found that deletion of the circadian genes can lead to obesity and bone formation defects. 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.

(d) Proteasomal targeting. Dr. Floyd is leading multidiscipline studies examining the pathways of protein turnover in adipose tissue derived stem cells. Her collaborators include Drs. Cefalu, Gimble, and Wang. Her studies have demonstrated that resvertrol, a chemical compound found in grapes and berries, has direct effects on the protein level of PPAR , a transcriptional regulator of adipocyte differentiation. In addition, this compound appears to sensitize adipocytes to insulin action, offering potential benefits to diabetic patients. These studies are supported, in part, through the NIH-funded Botanical Center at the Pennington Biomedical Research Center.

Research in this lab is supported by grants from the 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.
Instructor

Circadian Rhythm Transcriptomics



Epigenetics and Nuclear Reprogramming Laboratory

Faculty – Kenneth J. Eilertsen, Ph.D.
Research Team – Regina Beauvais, Heather Kirk

Focus

To investigate 1) the epigenetic basis of nutritional programming that may occur in utero and contribute to later in life diseases such as obesity, hypertension and type 2 diabetes; 2) methods that reprogram the epigenome in ways that restore developmental and differentiation potential; and 3) epigenetic basis of liposarcoma differentiation.

KENNETH J. EILERTSEN, PH.D.
Associate Professor

Current Projects

Nutritional programming:
Developmental "programming" has been proposed due to observations that associate low birth weight with adulthood hypertension, type 2 diabetes and other features of the metabolic syndrome. The "thrifty phenotype" hypothesis proposes a growth-restricted fetus associated with an undernourished maternal diet is programmed in utero for a life of nutritional hardship. More specifically, the hypothesis maintains that development of a predisposition to diseases such as type 2 diabetes may provide a survival benefit if postnatal nutrition is poor. However, if the postnatal environment does not match the prenatal environment, e.g., the diet is plentiful, developmental responses to an adverse diet in utero may be maladaptive in adulthood. To date, the molecular underpinnings of what constitutes programming have yet to be determined.

There is growing evidence that imprinted genes are promising candidates for developmental effects associated with in utero exposure to maternal diets. For most mammalian genes, two alleles typically contribute equally to the production of a gene product. In contrast, imprinted genes are expressed from one allele (either the allele provided from the father or the allele provided by the mother). Most imprinted genes reside in clusters and are regulated coordinately by complex mechanisms such as DNA methylation. It is possible that adaptations in utero to maternal dietary conditions may be either the silencing of or increasing the expression of monoallelically expressed imprinted genes.

Our lab has been testing the hypothesis that mice exposed to a maternal low protein diet during the preimplantation period of development have altered levels of imprinted gene expression later in life. In other words, imprinted gene expression may become 'fixed' in utero and in a manner that is persistent, possibly predisposing offspring to later in life diseases when the postnatal nutritional environment fails to match the in utero nutritional environment. To that end, we have measured the expression of three paternally expressed imprinted genes (Igf2, Ata3, and Peg3) and three maternally expressed genes (Igf2r, H19, and p57kip2), several of which have known functions related to growth or survival. Interestingly, mice exposed to a maternal low protein diet during the first week of gestation, but whose mothers were switched to a normal chow diet for the last two weeks of pregnancy, were characterized by differentially expressed imprinted genes when compared to controls whose mothers were fed a normal chow diet during the

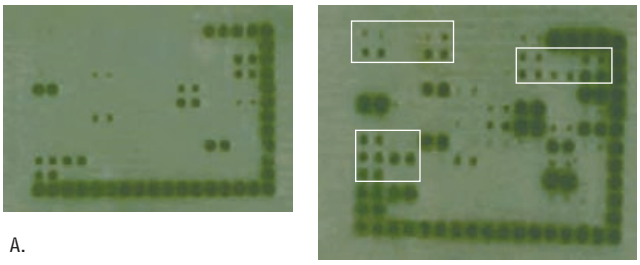
entire pregnancy. Moreover, the observed differential expression was in a tissue specific manner. One possible explanation may be differing patterns of DNA methylation that contribute to the regulation of imprinted genes. Current studies of this are underway. Planned future studies include exposure to a maternal low protein diet for the duration of development through lactation followed by weaning onto a high fat diet to assess programmed imprinted gene expression. These studies will also examine possible correlations with features of chronic diseases later in life.

Reprogramming: A second area of investigation is aimed at identifying mechanisms and methods that restore developmental and differentiation potential of differentiated somatic cells, a process called reprogramming. Reprogramming has been demonstrated by a technique referred to as "Somatic Cell Nuclear Transfer" (SCNT), often referred to in laymen's terms as "cloning." The mechanisms that enable reprogramming by SCNT are poorly understood, but one general agreement is that reprogramming requires some degree of erasure of DNA methylation patterns that help define the function of differentiated somatic cells. Our lab, in collaboration with a biotech company, NuPotential, LLC, is investigating methods to enable the erasure of methylation patterns and restore potential without the use of SCNT. One approach is by seeking novel demethylation activities that may reside in botanical sources. In conjunction with other PBRC and LSU faculty, we have identified three possible sources that may contain this type of activity and are continuing to screen additional botanical sources; isolation and characterization of these activities are the subjects of planned future studies. In addition, we are investigating potential nutritional and metabolic approaches that can restore developmental and differentiation potential of somatic cells in culture and the possibility that small molecules such as interfering RNAs, or other synthetic molecules, may have reprogramming activity.

Carcinogenesis. Lipomas and liposarcomas are among the most frequent benign and malignant soft tissue tumors clinically in the U.S. These fatty tumors derive from cells resembling the adipose derived stem cells. In collaboration with Dr. Jeff Gimble of the PBRC and investigators at Memorial Sloan Kettering Cancer Center, we are using novel approaches to characterize the epigenetic basis of soft tissue tumors. Over the last several years it has become evident that several tumors and cancers are often characterized by DNA that is hyper-methylated. The hypermethylated DNA is typically associated with regions that regulate the expression of genes. Many of these genes, when expressed, function as tumor suppressors. That is, when expressed, they prevent a healthy cell from becoming a cancer cell. When the regulatory region becomes hypermethylated, the tumor suppressor gene, or genes, can be turned off resulting in the formation of a cancer phenotype.

To date, we have screened human liposarcomas or hypermethylated regulatory DNA sequences and have identified over three dozen candidate DNA sequences associated with liposarcomas. (Fig. 1)

Research in this lab is supported by grants from the Clinical Nutrition Research Unit, the Botanical Research Center and the Pennington Medical Foundation.



A. B.

Figure 1 *Representative examples of identified hypermethylated DNA sequences in liposarcomas. Spots in boxes are hypermethylated DNA sequences identified in a liposarcoma sample (B) but absent in normal adipose tissue (A).*

Regenerative Biology Laboratory

Faculty – Barbara Kozak, Ph.D.
Research Team – Jessica A. Manuel, B.S.

Focus

To understand how tissues and organs can be rebuilt after injury or damage.

Current Projects

In general, there are two contrasting responses to injury: regeneration and repair. Regeneration, as opposed to wound healing, is characterized by a lack of scarring, a reconstruction of normal tissue architecture and a regrowth of damaged tissues. A remarkable regenerative capability is characteristic of some invertebrates, such as planarians, and vertebrate species, such as zebrafish and urodele amphibians. However, the phenomenon of regeneration has been almost completely lost in mammals, whose damaged tissues undergo typical wound healing processes characterized by scar formation.

Our studies have shown that Athymic Nude-nu mice display an ability for regeneration in holes punched into their ears, with dermal, vascular, cartilage and muscle regrowth. Moreover, our experiments revealed that the same mice, unlike other immunodeficient, athymic or wild type mice are able to heal skin wounds without scar formation. The process seems to be related to the phenomenon of scarless skin repair observed in mammalian fetuses. The results showed substantial differences between regenerative vs scar-forming mice in the levels of hyaluronic acid, collagen

and pro-scarring cytokines. However, the most striking difference was observed in the immunological status of animals. Our present effort in understanding the ability of Nude-nu mice to undergo regeneration processes has been focused on the interaction between resident cells of the injury site and infiltrating T-lymphocytes.

Regeneration processes require the presence of cells that are able to replace damaged or lost tissues. For example, planarians possess totipotent stem cells, whereas, amphibians have the ability to convert differentiated adult cells into a pool of progenitor cells (dedifferentiation), followed by a process of redifferentiation to replace lost tissues. Growing evidence suggests that most mammalian tissues contain adult stem and progenitor cells that are capable of supporting regenera-tion. However, the origin of the cells taking part in the regeneration process still remains unknown. We have identified a novel source of adult stem cells (ear mesenchymal stem cells - EMSC) in the outer ears of all murine strains independent of their ability for regeneration. EMSC are self-renewing, clonogenic and are considered multipotent, since they give rise to osteocytes, chondrocytes, myocytes and adipocytes (Figure 1). The implication of this research is that EMSC are necessary, but not sufficient, for regeneration. An additional important necessary condition is a cellular environment of reduced T lymphocyte function that is required to promote the repair process. Additionally, this study suggests that EMSC have the potential to function as myocytes and chondrocytes and may be of therapeutic value as a study in progress suggests.

Barbara Kozak, Ph.D.
Assistant Professor

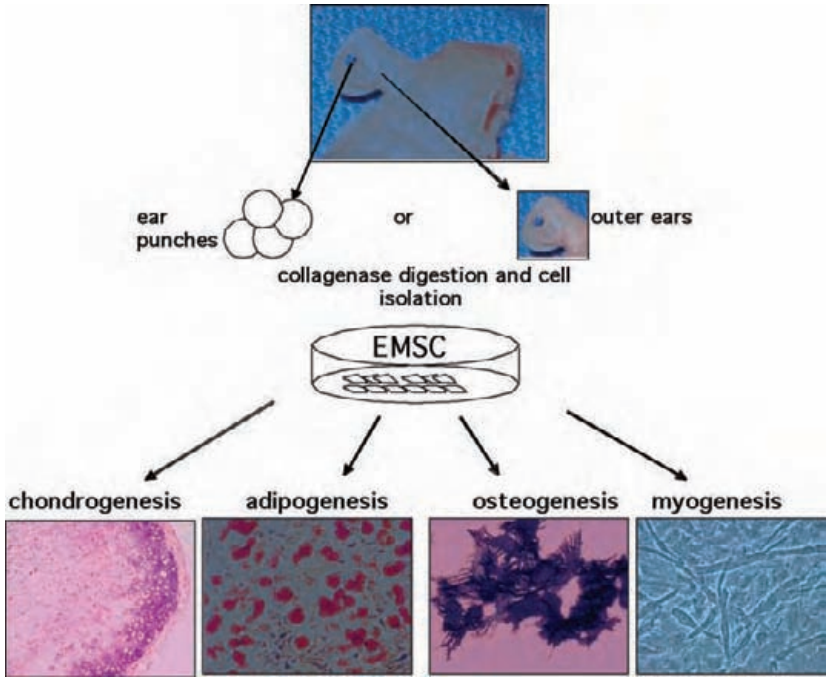


Figure 1 *EMSC isolated from the outer ears or from ear punches differentiate into chondrogenic, adipogenic, osteogenic or myogenic lineage under appropriate culture conditions.*

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

NUTRIENT SENSING

Adipocyte Signaling Laboratory

Faculty – Thomas W. Gettys, Ph.D.

Research Team – Aaron Adamson, Ph.D., Barbara Hasek, Ph.D., Natalie Lenard, Ph.D., Laura Stewart, Ph.D., Yubin Zhang, Ph.D., Tara Henagan, B.S., Anik Boudreau, B.S.

Focus

To investigate central mechanisms regulating SNS outflow to adipose tissue, mechanisms of SNS-dependent remodeling of adipose tissue, and functional consequences of adipose tissue remodeling.

Current Projects

Signaling pathways linking central leptin receptors to regulation of gene expression in adipose tissue – Using mouse lines with targeted disruption of the melanocortin receptor 3 (MCR3) or melanocortin receptor 4 (MCR4), we assessed the role of each component in mediating the anorectic and metabolic effects of leptin, and in regulating the partitioning of nutrient energy between fat and protein deposition. The absence of MCR4 blocked leptin's ability to increase UCP1 mRNA in both brown and white adipose tissue, but not its ability to reduce food consumption. In contrast, deletion of MCR3 compromised leptin's ability to reduce food consumption, but not its ability to reduce fat deposition or increase UCP1 expression in adipose tissue. Repeated measures of body composition over time indicate that the absence of either MCR3 or MCR4 increased lipid deposition and produced comparable degrees of adiposity in both lines. Moreover, modest increases in fat content of the diet (4 to 11%) accentuated fat deposition and produced a rapid and comparable 10-12% increase in percent of body fat in both genotypes. The results indicate that nutrient partitioning, as well as the anorectic and metabolic responses to leptin, are dependent upon integrated but separable inputs from the melanocortin 3 and 4 receptor subtypes.

Regulation of SNS-dependent remodeling of adipose tissue by a novel form of PGC-1 – The SNS integrates the function of metabolic tissues through regulation of transcriptional programs that effect remodeling of the cellular proteome. Evidence has emerged to support the view that PGC1 is the critical transcriptional co-activator linking - 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 PGC1 which produces a truncated protein representing the first 267 AAs of the N-terminus and an additional 3 AAs from the splicing insert. Expression of the N truncated 270 AA protein (NT-PGC1) is dynamically regulated in the context of physiological signals which regulate full length protein. More importantly, its unique domain structure conveys significant in vitro and in vivo properties that enhance SNS-dependent remodeling of adipose tissue. Our goal is to assess the in vivo and in vitro role of this novel protein with respect to how it regulates the functional activity of PGC1 and influences the translation of sympathetic input into adipose tissue.

THOMAS GETTYS, PH.D.
Professor

Dietary Methionine Restriction Extends Lifespan by Limiting Fat Deposition - Calorie restriction (CR) and dietary methionine restriction (MR) extend lifespan to comparable extents in rodents, but do so through opposite effects on metabolic efficiency. The consensus is that CR delays all causes of death by reducing oxidative metabolism and the associated formation of reactive oxygen species (ROS), thereby slowing the accumulation of oxidative damage. In contrast, MR increases lifespan through a mechanism independent of reduced food consumption that involves a significant increase in fuel oxidation and corresponding reduction in metabolic efficiency. Thus, both dietary regimens have a similar effect on fat deposition; CR through limitation of energy intake and MR through reduction in metabolic efficiency. Reduced adiposity improves insulin sensitivity, reduces systemic inflammation, and improves mitochondrial function in peripheral tissues, making a strong case that systemic benefits of reduced fat deposition derive from reciprocal modulation and release of deleterious and beneficial bioactive compounds from adipose tissue. Our studies show that MR reduces adiposity by producing a significant diurnal increase in O2 consumption and fatty acid oxidation in white adipose tissue. These complimentary responses indicate that adipose tissue may be a key target of the mechanism by which MR promotes metabolic inefficiency, limits fat deposition, preserves insulin sensitivity, maintains mitochondrial integrity in peripheral tissues, and increases lifespan.

Research in this lab is supported by grants from National Institutes of Health, American Diabetes Association, Orentreich Foundation

Skeletal Muscle Metabolism Laboratory

Faculty – Matthew W. Hulver, Ph.D.
Research Team – Julie Marchand, M.S., Ryan McMillan, B.S.

Focus

To understand and characterize the role of metabolic proteins in human skeletal muscle and to understand the relationship between whole-body insulin resistance and increased SCD1 activity in skeletal muscle as well as to discern the mechanisms by which SCD1 alters fatty acid handling.

Current Projects

Evidence from our group and others suggests that abnormal skeletal muscle fatty acid metabolism with obesity and type 2 diabetes results in intramuscular lipid accumulation. It is well established that the accumulation of lipids within the skeletal muscle cell impairs the insulin signaling cascade causing insulin resistance. Much effort has been devoted to better understanding how lipids cause insulin resistance with less attention to defining the mechanism(s) responsible for intramuscular lipid accumulation.

This laboratory is currently studying candidate metabolic proteins that we believe are contributing to the dysregulated lipid synthesis in skeletal muscle of obese humans. More specifically, we are studying the role of the lipogenic enzyme, stearoyl-CoA destaurase-1 (SCD1) in the preferential partitioning of fatty acids

Matthew Hulver, Ph.D.
Assistant Professor

toward lipid synthetic pathways as opposed to competing mitochondrial oxidative pathways. We have established that SCD1 is up regulated in skeletal muscle of obese humans and is strongly and positively associated with body mass index, plasma insulin, and muscle triglyceride synthesis (Figure 1). To test the cause and effect relationship between SCD1 and dysregulated fatty acid metabolism in skeletal muscle, we over expressed SCD1 in human primary muscle cells cultured from non-obese human donors. The hypothesis was that the phenotype observed

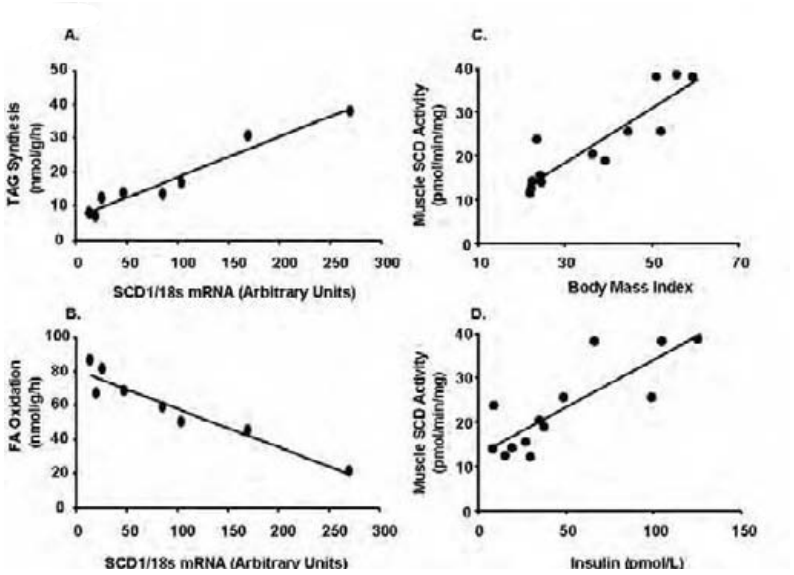


Figure 1

Relationship between muscle fatty acid metabolism and SCD1 expression. Muscle samples were obtained from lean and obese humans with a body mass index ranging from 22-60 kg/m2. Gene expression data were combined with results from in vitro metabolic assays (detailed in Hulver et al. [2003]) to show strong correlations between SCD1 mRNA levels (A) rates of intramuscular triacylglycerol (IMTG) synthesis and (B) fatty acid oxidation. The relationships between SCD1 activity and (C) body mass index and (D) serum insulin levels were evaluated using rectus abdominus specimens that were harvested from a second cohort of subjects.

in skeletal muscle obese humans (reduce fatty acid oxidation, increased triglyceride synthesis) would develop. Over expression of SCD1 indeed resulted in a significant reduction and increase in fatty acid oxidation and triglyceride synthesis, respectively. Moreover, when SCD1 is over expressed in human muscle cells, AMP-kinase and acetyl-CoA carboxylase phosphorylation is reduced, which are the likely mechanism(s) responsible for preferential partitioning of fatty acid towards storage vs. oxidation. This work was published in the October 2005 issue of Cell Metabolism and was featured on the cover of the journal. Currently, my laboratory is focused on three research questions with regards to SCD1:

1. Why is SCD1 up regulated in skeletal muscle of obese humans?
2. What are the mechanism(s) by which an up regulation of SCD1 in skeletal muscle results in suppression of fatty acid oxidation and increased triglyceride synthesis?
3. What role does an up regulation of SCD1 in skeletal muscle play in the development of whole body insulin resistance?

Research in this lab is supported by a grant from the American Diabetes Association and the Pennington Medical Foundation.

Endocrinology Laboratory

Faculty – Steven R. Smith, M.D.

Research Team – Hui Xie, M.Ap.Stat., Shaoyun Wang, M.D., Olga Sereda, M.D., Michele McNeil, M.S., Jana Smith, B.S., Shantele Thomas, B.S.

Focus

To harness multiple experimental approaches to understand the physiological, cellular and molecular connections between diets, particularly those high in fat, and the development of insulin resistance, a precursor to type 2 diabetes.

Current Projects

We are interested in how people differ in their ability to burn fat and the cellular systems that control fuel selection in muscle (i.e. what nutrient cells prefer to burn). We recently discovered that after taking muscle cells out of the body and growing them in a Petri dish, they retain the characteristics of their donors. In other words, cells that burn fat in the Petri dish come from lean, insulin sensitive people and cells that come from obese insulin resistant people are unable to oxidize fat effectively in the clinic. This tells us that a large portion of the inter-individual variability in the risk for developing obesity and diabetes is attributable to fundamental differences in fuel metabolism in muscle cells.

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

These studies are complemented by our studies of fat cells. The fat cell or adipocyte, once thought of as a simple reservoir of energy storage, is now recognized as a hormone secreting endocrine organ. The ability of adipocytes to store and oxidize fats is a critical event in the development of diabetes. If fat cells cannot store fat effectively, fat 'spills over' into the liver and the muscle producing deleterious effects such as insulin resistance.

Our efforts are focused on trying to coax fat cells into burning more fat instead of storing fat. Recent progress in this area came from our clinical studies examining the role of drugs used to treat diabetes. We found that pioglitazone, a drug used to treat diabetes, increases the number of mitochondria in adipose tissue and increases the expression of genes involved in fat oxidation. Ongoing clinical studies are trying to take advantage of the 'bigger engine' for fat oxidation in fat cells and 'mash the accelerator' to help people lose body fat and improve metabolism.

Our interest in adipose tissue can also be seen in our clinical studies of body fat in the peri-menopausal period. We are closely following a cohort of women as they go through the menopause and carefully measuring energy metabolism and body composition. Quite surprisingly, we discovered that most of the changes in visceral fat (the bad fat stored inside the abdomen) occurs prior to menopause. We are now studying the adipose tissue in these women using modern molecular techniques to see if we can find out why the fat accumulates in the peri-menopausal years.

Lastly, our lab is interested in the field of microarrays and the bioinformatics analysis of these large datasets. Microarrays are small 'chips' that allow us to measure the expression of thousands of genes at one time. This mass of information presents great opportunities and challenges the researcher. Harnessing this horsepower is

Steven Smith, M.D.
Professor

a challenge and in collaboration with statisticians and bioinformaticians, we are using these tools to better diagnose subtypes of obesity and diabetes. Our hope is that these tools will allow us to personalize treatment and improve patient care.

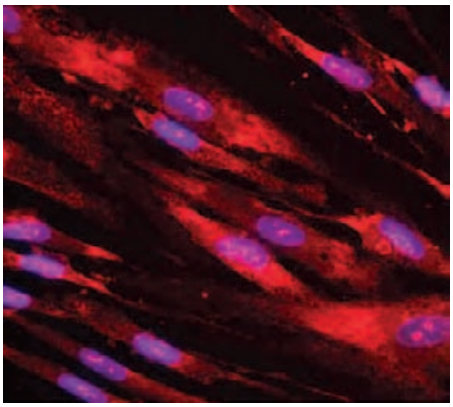


Figure 1
Photomicrograph of a primary culture of human skeletal muscle cells. These cells are stained with a dye specific to mitochondria (orange) and nuclei (blue). Skeletal muscle cells that are grown ex vivo retain the characteristics of their donors in terms of their ability to oxidize fatty acids. This suggests that a large portion of the inter-individual variability in the risk for developing obesity and diabetes is attributable to fundamental differences in fuel metabolism in muscle cells.

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

LESLIE P. KOZAK, PH.D.
Professor, Claude Bernard Pennington Chair

MOLECULAR GENETICS

Molecular Genetics and Thermogenesis Laboratory

Faculty – Leslie P. Kozak, Ph.D., Robert A Koza, Ph.D., Jong-Seop Rim, Ph.D.
Research Team – Larissa Nikonova, Ph.D., Rea V. P. Anunciado, D.V.M., Ph.D., Jessica Hogan, Ph.D., Tamra Mendoza

FOCUS

Understanding biological processes associated with the obesity problem.

Current Projects

We are currently investigating two processes associated with obesity. Thermogenesis and obesity. We seek to identify thermogenic mechanisms that can be activated to burn off excess fat in obese individuals. A major reason for the obesity epidemic comes from the historical disappearance of rigorous physical activity formerly required of human beings to acquire food and shelter. In a physically demanding life style, thermogenic physiological mechanisms to maintain a healthy energy balance were unnecessary. Consequently, although there is strong scientific evidence for mechanisms controlling food intake, evidence for thermogenic mechanisms that are designed for maintaining energy balance in man does not exist. Although scores of biochemical pathways that are present in humans could be thermogenic, the normal function of these pathways are directed towards other needs, such as maintaining body temperature during cold exposure. Our studies are based on mice that have been genetically engineered by knocking out the mitochondrial uncoupling protein (UCP1) to more closely resemble humans with respect to their repertoire of potential thermogenic mechanisms. We are attempting to identify those mechanisms that could be induced to burn off fat when stimulated with an appropriate hormonal or pharmacological agent. Encouraging evidence indicates that mechanisms

resembling those involved in Ca++ cycling in muscle are able to be induced in both fat and muscle tissues of mice exposed to the cold. Thyroid and leptin hormone seem to be involved in this Ucp1-independent cold- induced mechanism.

Mice have the ability to induce brown adipocytes in normal white fat tissues and this ability enables them to resist the development of obesity. Although humans have brown adipocytes, particularly in neonates, a method to induce brown adipocytes in adult humans has not been discovered. The cellular and molecular mechanisms for inducing brown adipocytes is very complex, and it is likely that in humans, like in mice, it is a genetically variable trait. Investigating the mechanisms of brown adipocyte induction has been a major effort of our lab. Our present effort has been to determine how a genetically variable and transient induction of the brown adipocytes in mice during the weaning period may affect the capacity of certain genetic strains of mice to induce the cells when they are adults. The development of this capacity can be used to reduce obesity in response to pharmacological intervention.

Epigenetics of diet-induced obesity. We are all familiar with the anecdotal stories of family members with seemingly similar genetic backgrounds and life styles, yet are very different in their susceptibility to obesity. We are studying this phenomenon in mice that are susceptible to diet-induced obesity and have found that some genetically identical mice maintained in a controlled laboratory environment become obese, whereas others remain lean. These traits are stable and are retained even if the obesogenic environment is removed by feeding mice a restricted low fat diet. These traits are consistent for an epigenetic modification of the expression of genes associated with the expansion of adipose tissue in response to the state of energy balance in the mouse. The known epigenetic mechanisms currently being studied in the cancer field are those that alter the methylated state of CpG dinucleotides in the regulatory domains of genes or modify nucleosome structure by methylation and/or acetylation of histones. Using microarray analysis with a system which can scan gene expression in almost the complete genome, we have found major changes in genes involved in Wnt signaling, a pathway that has been shown to be epigenetically modified in cancer and has been implicated as a regulatory mechanism of adipogenesis. Future research will seek to establish the identity of the epigenetically modified genes that control the development of obesity in mice and eventually in humans. The implication of this research is that the susceptibility of a person to develop obesity is in large part a stochastic event, not involving genetic background or lifestyle, but a roll of the molecular epigenetic dice that determines how the interactions of genetics and environment will determine an obese state. Thus, the anecdotal stories we often hear may be very real.

Research in this lab is supported by grants from the National Institutes of Health, the Louisiana State University Board of Regents and the Claude Bernard Pennington Endowed Chair in Molecular Genetics.

Robert A. Koza, Ph.D.
Assistant Professor

Jong-Seop Rim, Ph.D.
Instructor

Taste Genetics Laboratory

Faculty – Brenda K. (Smith) Richards, Ph.D.
Research Team – K. Ganesh Kumar, Ph.D.; Barbara York, Ph.D.; Lauri Byerley, Ph.D. (adjunct); Julia Volaufova, Ph.D. (adjunct); Griffin Gremillion, B.S.; Eric Penedo, B.S.; Brenda Belton, M.S.; Angela Poole, B.S.; Kristen Foley; Corey Rohrback; and Brittany Deshotels

Focus

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

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

Current Projects

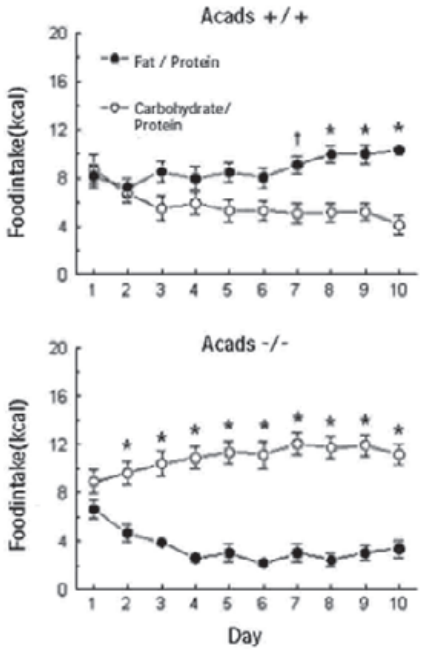
Previously we evaluated macronutrient selection in thirteen mouse inbred strains and identified a three-fold difference in fat intake between the C57BL/6J (B6) and CAST/Ei (CAST) strains. Remarkably, the CAST strain eats more carbohydrate (60%) and more calories (30%) per body weight than B6 mice but remains extremely lean. Using this experimental animal model and quantitative trait loci (QTL) methodology, we identified a number of chromosomal (Chr) regions influencing voluntary fat, carbohydrate, and total calorie intake, thus providing clear evidence for the genetic determin-ation of these traits. This was the first mouse study identifying genetic loci for nutrient preference or energy intake.

Over several years, we developed new congenic strains in which more than 99% of the genome is B6 while carrying CAST-derived genomic segment in the QTL region of interest. Recently, interval-specific congenics (proximal Chr 17) developed in our laboratory have recapitulated the higher carbohydrate and total energy intake revealed in the original QTL mapping study, thus confirming that these traits are genetically linked to this Chr 17 locus.

The difference between the genome of B6 and congenic mice is confined to the QTL region. Currently we are searching for candidate genes located within this chromosomal 17 region by using DNA microarray analysis to compare gene expression between B6 and B6.CAST-17 congenic mice. Gene expression differences outside the QTL region are likely due to downstream or upstream effects of the QTL gene(s). Analyses of differentially expressed genes both within and outside the genetically linked regions (QTL), combined with what is known about the biology of feeding, will allow us to begin modeling the genes and pathways through which these ingestive behaviors are determined.

We have also identified a positional gene candidate located within the congenic interval on Chromosome 17 that is polymorphic between the B6 and CAST strains and has physiological relevance to the regulation of food intake: Glp1r (glucagon-like peptide 1 receptor). Along with its role in insulin secretion and glucose homeostasis, GLP-1 released from the intestine inhibits gastric emptying. Results from genetic, genomic, and physiologic studies support Glp1r as a gene candidate in both the parental and congenic strains. Notably, a strain difference in gastric emptying rate, a relevant physiological

Figure 1



Acads +/+ and Acads -/- mice selecting from a choice between carbohydrate/protein and fat/protein diets. n=15-16 mice/strain. †P < 0.05, *P < 0.005.

phenotype, has been demonstrated. We are now testing the hypothesis that Glplr contributes to the modification of food intake in our model.

The mechanisms underlying the phenotypic strain differences in nutrient intake could involve genetically determined components in the taste or gastrointestinal systems, intermediate metabolism, or central nervous system. In parallel with the genetic studies described above, we are investigating candidate pathways in other mouse models including a strain that is deficient in short-chain acyl-CoA dehydrogenase (SCAD). We found that mice bearing a spontaneous mutation in Acads avoid fat and compensate calorically by eating more carbohydrate in a choice diet paradigm. Acads is the structural gene for SCAD which is a key enzyme of fatty acid oxidation, therefore this observation provides further evidence for the metabolic control of food intake.

The mechanism controlling fat selection in this mutant strain has not been determined but our studies point to a physiologic signal arising from the postingestive consequences of eating fat rather than from an effect of Acads on taste. This genetic model offers a new tool for studying the role of oxidative signals in regulating fat intake. Identifying genes that regulate macronutrient intake in mice will help us to understand the contribution of genetic versus environmental factors affecting food preferences in humans.

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

Neuropeptides Laboratory

Faculty – Andrew A. Butler, Ph.D.
Research Team – James L Trevaskis, Ph.D., Gregory Sutton, Ph.D., Emily Meyer, B.S.

Focus

To understand the regulation of the balance of energy intake and energy expenditure by melanocortins.

Current Projects

Obesity is a disorder of energy imbalance, and increases risk of insulin resistance and the Metabolic Syndrome. Hypothalamic lesions have long been known to be associated with obesity and increased appetite in humans and rodents. The melanocortins (-, - and -melanocyte stimulating hormone) are synthesized in neurons of the hypothalamus that respond to peripheral and central regulators of food intake and energy expenditure. Administration of

ANDREW A. BUTLER, PH.D.
Assistant Professor

melanocortins directly into the brain reduces food intake and increases energy expenditure, with two 7 transmembrane g-protein coupled receptors expressed in the central nervous system. Analysis of mice lacking melanocortin-4 receptor (Mc4r-/-) indicates that this receptor is required for inhibition of feeding and stimulation of energy expenditure associated with melanocortin treatment. Mc4r mutations in human subjects can be associated with a severe childhood obesity syndrome, characterized by rapid growth and weight gain and severe over eating. The Mc4r is obviously important for regulating energy balance, and is considered the most promising melanocortin receptor target for treating obesity.

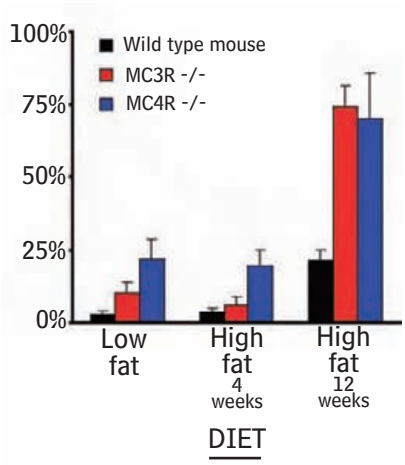


Figure 1 High fat diet increases body weight by 80% in mice lacking Mc3r or Mc4r. Mice lacking Mc3r or Mc4r (Mc3r-/-, Mc4r-/-) are obese compared to wild type controls (top panel, 6 month old female mice after being fed high fat diet for 3 months).

The Neuropeptides Laboratory has demonstrated that another melanocortin receptor expressed in the brain (Mc3r) is also critical for preventing weight gain on high fat diets. Body weight increases by 80% in mice lacking Mc3r (Mc3r-/-) and in mice lacking Mc4r (Mc4r-/-) which were fed a high fat diet (Fig 1). Fat mass as a percentage of total body weight also increased approximately 45-50% in both Mc3r-/- and Mc4r-/- mice on high fat diets.

One interest of the laboratory is determining reasons for rapid weight gain of Mc3r-/- mice fed high fat diets. The Mc3r is expressed in areas of the brain that are important to regulation of appetite, yet loss of Mc3r in mice does not appear to result in the over eating observed in Mc4r-/- mice. This observation suggests that the contribution of the Mc3r to energy balance is primarily through effects on metabolism, increasing the efficiency with which fat is stored in adipose tissue.

We are interested in two potential, possibly related mechanisms by which the Mc3r regulates metabolic efficiency. Metabolic analysis using indirect calorimetry suggest that Mc3r-/- mice are consuming more fat than is being used a fuel source. We have recently observed that mice lacking Mc3r exhibit a reduction in mitochondrial function in muscle.

This observation suggests that reduced mitochondrial capacity for metabolizing fat is one factor contributing to weight gain in Mc3r-/- mice. Hypothalamic Mc3r might regulate muscle metabolism through the autonomic nervous or neuroendocrine systems known to regulate energy

expenditure. On the other hand, Mc3r are also located in centers of the brain involved in regulating physical activity. We have demonstrated that the coordination of the daily rhythms in physical activity with food consumption is impaired in mice lacking Mc3r. We are currently investigating how the Mc3r may be involved in coordinating physical activity with food intake.

A marked difference in the insulin resistance syndrome has been observed in Mc3r-/- and Mc4r-/- mice. Mc4r-/- mice develop severe insulin resistance; whileMc3r-/- mice exhibit only mild insulin resistance. This observation is important, since it may allow for the investigation of why some obese patients escape from developing severe insulin resistance. Conversely, the investigation of these models may also yield clues to the origin of insulin resistance in the obese state.

In summary, the Neuropeptides Laboratory has been focusing on how melanocortins regulate energy balance. We have made several interesting, and very novel, observations that suggesting that the Mc3r is important for regulating energy balance.

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

HUMAN GENOMICS

Human Genomics Laboratory

Faculty – Claude Bouchard, Ph.D., Tuomo Rankinen, Ph.D., Jacob Brand, Ph.D.

Research Team – Eric E. Snyder, Ph.D. (adjunct), Arto Hautala, Ph.D., Timo Lakka, M.D., Ph.D. (adjunct), Hanna-Maaria Lakka, M.D., Ph.D. (adjunct), Ruth Loos, Ph.D., Tomohiro Okura, Ph.D., Nadine Spielmann, Ph.D., Margarita Teran, M.D., Ph.D., Anik Boudreau, B.S., Kathryn Redd, B.S., Christina Riley, B.S., Sunita Seemanapalli, M.D., Shannon Sonnier, B.S., Brandon Walts, M.S., Jessica Watkins, B.S.

CLAUDE BOUCHARD, PH.D.
Professor
George A. Bray Chair in Nutrition

FOCUS

The Human Genomics Laboratory investigates the genetic and molecular basis of the response to a physically active lifestyle with an emphasis on cardiorespiratory endurance, cardiovascular disease, and type 2 diabetes risk factors, as well as genetic and molecular background of obesity and abdominal obesity and their co-morbidities.

Current Projects

The laboratory relies primarily on the resources of the HERITAGE Family Study and the HYPGENE / Dallas Aerobic Center Longitudinal Study. In addition, the laboratory is closely involved in the GET-READI study, a dietary intervention study in African-American families investigating the genetic and non-genetic determinants of cardiovascular disease risk factor responses to a heart-healthy diet.

During this report period, eight genome-wide linkage scans have been published based on the HERITAGE

TUOMO RANKINEN, PH.D.
Assistant Professor

JACOB BRAND, PH.D.
Instructor

Family Study data. These studies have yielded several quantitative trait loci (QTL) for various exercise-related phenotypes, such as submaximal exercise stroke volume, cardiac output and blood pressure, physical activity levels (particularly sedentarism), cardiorespiratory fitness, and fasting plasma insulin exercise-training response. In addition, several QTLs have been found for resting blood pressure, abdominal visceral fat, insulin and glucose metabolism traits, steroid hormones, and sex-hormone-binding globulin measured in the sedentary state.

Fine mapping of several QTLs derived from the genome-wide scans is currently in progress. The first QTL that has been solved in terms of positional candidate gene is for submaximal exercise stroke volume training response on chromosome 2q31 in the titin gene locus. In addition, positional candidate genes are already available for a submaximal exercise stroke volume training response QTL on chromosome 10p11 (KIF5B) and for maximal exercise heart rate on chromosome 10p14-p13 (ITGA8).

Skeletal muscle gene expression studies using microarray technology have been carried out to identify new candidate genes for the regulation of exercise training - induced changes in peripheral insulin sensitivity. More than 360 genes showed at least 1.4-fold difference in expression levels when samples from 8 individuals showing vast improvements in insulin sensitivity (high responders) were compared with samples from 8 subjects who showed no changes (low responders) after a 20-week exercise-training program: 240 transcripts were upregulated and 121 were downregulated in high responders as compared to the low responders. Four of the strongest candidate genes were validated using real time RT-PCR (Figure 1).

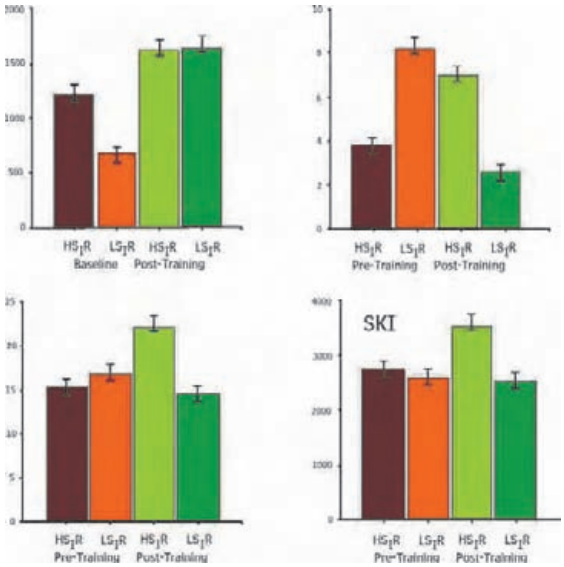


Figure 1 Quantitative RT-PCR validation of genes for the insulin sensitivity response to exercise training identified in microarray experiments. HISR = high responders, LSIR = low responders

In collaboration with the Cooper Institute in Dallas, TX, the Human Genomics Laboratory has established a DNA bank of all consenting participants of the Aerobics Center Longitudinal Study (ACLS) cohort. As of October 2005, we have banked ~ 22,000 samples from ~16,000 subjects. The overall goal of the collaboration is to investigate genotype-by-fitness and genotype-by-obesity interaction on the risk of chronic diseases utilizing the longitudinal design and multiple visits of the ACLS cohort. The first project based on the ACLS resource is targeting hypertension

(the HYPGENE Study), and it is funded by the NHLBI (2004-2007). The aim of the HYPGENE Study is to investigate the contributions of DNA sequence variation in candidate genes, cardiorespiratory fitness and obesity, as well as their interactions, to the incidence of hypertension. As of September 2005, we have identified 1,400 subjects, who were normotensive and free of cardiovascular disease and diabetes at the time of their first preventive medical examination. Half of these subjects (n=700) developed a physician-diagnosed hypertension during the follow-up period (duration 2 to 20 years), whereas the other half remained normotensive. Genotyping of single nucleotide polymorphisms in the first set of candidate genes is in progress and first manuscripts will be submitted by summer 2006.

From January 1, 2004 to December 5, 2005, the laboratory has published 65 peer-reviewed original papers. The Human Genomics Laboratory maintains two major resources for researchers and educators interested in molecular genetics of obesity and exercise-related traits: the Human Obesity Gene Map and the Human Gene Map for Performance and Health-Related Fitness Phenotypes. Both maps are updated annually and the 2005 publications marked 11th and 4th updates of the obesity and fitness gene maps, respectively. The obesity gene map database is also available online (**http://obesitygene.pbrc.edu**).

Research in this lab is supported by grants from National Institutes of Health and by an unrestricted grant from Bristol - Meyers - Squibb.

Energy Balance Laboratory

Faculty – George Argyropoulos, Ph.D.

Research Team – M. Ali Sözen, Ph.D., Adrian Stütz, Ph.D., Adrienne Cain, B.S., Laura Fendick

Focus

Understand the regulation of food intake by central and peripheral agents.

Current Projects

We study in detail the functional properties of the human Agouti Related Protein (AgRP) gene, which is a powerful operator of food intake. This gene is expressed in the hypothalamus, the adrenal gland, the lung, and the testis and causes a marked increase in food intake when overexpressed in transgenic mouse models or when injected into the hypothalamus. We are employing an array of experimental procedures to determine the functional properties of the AgRP gene and to determine the means by which it is expressed in the brain and peripheral tissues.

We follow two lines of research: (1) *in vitro* studies using cell culture, and (2) *in vivo* studies using transgenic mice. For the *in vitro* studies we utilize various cell lines derived from hypothalamic neurons or adrenocortical cells, representing the sites of predominant expression of the gene. For the *in vivo* studies we utilize mouse models to determine long-term effects on food intake when AgRP is overexpressed peripherally but not centrally (i.e. not in the

George Argyropoulos, Ph.D.
Assistant Professor

hypothalamus). These studies use mice that have been engineered to overexpress AgRP specifically in the adrenal gland.

Every gene requires a driving mechanism called the "promoter" that is responsible for "driving" expression (i.e. starting the gene to make the protein product). In the case of AgRP we aim to identify regions of the promoter that are responsible for driving expression of the gene specifically in the adrenal gland or specifically in the hypothalamus. One such experiment has shown that a region (region "B") is sufficient to drive expression of AgRP in the adrenal gland (295R) only but not in the hypothalamus (N38), as shown by the horizontal bars in Figure 1.

We also wish to identify specific sequences in the promoter of AgRP that are used by various factors to bind and influence expression of the gene in different tissues. Indeed, every gene is regulated by "transcription factors," which are proteins that bind to specific DNA motifs on the promoter and can direct the gene to start expressing or shut down its expression. Such transcription factors can therefore be significant players in determining the functional impact of a gene by modulating its expression levels. We have identified one such transcription factor that binds to a specific sequence on the promoter of AgRP. Addition of this transcription factor to cells carrying the target sequence of the AgRP promoter, leads to an increase of the promoter activity of AgRP. Using extracts from the nuclei of cells transfected with this transcription factor we were also able to pinpoint the exact eight DNA bases to which this transcription factor binds, in order to exert its effects on AgRP promoter activation.

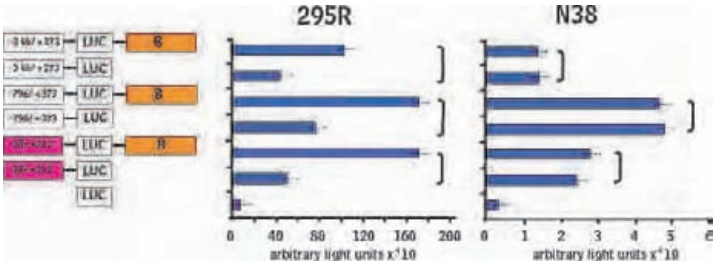


Figure 1 *A region (B) has been identified that is able to drive expression of AgRP specifically in the adrenal gland (h295R) but not in neuronal cells (N38).*

In the case of the *in vivo* studies, we have generated a new transgenic mouse model that overexpresses AgRP specifically in the adrenal gland. To generate this mouse we used the promoter from another gene that has been shown to operate only in the adrenal gland. We added to this promoter the mouse AgRP gene and using recombinant technologies, the new gene was inserted into mouse fertilized eggs. Our preliminary data show that mice overexpressing AgRP in the adrenal gland become overweight.

In the future, we aim to identify more regions in the promoter of AgRP that are responsible for expression of the gene in the hypothalamus. We also aim to identify how (and if) hormones like leptin and insulin regulate the expression levels of AgRP and to identify the exact sequences on the promoter of the gene that are

required for such effects by hormones. With regard to the transgenic mice overexpressing AgRP, we aim to further characterize these mice and examine their metabolic profile. We also aim to examine the long term effects of AgRP overexpression in the adrenal gland in the prevention of cancer cachexia.

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

NEUROSCIENCE

Neurobiology and Nutrition Laboratory-I

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

Research Team – Gregory M. Sutton, Ph.D., Bronwyn Duos, M.S., Laurel M. Patterson, B.S., Robbie Leigh Townsend, B.S., Phillip Ray, Amanda Noel, Adrienne Netterville, and Brian Etier

Focus

To understand Neural mechanisms of nutrient detection, control of appetite and regulation of energy balance.

Current Projects

Although the anecdotal saying "we are what we eat" is clearly an overstatement, the food we eat affects the nervous system in many ways, and the brain in turn controls to a large extent what we eat, how much we eat, and what portion of ingested energy we expend. Given the obesity epidemic, the nutritional neurobiologist's challenge is to identify neural mechanisms controlling energy balance and adiposity, with a view to develop pharmacological and behavioral therapies.

Our Laboratory is focusing on three main aspects of the neural control system.

First, we have started to investigate 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 (-MSH), and cocaine and amphetamine-regulated transcript (CART), orexin, and melanin-concentrating hormone (MCH), all project to the dorsal vagal complex in the medulla oblongata, where they contact neurons receiving vagal afferent inputs signaling nutrient arrival. We have further shown that the MC3/4-receptor agonist MTII decreases and the antagonist SHU9119 increases meal size when injected into the 4th ventricle or directly into the dorsal vagal complex, suggesting that these peptidergic projections from the hypothalamus modulate the level of satiety and meal size. We have demonstrated that the phosphorylation status of mitogen-activated protein kinase ERK 1/2 is critically involved in the satiation process, as blockade of this intracellular signaling cascade inhibits satiety induced by exogenous cholecystokinin and by local brainstem administration of the melanocortin receptor-4 agonist MTII. Our current attempts to identify the downstream signaling steps in specific NTS

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

Huiyuan Zheng, Ph.D.
Instructor

neurons have demonstrated the involvement of tyrosine hydroxylase phosphorylation in catecholamine-synthetizing neurons and phosphorylation of the voltage dependent potassium channel Kv4.2. We believe that these rapid mechanisms are critically involved in meal termination and that slower transcriptional events mediated through phosphorylation of the cAMP response element binding protein (CREB) are involved in the determination of the intermeal interval

Second, we are continuing our research on the anatomical and neurochemical organization of vagal and sympathetic output to the gastrointestinal tract, liver, pancreas, and fat tissue. In one project using genetically altered pseudorabies virus for transneuronal retrograde tracing, we have identified neurons in the caudal raphé nuclei and other medullary sites that receive input from hypothalamic peptidergic projections such as -MSH, orexin, and MCH and project to brown adipose tissue. In another project we have demonstrated that vagal stimulation is effective in suppressing the acute inflammatory response to mechanical manipulation of the intestines, serving as a model for postoperative ileus, and we have identified vagal efferent contacts with macrophages in the gastrointestinal tract to play a crucial role of this vagal anti-inflammatory effect.

Third, we have successfully started a new program to investigate 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. While the control circuits for the homeostatic controls that tend to keep body weight within narrow limits are located mainly within the hypothalamus and brainstem, cortical and limbic areas seem to be involved in the rewarding, cognitive, social, and environmental factors characterizing food intake in the modern world. 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.

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

Neurobiology and Nutrition Laboratory-II

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

Research Team – Zhongling Zheng, M.D., Ph.D., Shuxia Wan, M.D., Vander Baptista, D.V.M., Ph.D., F. Holly Coleman, B.S.

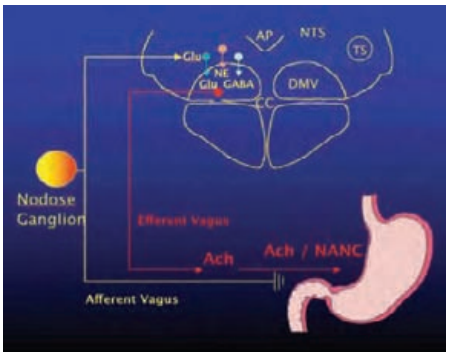
Focus

To understand the cellular mechanisms underlying the central control of gastrointestinal (GI) functions.

Current Projects

We use a combination of *in vitro* electrophysiological techniques (whole cell patch clamp in thin slices and in primary neuronal cultures of rat brainstem), *in vivo* techniques (microinjections and extracellular recordings) and immunocytochemical techniques to study the characteristics of both the sensory and motor components of the autonomic circuits controlling GI functions. It is our aim to elucidate the cellular mechanisms underlying the control that the central nervous system exerts on the physiological functions of the upper gastrointestinal tract.

One project deals with the basic organization and the underlying short-term plasticity of brainstem vagal circuits controlling GI motility and homeostasis. Sensory information from the GI tract is perceived and modulated by neurons in the nucleus of the tractus solitarius (NTS) before being transmitted to motoneurones of the dorsal motor nucleus of the vagus (DMV); these nuclei are essential for the coordination of vago-vagal reflexes. Although vago-vagal reflex control of the gut is understood at a basic mechanistic level, there are many factors (e.g. the organisms' place in the environment, time of day, taste of food, stress, pain, cytokine production in disease, hormonal background, etc.) that can radically alter feeding behavior or GI function. The integration of digestive function in relation to the state of the GI tract is dependent on visceral afferent data carried by the vagus nerve. Although several neurotransmitters are known to influence GI functions via either the NTS or the DMV, very few studies have investigated the synaptic contacts between these nuclei. Data collected from our laboratory suggest



"Schematic of Gastrointestinal Vago-Vagal Reflexes"

R. Alberto Travagli, Ph.D.
Professor

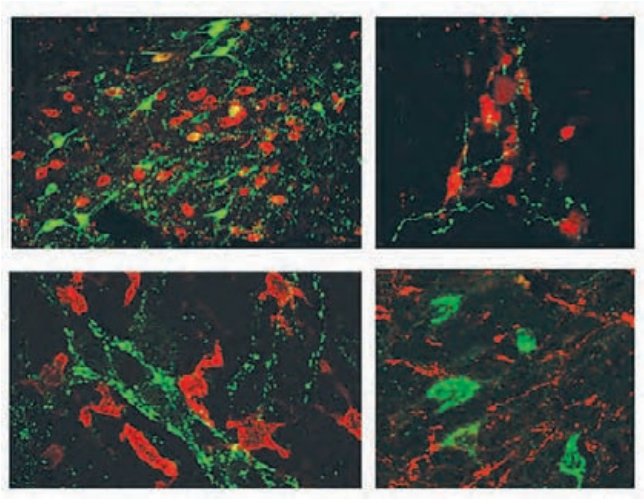


Figure 1 *Top left: Some hypothalamic orexin neurons project to the dorsal vagal complex in the caudal brainstem. Orexin neurons are shown in red, neurons retrogradely labeled from dorsal vagal complex in green, and double-labeled neurons in yellow. Top right: Innervation of neurons in the Raphé pallidus projecting to brown fat tissue (red) by orexin containing nerve fibers (green). Bottom left: Close anatomical appositions between cholinergic nerve fibers (green) and macrophages (red) in the myenteric plexus of the rat stomach. Bottom right: Innervation of hypothalamic orexin neurons (green) by anterogradely labeled fibers (red) originating in the nucleus accumbens.*

KIRSTEEN N. BROWNING, PH.D.
Assistant Professor

that neuropeptides and hormones can drastically alter the processing of vagal afferent input through differential gating of neuronal transduction mechanisms in the NTS. Our electrophysiological data suggest that subthreshold manipulations of vago-vagal circuits unmask responses in otherwise silent inhibitory synapses. Our immunohistochemical data support this concept of short-term circuit plasticity since similar manipulations allow the detection of otherwise concealed membrane receptors.

Our *in vivo* data support this concept of short-term plasticity suggesting that this type of response highlights a generalized way of activating synaptic transmission as the need arises. In fact, we have shown recently that the swallowing-induced relaxation of the stomach (the receptive relaxation reflex) is reversible, according to the feeding status of the animal. For example, when the animal is fed or has a full stomach, distention of the esophagus (as would occur during swallowing of food) induces a *contraction* of the stomach. Only after the stomach is emptied, does distention of the esophagus cause the more expected gastric relaxation. Indeed, it appears the tonic sensory inputs arising from the GI dampen the responsiveness of vagal circuits to circulating transmitters and hormones and, by preventing unnecessary responses, keeps the vagal

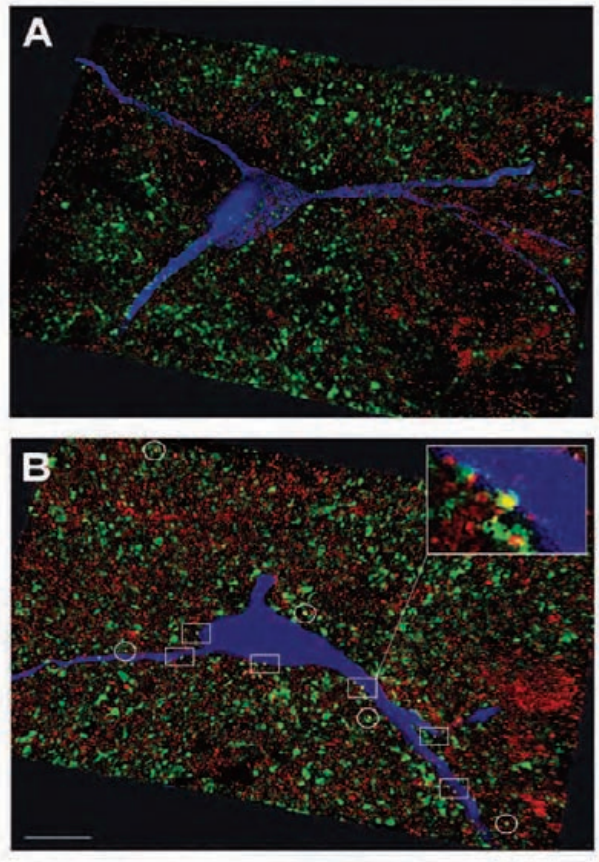


Figure 1 *(from Browning et al. J.Neurosci. 24:7344; 2004) MOR and GAD co-localized profiles apposing electrophysiologically identified neurons. Images represent 3D reconstructions from Z-stack image series (see Material and Methods). Neurobiotin-Texas red labeled cell: blue; MOR-IR: red; GAD-IR: green; profiles double-labeled for MOR and GAD: yellow. Panel A. View of a neuron in control conditions (i.e. no pharmacological treatment). Note the absence of double-labeled profiles in the field of view. Panel B. View of a neuron in which forskolin uncovered the presynaptic inhibition of IPSC amplitude by ME. Note the presence of both, non-apposing (outlined by circles) and apposing (outlined by rectangular boxes) MOR/GAD double-labeled profiles onto the Neurobiotin-labeled neuron.*
On the top right, note the exploded view of the area outlined by the highlighted rectangular box.
Scale bar = 10 microns.

Figure 2 *(from Browning et al. AmJPhysiol. 288: G950; 2005). Morphology and localization of identified pancreas-projecting DMV neurons.*

A. Brightfield micrograph at low magnification of a coronal brainstem slice at approximately +1.2 mm from obex.

Aa. Computer aided reconstruction of the neuron depicted in panel A. Note that the cell has a multipolar dendritic arbor. The axonal terminal has been indicated by an arrow.

B. Brightfield micrograph at low magnification of a brainstem slice at approximately +1mm from obex. Note that some of the dendrites make contact with the ependymal layer of the fourth ventricle.

Bb. Computer aided reconstruction of the neuron depicted in panel B. Note that the cell has a bipolar dendritic arbor. The axonal terminal has been indicated by an arrow.

C. Location of DMV neurons in the horizontal plane. Note that neurons with bipolar (open circles) or multipolar (black squares) shape are distributed evenly throughout the rostro-caudal and medio-lateral extent of both the right and left portions of the DMV.

output in an idle state. When, instead, the need to modulate the gastric motor response arises, sensory vagal inputs that dampen the system are overridden, the now "awaken" brainstem circuits are able to withstand modulation by circulating or endogenous transmitters and finely tune gastric motility.

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

In another project, we have examined the actions of CCK further, particularly its ability to increase exocrine secretion of the pancreas. This was assumed to occur via a paracrine action to activate peripheral vagal afferent fibers, but our recent *in vitro* and *in vivo* studies have shown that CCK can directly excite DMV neurons innervating the pancreas, resulting in an increase in exocrine secretion. Moreover, when tested with pancreatic polypeptide (PP, which reduces pancreatic exocrine secretion), DMV neurons that were excited

by CCK were, instead, inhibited by PP. These data confirm our original hypothesis that neurons of the DMV controlling particular visceral functions are organized into discrete subpopulations that can be distinguished according to electrophysiological, morphological and pharmacological properties. We anticipate that our studies will provide new insights into the processing of information in the DMV as well as contributing to our understanding of the neurophysiological substrates of control of visceral functions by the brainstem.

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

ROY J. MARTIN, PH.D.
Professor

Neurobehavior Laboratory

Faculty – Roy J. Martin Ph.D.
Research Team – Mike Keenan Ph.D., Maren Hegsted Ph.D, (adjunct), June Zhou Ph.D., Xioachun Xi, M.S., Kathy McCutchen, B.S.

FOCUS

The theme of this laboratory is "Nutrient (macronutrient) sensing mechanisms are important in the control of feeding behaviors." Our goal is to modulate nutrient sensing mechanisms to control food intake and obesity.

Current Projects

The specific aim of this past year has been to determine the final common signaling mechanisms by which carbohydrates, fatty acids and amino acids are sensed by neurons to regulate neuropeptides involved in feeding behavior.

A large body of evidence supports the roles of the central nervous system in regulating feeding behavior and body fat content. The brain is the central controller – this is the coordinating and integrating component which assesses input from the sensors and initiates a feeding response. Our main hypothesis is that ***"nutrient sensing in neuronal cells is tightly coupled to the ATP and AMPK status of the cell. In turn, the nutrient sensing cell of the brain translates this signal of energy need into feeding behavior."***

Nutrient Sensors – these are receptors or pathways which respond either directly or indirectly to a change in the controlled variable or nutrient. The mechanisms by which signals from metabolites are translated into neurochemical signals still remain unsolved. To address this issue, we developed *in vitro* and *ex vivo* systems for cellular level studies. In the N1E-115 and GT1-7 neuroblastoma cell lines,

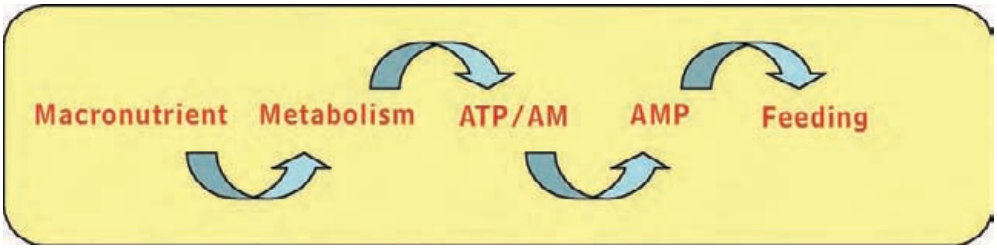


Figure 1 Neurobehavior Lab

glucose suppressed expression of AgRP, whereas 2-DG induced AgRP expression. Next, we provided evidence that the modulation of cellular ATP concentration by glucose, 2-DG, pyruvate, and ATP synthesis inhibitor regulates AgRP expression, probably through the AMP-activated protein kinase (AMPK) pathway. Our findings *in vitro* were further confirmed by ex vivo and *in vivo* studies where changes in neuronal energy status affect AMPK phosphorylation and neuropeptide expression, leading to changes in food intake. Our present data suggest that energy sensing through ATP status is a main switch to regulate neuropeptide expression and food intake regulation.

Sensing of Amino Acids – the protein content of a diet plays an important role in controlling food intake and body fat through the elevation of blood levels of amino acids. In humans and laboratory animals, dietary protein decreases food intake more than fat or carbohydrate, and at a level greater than that which can be accounted for by their energy content alone. Therefore, we have initiated a project that is focused on amino acid signaling and the control of peptides involved in feeding behavior. This year we determine that AgRP expression is decrease by high protein diets and that the direct application of amino acids to neuroblastoma cells decreases the expression of this gene. The mechanism by which amino acids decrease AgRP expression appears to involve mTOR signaling. mTOR is a protein kinase that is responsive to amino acid status and participates in the regulation of numerous cellular functions. It is proposed that mTOR mechanisms are important in amino acid sensing of neuronal cells and that this signaling pathway is important in control of food intake by protein content of the diet.

Sensing of Short Chain Fatty Acids – We believe that short chain fatty acids like butyrate that are produced in the large intestine suppresses body fat by stimulation of gut signaling peptides. We have shown that rats fed a resistant starch diet that elevates production of butyrate in the large intestine also had greater serum levels of glucagon – like peptide – 1 and peptide YY and greater gene expression of these peptides in cecal and colon cells. We are currently developing cell culture methods to determine the cellular mechanisms by which butyrate acts on gene expression in the colon.

From our studies it is evident that all three macronutrients (carbohydrates, fatty acids and amino acids) are capable altering gene expression in nutrient sensing cells to alter feeding behavior. It appears that AMPK and mTOR mechanism are important components of nutrient sensing and may be the final common signaling mechanisms by which carbohydrates, fatty acids and amino acids are sensed by neurons to regulate neuropeptides involved in feeding behavior.

Research this laboratory is supported by grants from, LSU AgCenter, Gordon Cain Professorship, Gordon Cain Biotechnology for Students and Teachers Program, National Starch Inc., and Pfizer Inc.

Autonomic Neuroscience Laboratory

Faculty – Richard C. Rogers, Ph.D., Gerlinda E. Hermann, Ph.D.

Research Team – Montina J. Van Meter

Focus

To understand the relationship between the brain and the digestive tract.

Richard Rogers, Ph.D.
Professor

Gerlinda Hermann, Ph.D.
Assistant Professor

Current Projects

We are currently examining how specific neural circuits in brainstem integrate visceral afferent, descending neural command, hormone and cytokine signals to control digestive processes. We are especially interested in how factors related to the development of disease states feed back upon autonomic control circuits in the brainstem.

Immune activation in cancer, infection and autoimmune disease often causes a collapse in CNS control of digestion characterized by gastric stasis, nausea, emesis and anorexia. We have recently shown that tumor necrosis factor [TNF], a protein signal generated by the activated immune system, not only helps direct the immune attack, but also affects CNS circuitry in the brainstem. TNF powerfully modulates gastric control circuitry in the brainstem; the result being the complete suppression of gastric function thru action on vagal reflex control of the stomach. Our recent physiological papers have suggested a mechanism for this TNF action: TNF actually synergizes with glutamate released from afferent nerve terminals to dramatically activate gastric reflex-inhibiting neurons in the brainstem. Not surprisingly, we find a high concentration of TNF receptors on vagal afferents in the brainstem that are probably responsible for this effect. These results suggest that TNF effects on the brain are caused by "amplifying" vagal afferent synaptic transmission in the brainstem.

The fact that TNF receptors are located on vagal afferent nerve terminals suggests that this cytokine exerts its effects by regulating synaptic transmission between the vagus and the CNS. Studying this process directly offers a significant technical challenge. Vagal afferent terminals, and the second-order neurons they synapse on, are extremely small. This fact makes direct study of this process using standard neurophysiological methods difficult, if not impossible.

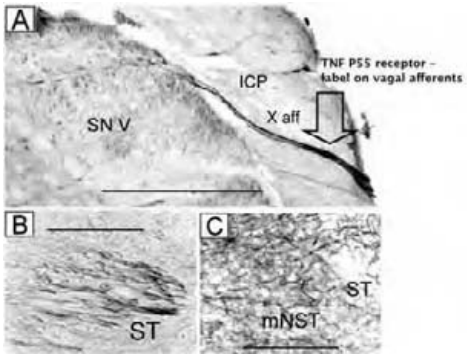


Figure 1 *A Low power micrograph showing TNF receptor [P55] covering vagal afferents entering the brainstem. B, P55-labeled vagal afferents collecting in the solitary tract on their way to making contact with neurons in the solitary nucleus. C, P55-labeled vagal afferents dispersing throughout the solitary nucleus.*

However, dramatic improvements in CCD camera technology, confocal microscopy and the advent of calcium sensitive transportable dye molecules make it possible to find and record the activity of vagal afferent terminals. Our preliminary results with this technology suggest that TNF essentially "amplifies" normal vagal afferent signal traffic from the gut. This effect could cause the nausea, emesis and anorexia and gastric stasis associated with disease-related TNF release.

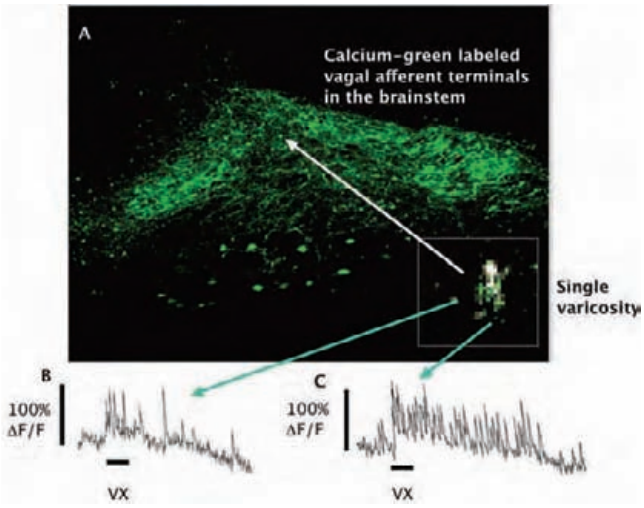


Figure 2 *A, Confocal image of calcium dye labeled afferents in the solitary nucleus. Inset = single varicosity. B. Effects of stimulation [VX] of single vagal varicosity before treatment with TNF. C. Effects of VX stimulation after treatment with TNF. TNF appears to amplify synaptic transmission between vagal afferents and the brain.*

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

Blood-Brain Barrier Laboratory I

Faculty – Weihong Pan, M.D., Ph.D.
Research Team – Jasmine Yu, Ph.D., Yongmei Yu, M.S., Courtney Cain, B.S., Laura Feucht, B.S.

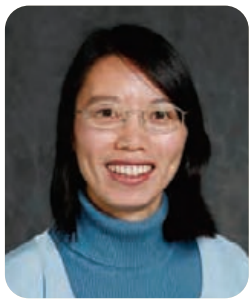
Focus

To identify mechanisms, regulation, and clinical applications of cytokine transport across the blood-brain and blood-spinal cord barrier (BBB).

Current Projects

The presence of the BBB distinguishes the brain and spinal cord (the CNS) from the rest of body. As a regulatory interface, the BBB determines the extent of permeation of cytokines from the peripheral circulation to the CNS. There are several strong reasons to investigate how cytokines cross the BBB: (1) Cytokines participate in many physiological functions such as sleep, appetite, body temperature, attention, and memory; (2) Cytokines are important in both development and regeneration of the CNS; and (3) Cytokines may worsen neurological diseases such as Alzheimer's dementia, Parkinson's disease, stroke, and multiple sclerosis. Our goals in the next few years are to identify the mechanisms of transcytosis of cytokines in the cerebral endothelial cells composing the BBB, to determine regulatory factors for intracellular trafficking, and to enhance drug delivery to treat cytokine-related disorders in the brain and spinal cord.

Our first aim is to tag cytokines for transport assays. By use of PCR-cloning techniques, we make GST-fusion proteins of tumor necrosis factor (TNF) and



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

leukemia inhibitory factor (LIF). We then cleave and purify the proteins. We also purchase cytokines and tag them with fluorescent markers, biotin or radioisotope.

Our next job is to perform various cellular assays of endocytosis and exocytosis, using native cells or those overexpressing transport-associated proteins after transfection. By use of radiotracers, we can identify the kinetics of cytokine transport and determine interacting factors in different steps of trafficking. With fluorescent microscopy and confocal analysis, we can show the subcellular distribution of endocytosed cytokines and their degradation pathways.

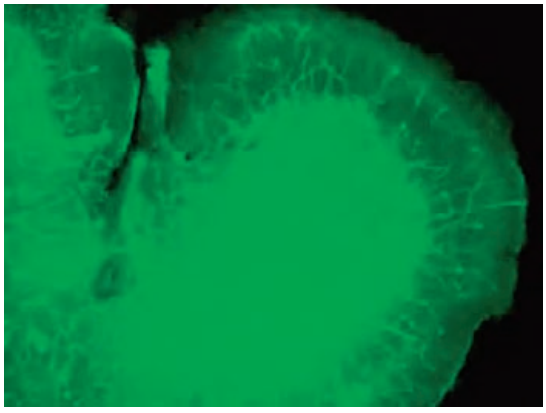


Figure 1 *Blood vessels in the spinal cord that compose the uniprevalent blood-spinal cord barrier.*

Working with cellular models of hypoxia and cytokinemia, we have gained some insight into how dynamic changes in cell surface cytokine receptors are related to transport and endothelial function. The results illustrate how cytokines are involved in the development of hypoxia tolerance, which is important in disease situations such as stroke.

Our major progress lies in the understanding of how BBB transport of cytokines regulates stroke, brain trauma, and spinal cord injury. Using mouse models and methods of transport assays, immunohistochemistry, Western blot, and real-time PCR of endothelial cells, we are able to tease out the individual players in the pathological processes that will eventually facilitate drug delivery.

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

Blood-Brain Barrier Laboratory - II

Faculty – Abba J. Kastin, M.D., Hong Tu, M.D., Ph.D.

Research Team – Ester Carreras-Marglef, Ph.D., Jeremy Daniel, B.S., Misty Barron, B.S., Ruth Yemane, B.S., Sarah Waters, B.S.

Focus

To determine the role of the Blood-Brain Barrier (BBB) in neuroendocrine control, particularly in feeding behavior and alcoholism.

Current Projects

After pioneering the concept that peptides in the periphery have CNS effects, an idea not accepted for decades, we have extended our investigations to the BBB. Now peptides are recognized to have widespread effects, and the 25 year-old international journal Peptides reports rapid progress in this field monthly, progress that will be summarized in the 210 chapter Handbook of Biologically Active Peptides

to be published in the spring of 2006. Our BBB Group and the journal moved more than a year ago to PBRC, one of the leading centers for nutritional studies in the world. The improved environment was even more fortuitous than it originally seemed, particularly after the devastating effects of the hurricane to our homes in New Orleans.

At the cellular level, we are determining the mechanisms of the intracellular trafficking of feeding-related peptides and proteins across cerebral endothelial cells. Peptide and protein ligands were usually thought to be degraded within cells, but the BBB cells may be an exception. Protein-protein interactions during transport across the BBB are being investigated by various techniques, including transport assays, immunofluorescence, FRET, electron microscopy, pull-down assays, and proteomics.

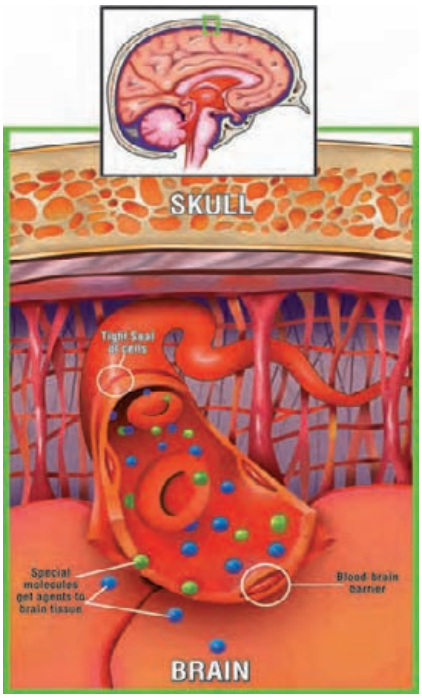
In the normal mouse, we continue to characterize transport systems for peptides and proteins. How does the transport of feeding-related peptides change in altered feeding and nutritional states? How do different peptides and polypeptides, such as urocortin and leptin, or growth hormone and insulin, interact at the BBB level? Then, how can we use this information to assist in the treatment of pathological obesity?

In the study of the physiological regulation of BBB transport, we know that there are not only age and gender differences but also circadian rhythms. With inspiration from the group of Franz Halberg, the father of chronobiology, we will find more opportunity to work on the rhythms of the BBB.

Apart from several research papers on BBB transport of urocortin and leptin, on interactions of alcohol and the BBB, and on insulin-like growth factors, we also published studies on growth hormone and agouti-related peptide as well as several reviews in books.

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

Blood-Brain Barrier



Structure of the Blood-Brain Barrier. The cartoon shows that the BBB is composed of endothelial cells joined by tight junctions and underlined by a continuous basement membrane.

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

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

Neurotrauma and Nutrition Laboratory

Faculty – Gregory M. Holmes, Ph.D.
Research Team – Melissa Tong, B.S.

Focus

To understand the effects of spinal cord injury upon GI reflexes and metabolism.

Gregory M. Holmes, Ph.D.
Assistant Professor

Current Projects

Current literature indicates gastrointestinal (GI) reflex function is diminished in humans after spinal cord injury (SCI). SCI patients often demonstrate gastric feeding intolerance immediately after injury, and failure to regulate gastric function is a significant cause of post-trauma morbidity and mortality. A question that arises is: Since the main neural circuitry controlling the stomach remains physically intact after human SCI, why is gastric function so severely compromised?

Our hypothesis is that high thoracic SCI interrupts ascending (spinosolitary) circuits regulating vagal parasympathetic control of the stomach and leads to gastroparesis. This lab is attempting to identify this unknown spinal circuit affecting stomach reflexes. Our current data demonstrates a profound gastroparesis after SCI that is similar to the effects of lost vagal input to the stomach (truncal vagotomy). The usual outcome of truncal vagotomy is reduced transit of solid gastric contents, gastric rigidity and a reduction of reservoir capacity. Following an experimentally controlled high thoracic spinal cord injury, the reservoir capacity of the stomach diminishes significantly. This is mainly due to an increase in the tone of the stomach wall coupled with an inability of the stomach to reflexively relax and accommodate the addition of gastric contents.

Because eliminative function is universally compromised after SCI, regardless of level of injury, we are also investigating intestinal transit and eliminative reflexes after SCI. Despite patient care strategies to minimize chronic constipation, fecal impaction, and episodic bouts of incontinence, patients with SCI continue to experience eliminative disturbances that necessitate stringent daily attention and, often, recurrent medical intervention. Data from my laboratory, and those of colleagues, has demonstrated that several descending neural circuits originate in the brainstem and terminate

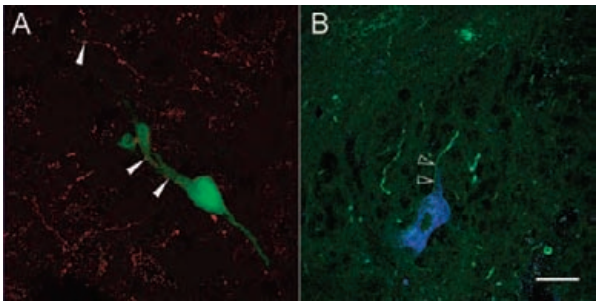


Figure 1 *A. Confocal image of noradrenergic (NA, red) fibers in close apposition to lumbosacral parasympathetic preganglionic neurons that control distal gut smooth muscle. Neurons were labeled by injection of enhanced green fluorescent protein expressing pseudorabies virus (green). B.Confocal image of NA fibers in close apposition to fluorogold labeled lumbosacral motoneurons innervating distal gut striated muscle (blue). Most appositions appear to terminate on EAS dendritic processes (open arrows). However labeling is occasionally observed in apposition to EAS cell bodies. 40X, 50 _m calibration.*

on the spinal neurons involved in coordinated distal GI sphincter reflexes. Immediately after SCI, immunocytochemical evidence of these descending fibers disappears below the injury site. Depending upon the severity of the injury, one class of fibers (those that contain the neurotransmitter serotonin) gradually establish limited reinnervation of the efferent sphincter neurons. Recent data has further demonstrated that these target neurons contain an appropriate sub-class of receptors for serotonin. Serotonin is presumed to inhibit the firing rate of the target sphincter neurons, therefore, loss of descending serotonergic inhibition would render the sphincter neurons hyperactive.

Recently published data from this lab demonstrates this phenomenon in spinal cord injured rats, and new data identifies that fibers containing the neurotransmitter noradrenaline (NA) also project to these same target neurons controlling distal GI reflexes. (Figure 1.) Prior data indicates that NA is excitatory to GI sphincter activity. Loss of descending noradrenergic (NA) facilitation would render sphincter neurons hypoactive and unable to maintain sufficient functional tone. I have found that these NA fibers also disappear immediately after spinal injury but, unlike serotonin fibers, they do not reinnervate neurons within the spinal cord that lie below the injury site. This disparity in anatomical plasticity suggests that eliminative reflex pathologies after SCI may reflect imbalances in the recovery of descending control from the brain.

This laboratory has also begun to explore the prevalence of obesity related disorders, including type 2 diabetes, that occur after human SCI. Pilot experiments from SCI rats have demonstrated that the fat content (adiposity) of muscle and liver samples is significantly higher than in control subjects, and SCI subjects exhibited significantly accelerated blood glucose response than intact subjects. Studies are ongoing to better characterize the change in insulin sensitivity after SCI in long-term subjects. Identifying the development of the metabolic syndrome in the animal SCI model that is used by my laboratory is essential toward empirically addressing the mechanistic changes that lead to the onset of type 2 diabetes after SCI.

Research in this laboratory is supported by a grant from the Pennington Biomedical Research Center Medical Foundation

CANCER LABORATORY

The William Hansel Cancer Prevention Laboratory

Faculty – William Hansel, Ph.D., Carola Leuschner, Ph.D.

Research Team – Fred Enright, Ph.D. (adjunct), Marek Bogacki, Ph.D., Janice Keener, Martha Juban, M.S., Karen McDonough, B.S.

WILLIAM HANSEL, PH.D.
Professor

Focus

To develop new drugs and techniques for treatment and prevention of recurrent cancer.

Current Projects

Contrary to popular belief and despite the expenditure of an estimated 14.4 billion

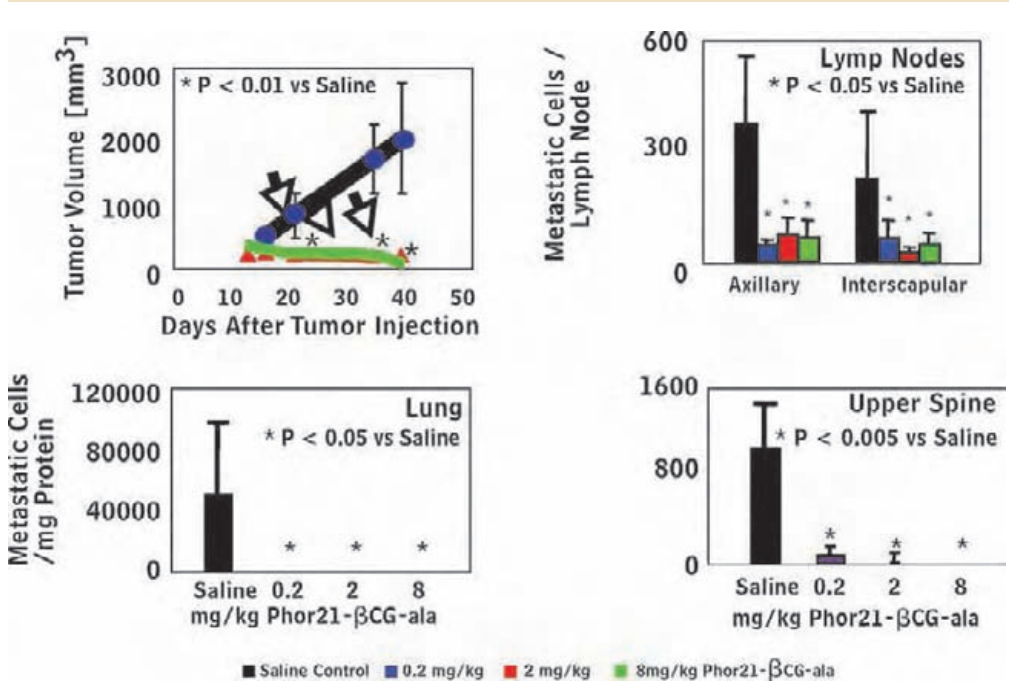


Figure 1 *The effects of Phor21- CG(ala) injections (0.2, 2.0 and 8.0 mg/kg body weight, once a week for 3 weeks) on tumor volumes and numbers of metastatic cells in lymph nodes, lungs and spines of nude mice bearing human breast cancer cell (MDA-MB-435S) xenografts. The MDA-MB-435S cells were stably transfected with the luciferase gene and luciferase positive (metastatic) cells were quantified in homogenates of lymph node, lung, and spine tissue.*

CAROLA LEUSCHNER, PH.D.
Assistant Professor

dollars annually for cancer research in the U.S. alone, there has been no measurable improvement in the survival rate of patients with distant metastases of breast, prostate, lung or colorectal cancers, since 1973. This sobering fact led us to concentrate our research efforts on the development of drugs capable of targeting and destroying both the primary tumors and the metastatic cells in lymph glands, bones, lungs and other tissues distant from the primary tumor. Recently, we reported that three compounds, Hecate- CG, Phor14- CG, and Phor21- CG(ala) are effective in causing regression of primary human prostate (PC-3) cancer tumors and in destroying metastatic cells in lymph nodes, bones, kidneys, lungs and other tissues of nude mice (Fig. 1). These compounds all contain a lytic peptide (Hecate, Phor14, or Phor21) which destroys cell membranes and a targeting moiety, CG, a 15-amino acid segment of the chain of human chorionic gonadotropin (hCG) which selectively binds to cancer cells that express CG receptors. These lytic peptide- CG conjugates also decrease tumor burden and destroy metastatic cells in mice bearing human breast cancer (MDA-MB-435S) cell xenografts and ovarian cancer cell xenografts. The lytic peptides alone are ineffective. To our knowledge, these lytic peptide-CG compounds are the first reported to specifically target metastatic cells.

Recently, we have included in our research efforts the development of compounds that increase the sensitivity of magnetic resonance imaging for the early detection of cancer and dormant metastatic disease. These compounds are comprised of superparamagnetic iron oxide nanoparticles (SPIONs), which are linked to luteinizing hormone releasing hormone (LHRH). In vitro, these particles are incorporated into breast and prostate cancer cells. In vivo, systemically administered LHRH-SPIONs are remarkably well incorporated in tumor cells and their metastases suggesting that they may also be useful as a vehicle for administering the lytic peptide constructs.

Research in this laboratory is supported by grants from the Gordon and Mary Cain Foundation, the Department of Defense, and the Downey Fund.

DNA Damage and Repair Laboratory

Faculty – Walter A. Deutsch, Ph.D., Vijay Hegde, Ph.D.,
Research Team – Lea Spyres, Ph.D., Sridevi Yadavilli, Ph.D., Amanda Broussard, B.S.

Focus

To understand genomic instability and its impact on aging and cancer etiology.

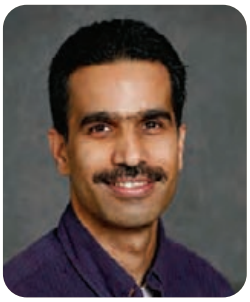
Current Projects

Ongoing research in the DNA Damage and Repair Laboratory is focused on two areas that are relevant to genomic instability and its impact on aging and cancer etiology.

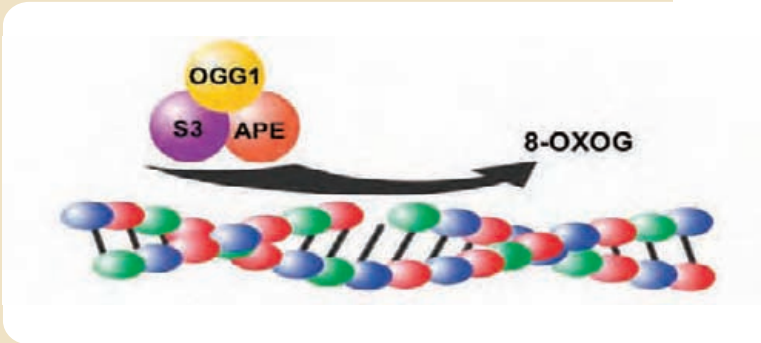
One area of concentration is our attempt to better understand the factors involved in removing base modifications that result from free radical attack on DNA. Numerous DNA lesions are formed under conditions of oxidative stress, the most notable being 7, 8-dihydro-8-oxoguanine (8-oxoG). This DNA adduct is known to be mutagenic if not repaired. It is also known to persist in certain human tissues, such as the lung, where its presence has been hypothesized to be a key ingredient in the etiology of cancer.

We have discovered a multifunctional human S3 ribosomal protein that possesses an apparent high binding affinity for 8-oxoG that exceeds that of any other known DNA binding protein. We have hypothesized that because this protein binds with such high affinity to 8-oxoG, that it could, in fact, create an obstacle to the efficient repair of an 8-oxoG DNA lesion. Using RNA interference (iRNA) assays, we have found that cells that express the iRNAs are much more resistant to challenges with a variety of mutagens, thus proving that S3 expression can have deleterious consequences on cell survival. Several sites that could be involved in the high affinity of S3 for 8-oxoG have been identified using a combination of a Hidden Markov modeling system and known

Walter A. Deutsch, Ph.D.
Professor



Vijay Hegde, Ph.D.
Instructor



databases for non-synonymous, coding single nucleotide polymorphisms (cSNPs). One cSNP site was a lysine (K) residue found to be embedded in a helix-hairpin-helix motif generally important for protein: DNA interactions. Mutants have been generated to produce a change at this site to create K132A. Through the use of surface plasmon resonance (SPR) analysis, the K132A mutation was found to have completely abrogated the binding affinity of S3 to sites of 8-oxoG. Using other in vitro tests, K132A, unlike wild-type S3, no longer inhibited the repair of 8-oxoG. In fact, the absence of DNA binding resulted in K132A stimulating the removal of 8-oxoG, suggesting that hS3 also possesses the ability to positively interact with the base excision repair proteins OGG1 and APE that are involved in the removal of 8-oxoG (Fig). Future studies will focus on mice that overexpress S3 or those that possess iRNAs to knockdown endogenous S3. Our expectation is that the knockdowns will, in fact, produce a more robust phenotype that could involve an extended life span.

In our second area of focus, our laboratory has also developed two different assay systems that are presently being used to monitor DNA damage in human cells. The single cell electrophoresis, or Comet, assay has been used to assess changes in the levels of DNA damage in two different populations of individuals, those that are undergoing caloric restriction, and those partitioned into different age groups, including individuals over 90 years of age. Surprisingly, we have found that individuals in excess of 90 years have significantly less oxidized-base lesions in their DNA than do individuals that are middle age. Individuals undergoing caloric restriction have significantly reduced the levels of oxidized bases in their DNA after six months. A second assay that is more quantitative than the Comet assay is presently being used to determine the amount of base modifications that are actually lost under conditions of calorie restriction.

Research in this laboratory is supported by grants from the National Institutes of Health and the Governor's Biotechnology Initiative.

EXPERIMENTAL OBESITY

Experimental Obesity Laboratory

Faculty – David York, Ph.D.
Research Team – MieJung Park, Ph.D., Ling Lin Ph.D., Leslie McLaughlin, D.V.M., Ph.D., Adam Hawley

Focus

To investigate the biology of a small natural peptide, enterostatin and to understand the variability of voluntary physical activity.

Current Projects

During the last few years, we have focused our attention on identifying the peripheral and central pathways and networks through which enterostatin selectively attenuates the intake of dietary fat. We have shown that enterostatin and its precursor protein procolipase are expressed in specific regions of the brain. Enterostatin activates neurons in the

amygdala, from where axonal pathways to both the paraventricular nucleus and arcuate nucleus affect activity at these sites including 5HT release in the PVN. 5HT 1B receptors in the PVN and MC4 melanocortin receptors appear to be required for the enterostatin activation of these centers.

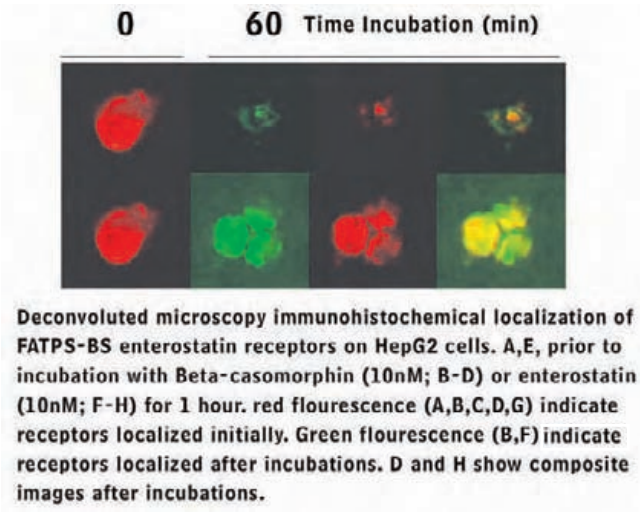
In the last two years, we have turned our attention to understanding the biology of enterostatin at the cellular, subcellular and molecular levels. In this work, we have produced substantial data to show that a protein normally found in mitochondria, the beta subunit of ATP synthase is a receptor protein for enterostatin. We have shown that this subunit protein is present on the plasma membrane of many cell types. We have shown that there is a strong correlation between the ability of many different enterostatin analogs to affect food intake and to bind to this beta subunit protein, We have also used confocal microscopy and western blotting techniques to show that enterostatin promotes the movement of its own receptor from the intracellular compartment into the plasma membrane (see figure).

Recognizing that this receptor protein was present on the plasma membrane of both HepG2 liver cells and GT1-7 neuronal cells allowed us to investigate which signaling pathways were regulated by enterostatin. These studies show rapid changes in cyclic AMP, pERK and JNK pathways and a subsequent downregulation of the orexigenic gene AgRP, probably explaining the fat specificity of enterostatin on feeding behavior.

Genomic and subsequent functional studies have identified effects of enterostatin on a number of other biological processes in addition to the regulation of feeding behavior and insulin secretion. These include effects on intracellular protein trafficking and direct effects on muscle to promote fatty acid oxidation through activation of the AMPkinase pathway. These and other observations suggest to us that enterostatin has far wider physiological effects than had been thought to date and promise an exciting future for studies with this peptide.

An additional focus in the last few years was to understand the variability of voluntary physical activity levels in genetically identical mice. Using microarrays to study gene expression levels, we showed that a variety of genes associated with the endoplasmic reticulum stress response were downregulated in the hippocampus of mice that were high runners rather than low runners. These differences were shown to be a consequence, not a cause, of the different activity levels. The data suggests that

DAVID YORK, PH.D.
Boyd Professor, Hibernia National Bank/Edward G. Schlieder Chair



Deconvoluted microscopy immunohistochemical localization of FATPS-BS enterostatin receptors on HepG2 cells. A,E, prior to incubation with Beta-casomorphin (10nM; B-D) or enterostatin (10nM; F-H) for 1 hour. red flourescence (A,B,C,D,G) indicate receptors localized initially. Green flourescence (B,F) indicate receptors localized after incubations. D and H show composite images after incubations.

high voluntary exercise levels are neuroprotective to the brain in that a downregulation of the ER stress related genes suggests that the unfolded protein response is attenuated. This mechanism may be fundamental to the recognized beneficial effects of physical activity on memory, cognitive function and protection from neurodegenerative disorders.

Research in this laboratory is supported by the National Institutes of Health and by the Louisiana Health Excellence Fund.

GEORGE A. BRAY, M.D.
Boyd Professor

Dietary Obesity Laboratory

Faculty – George A. Bray, M.D., Douglas Braymer, Ph.D.
Research Team – Maria Barnes, Ph.D., Stefany Primeaux, Ph.D.

FOCUS

To investigate why some animals become obese eating dietary fat and other animals do not.

Current Projects

The Laboratory has been interested in the role of two peptides that modulate feeding. The first of these, neuropeptide Y (NPY) is the most potent stimulator for food intake, but it is also involved in modulation of reproductive function, and in depression and alcohol preference. The second peptide is the opioid peptides, and the specific role of the mu-opioid receptor which mediates important responses to opioids.

The orexigenic effects of NPY are mediated through the hypothalamus, while the anxiolytic effects of NPY appear to be mediated through the amygdala. We hypothesized that intra-amygdalar administration of NPY might alter food preference without changing total food intake. Neuropeptide Y was administered into the central nucleus of the amygdala in both satiated and overnight fasted rats, and intake and preference for a high fat diet (56%)/low carbohydrate (20%) diet or a low fat (10%)/high carbohydrate (66%) diet were measured. Intra-amygdalar NPY administration in satiated rats did not change total caloric intake, but produced a dose-dependent decrease in intake of and preference for high fat diet relative to low fat diet over 24 hours. In overnight fasted rats, intra-amygdalar NPY also decreased the intake and preference of high fat diet relative to low fat diet over 24 hours, without altering total caloric intake. Intra-amygdalar NPY administration did not produce conditioned taste aversions to a novel saccharin solution. These results suggest that amygdalar NPY may have a role in macronutrient selection, without altering total caloric intake.

Neuropeptide Y has also been implicated in a variety of behaviors including those associated with anxiety and ethanol administration. One experiment investigated the predictive role of anxiety-like behaviors in ethanol self-administration and the relationship of amygdalar NPY to anxiety and ethanol self-administration. Rats were divided into Anxious and Non-Anxious groups based on behavior in the elevated plus maze. Following elevated plus maze testing, rats

were allowed to consume increasing concentrations of ethanol (2%, 4%, 6%) in a two bottle choice procedure over a period of 31 days. Anxious rats showed an increased preference for 4% ethanol and 6% ethanol as compared to Non-Anxious rats. Following 20 days access to 6% ethanol, rats underwent gene transfer surgery with replication-defective recombinant herpes simplex 1 vectors encoding prepro-NPY, an anti-sense NPY RNA or LacZ (control) into the amygdala. Bilateral amygdalar injections with the NPY-antisense vector increased 6% ethanol preference in Anxious rats. Bilateral amygdalar injections with the vector encoding NPY decreased 6% ethanol preference in Anxious rats. HSV-mediated alterations in amygdalar NPY expression did not alter 6% ethanol preference in Non-Anxious rats. These results suggest that virally mediated alterations in amygdalar NPY levels may differentially affect rats with low and high basal levels of anxiety.

Mu opioid receptors stimulated by pharmacological agonists that activate these receptors, increase the preference of a high fat diet. One study investigated whether mu opioid receptor expression could be increased by a diet high in fat and whether this change could be demonstrated in animals that were resistant or prone to diet induced obesity.

Fluorescence immunohistochemistry was used to investigate the expression of mu opioid receptors in Osborne-Mendel (sensitive) and S5B-Pl (resistant) rats after being exposed to a high fat or low fat diet for six weeks. Our data demonstrate that animals eating a high fat diet have a significant increase in the expression of mu opioid receptors in the nucleus accumbens, amygdala, hindbrain, and various hypothalamic areas. This diet-induced increase in expression of mu opioid receptors was present in animals that were both prone and resistant to diet induced obesity. These results suggest a positive feedback system in which a high fat diet increases the expression of mu receptors while increased activity of mu receptors increases the intake of a high fat diet. Such a feed-back system could ultimately lead to the development of obesity.

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

Douglas Braymer, Ph.D.
Professor

Neurosignaling Laboratory

Faculty – Christopher Morrison, Ph.D.
Research Team – Christy White, D.V.M.

Focus

To understand the cellular mechanisms underlying the neural regulation of body weight homeostasis, with particular interest in the signaling molecules and neuronal circuits involved in the brain's 'perception' of nutritional state and subsequent regulation of feeding behavior.

Current Projects

Neuronal circuits within the brain are critically involved in the regulation of food intake and body weight homeostasis, with defects in the signaling of a variety of neuropeptides or receptors within the brain leading to alterations in food intake and body weight. Recent work by our lab has

CHRISTOPHER MORRISON, PH.D.
Assistant Professor

focused on the neuronal circuits and signaling molecules utilized by the hormones leptin and insulin to regulate body weight and adiposity. Defects in leptin or insulin signaling, or in the downstream circuits they regulate, lead to obesity and diabetes, indicating that neuronal leptin and insulin action is necessary for appropriate body weight and glucose homeostasis.

Work by our group and others indicates that obesity is associated with an inability of either leptin or insulin to engage key neuronal circuits within the brain. This resistance to the neural effects of these hormones is in many ways similar to the insulin resistance that develops in peripheral tissues during diabetes. There are many factors that predispose individuals to obesity and diabetes, and one that has been a recent focus of our lab is aging. Aging, and particularly the transition from youth to middle age, is associated with an increased propensity to gain weight and body fat in many species. Aging is also associated with a progressive decrease in leptin sensitivity, and we propose that an inability of leptin to regulate key neuronal populations potentially contributes to the increased risk for obesity as individuals reach maturity. However, the molecular mechanisms underlying this aging-induced leptin resistance is poorly characterized. Recently we have focused on a protein called protein tyrosine phosphatase 1B (PTP1B) as a potential mediator of aging-induced leptin resistance. PTP1B acts to inhibit both leptin and insulin signaling, and thus increases in PTP1B would be predicted to promote leptin resistance. In support of this hypothesis, our data indicate that mature, leptin-resistant animals have increased levels of PTP1B within the

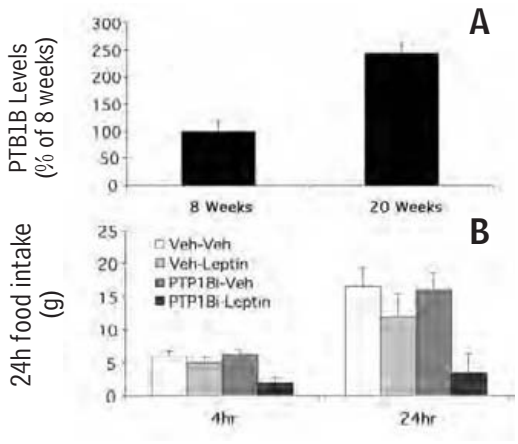


Figure 1 *Increased hypothalamic PTP1B contributes to leptin resistance in mature rats. A. Small punches of mediobasal hypothalamus were collected from chow-fed 8 and 20-week old male Sprague Dawley rats. Levels of PTP1B protein were determined via Western Blot. Mature (20-week old) rats exhibited significantly greater levels of PTP1B protein compared to 8-week old rats ($P < 0.05$). B. Mature (20-week old) rats bearing 3rd cerebroventricular cannula were injected with a pharmacological PTP1B inhibitor (0.3 nmole icv) or vehicle 1hr prior to icv treatment with leptin (3ug) or vehicle. Leptin alone had a small, non-significant effect on on food intake, indicating that these mature rats were leptin resistant. However, pretreatment with the PTP1B inhibitor markedly improved leptin-dependent suppression of food intake at both 4h and 24h (*$P < 0.05$). These data are consistent with the hypothesis that increases in hypothalamic PTP1B in mature rats contribute to hypothalamic leptin resistance.*

hypothalamus. In addition, the local administration of a pharmacological PTP1B inhibitor into the brain restores leptin sensitivity in formerly leptin resistant animals. Together, these data indicate that aging-induced increases in PTP1B underlie aging-induced leptin resistance, and we propose that these decreases in leptin sensitivity may contribute to the increased risk for obesity and diabetes that occurs with age. In the coming year, we will continue to examine the role of specific signaling molecules and neuronal circuits in mediating the action of nutritional signals, and believe that these advances will open new avenues for both basic research and the clinical treatment of obesity and diabetes.

Research in this laboratory is supported by grants from the Pennington Medical Foundation.

Functional Genomics Laboratory

Faculty – Aamir R. Zuberi, Ph.D.
Research Team – Yongjun Wang, Ph.D., Olga Debuisson, Ph.D., Bhavani Krishnan, MS., Rujun Teng, MS., Jacalyn MacGowan, Victoria McRoberts, Kay Baker, Mitchell Steen and Kylie Durand.

Focus

To identify and characterize important and unknown polymorphic genes that influence susceptibility to dietary obesity and adipogenesis.

Current Projects

Our laboratory uses inbred mouse strains and cell lines as genetic and molecular tools. Current projects include 1) The characterization of a small 8.6 Mbp region of mouse Chromosome 2 that contain one or more genes important in the regulation in the development of dietary obesity (Fig.1); 2) The characterization of Zfp106, a novel gene of unknown function that is implicated in the regulation of adipogenesis in cultured 3T3-L1 cell lines (Fig. 2); 3) Functioning as the Animal Research Core of the newly funded Botanical Research Center investigating the physiological effects of the Botanicals; Russian Tarragon, the Chinese plant, Shilianhua and Anthocyanin-enriched grape extracts,

Aamir R. Zuberi, Ph.D.
Assistant Professor

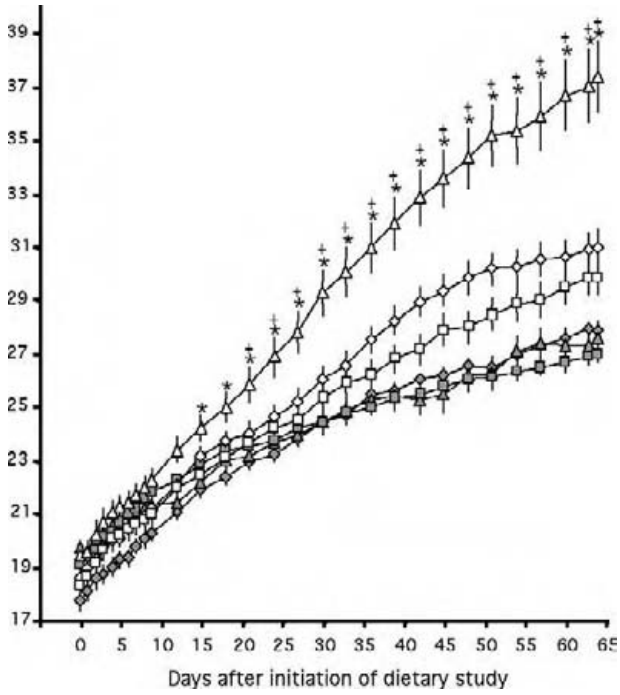


Fig. 1. Weight gain phenotypes of B6 (△), B6.LPa (◯) and heterozygous F1(□)male mice fed either a High fat (HF) diet (open symbols) or Chow diet (closed symbols). Mean body weights are shown ± SE. Numbers of mice in each group are as follows: HF diet, B6 (N = 9), B6.LPa (N = 16), F1 (N = 17). Chow diet, B6 (N = 9), B6.LPa (N = 12) and F1 (N = 12). The data from both (B6 x B6.LPa)F1 and (B6.LPa x B6)F1 mice were pooled as no significant differences in body weight, or other phenotypes, were found between them. Symbols; '" denote significant difference in body weight between B6 and B6.LPa (p<0.05), '+' denote significant differences in body weight between B6 and F1 mice (p<0.05)*

on the development and treatment of the obesity, insulin resistance and diabetes in mice.

In addition to in-vivo metabolic profiling, other technologies utilized by the laboratory include microarray screening to identify genes that differ in expression between different mouse strains and tissues, a more accurate quantitative PCR strategy to define the differences, protein characterization on western immunoblots to confirm changes in protein abundance and genetic manipulation of cell lines and mouse strains to alter expression levels of candidate genes in a more controlled manner. In combinations with other molecular techniques including the cloning and sequencing of novel genes, this allows us to more closely determine the effects of genetic or dietary manipulation on global and region-specific gene expression. We have identified several novel genes that are potential candidates for the dietary obesity phenotype. One of these, *Stard9*, is a novel gene that is predicted to encode a protein containing a kinesin-like domain, suggesting a possible role in the maintenance of cell -shape and the regulation of intracellular trafficking to the cell -membrane. These processes are critical for the cells ability to respond to extracellular ligands, such as insulin-stimulated glucose uptake. Two other genes have also been identified by are known only by clone IDs. The expression of these genes, *J12Rik* and *16255*, as well as *Stard9*

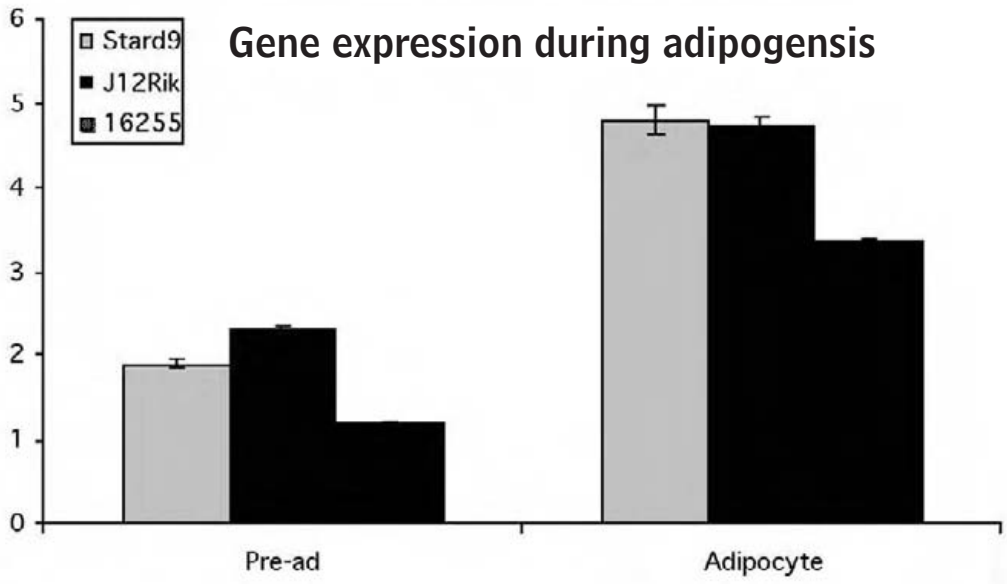


Figure 2 *Relative changes in mRNA abundance of the indicated candidate genes during adipogenesis of cultured 3T3-L1 cells. Data are presented as mean +/- SEM of 6 independent preadipocyte and 6 day 8 adipocyte cultures and normalized with respect to cyclophilin expression levels.*

are all induced during adipogenesis of 3T3-L1 cultured cells (Fig. 2), suggesting that they play a currently unrecognized role in the mature fat cell.

We are interested in how these genes (and other potential candidates) are regulating in vivo in fat tissue, skeletal muscle, liver and hypothalamus in chow and high fat fed mice and in the fed and fasted state. We are developing strategies to confirm whether that these changes in mRNA abundance have corresponding effects on protein abundance.

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

Infection and Obesity Laboratory

Faculty – Nikhil V. Dhurandhar, Ph.D.
Research Team – Scott Loiler, Ph.D., Pamela Rogers, M.S., Magdalena Pasarica, M.D., Miloni Rathod, M.Sc., Jonathan Hand

Focus

To understand obesity of infectious origin.

Current Projects

Various research groups have identified seven viruses that may cause obesity in animal models. We reported the first human virus, an adenovirus (Ad-36), which causes adiposity in chickens, rodents and non-human primates and shows association with human obesity. Our *in-vivo* and *in-vitro* data show that Ad-36 increases adiposity, lowers serum lipids and increases insulin sensitivity and preadipocyte differentiation. Increasing the number of fat cells and their lipid content may be one of the mechanisms by which Ad-36 induces adiposity in animals. Interestingly, human adipose tissue derived adult stem cells (ADAS) when infected with Ad-36 also respond in a similar way and increase lipid accumulation. Figure 2 shows that compared to the uninfected control group (CON), ADAS cells infected with increasing amount of Ad-36 show increasing lipid accumulation.

Nikhil V. Dhurandhar, Ph.D.
Associate Professor

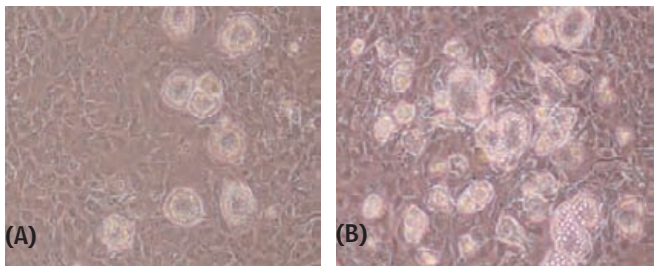


Figure 1: *Compared to the uninfected preadipocytes (A), the Ad-36 infected cells (B) show greater number of lipid containing adipocytes 6 days post-inoculation.*

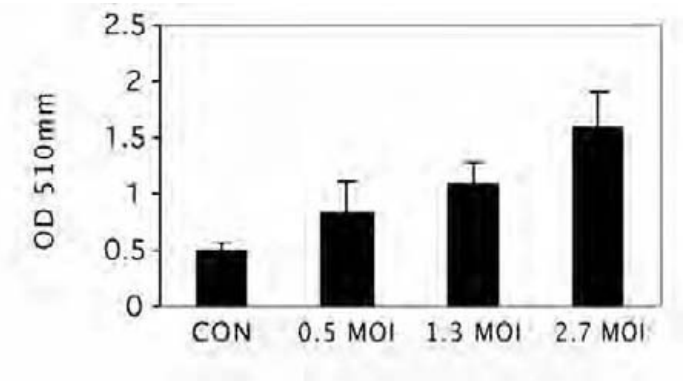


Figure 2 *Lipid accumulation in ADAS cells increases with increasing amount of Ad-36.*

We are currently investigating the molecular mechanism involved in adiposity promoting effect of Ad-36. Several genes of adipocyte differentiation pathway are up-regulated by Ad-36 and E4 orf1 is a viral gene that contributes to the effect. We are elucidating the interaction of the viral and cellular genes involved in the process. In addition, we are determining the role of Ad-36 in human obesity.

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

Research in this laboratory is supported by grants from the National Institutes of Health, the Pennington Medical Foundation and the United States Department of Agriculture.

RANDY MYNATT, PH.D.
Associate Professor

Agouti Research Lab

Faculty – Randy Mynatt, Ph.D.
Research Team – Jingying Zhang, Ph.D., Eric Jezek, B.S., Steven Bond, B.S., Rachael Marchand, Christine Blackmon

Focus

To use an integrative approach to understand the actions of the agouti protein and diet in obesity and diabetes

Current Investigations

This Lab uses an integrative approach combining genetic engineering techniques in mice, clinical studies, cellular physiology and nutrition in the study of obesity and type 2 diabetes. One proje ct focuses on the role of agouti/melanocortin system in the development of obesity with particular emphasis in adipose tissue. The second major project stems from our recent findings concerning the effects of dietary carnitine supplementation on insulin sensitivity. Listed below is a brief summary for each project.

Agouti Studies

It is well recognized that the agouti/melanocortin system is a critical component of body weight homeostasis. The focus of ongoing studies in my laboratory is to understand the function of agouti/melanocortin signaling in adipose tissue and evaluate its contribution to obesity and diabetes. The primary reason for this focus is that agouti and melanocortin receptors are present and regulated in human adipose tissue. Through work in my lab and some excellent collaboration with Drs. Steven Smith and Jackie Stephens, we have been able to demonstrate that agouti/melanocortin signaling is a key regulator of adipogenesis.

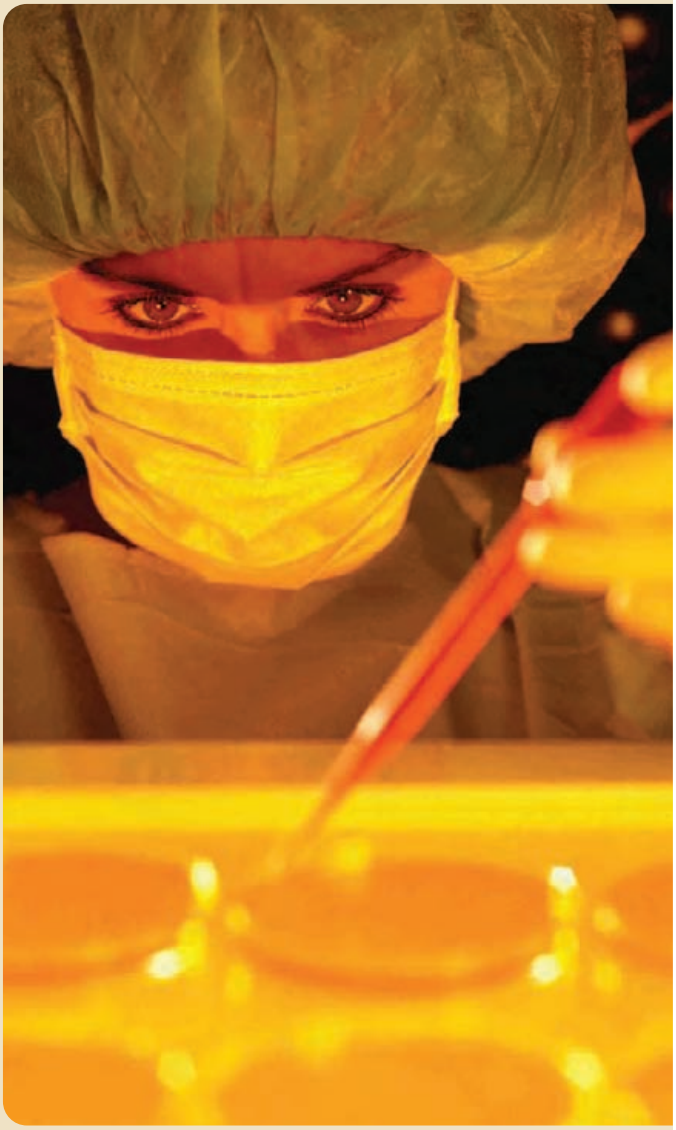
Perhaps the most clinically relevant findings are the data examining agouti expression in human adipose tissue. Since transgenic mice that express agouti in adipose tissue become obese, agouti mRNA was quantified in the subcutaneous fat from humans with a broad range of BMI. There was no correlation between agouti expression levels and BMI, but there were significantly higher levels of agouti expression in the diabetic subjects compared to non-diabetic individuals. We were also able to show that glucorticoids

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

Carnitine Studies

It is well established that Type 2 diabetes is a progressive disease, and the hallmark of pre-diabetes is insulin resistance, which is strongly associated with obesity and the ectopic accumulation of lipids in skeletal muscle and liver. The use of dietary supplements, such as L-carnitine, that ameliorate the lipid accumulation in skeletal muscle and liver represent a very attractive approach for adjunctive therapy of diabetes. L-carnitine plays a critical role in the shuttling of acyl moieties across mitochondrial membranes and it has been speculated that carnitine supplementation would improve glucose disposal by reducing the cellular concentrations of long-chain acyl-CoA's (LC-CoA) and acetyl-CoA, which are potent inhibitors of glucose utilization. Our pre-clinical studies suggest robust effects of carnitine supplementation on parameters contributing to insulin action. Carnitine supplementation completely restores insulin sensitivity in genetically obese/diabetic mice and prevents the development of insulin resistance in mice fed a high fat diet. Indirect calorimetry was used in mice to determine the effects of carnitine supplementation on substrate utilization and energy expenditure. Basal and insulin-stimulated carbohydrate oxidation was higher in the carnitine-supplemented group. These initial "proof-of-concept" experiments clearly demonstrate that dietary carnitine is very effective in improving insulin-stimulated glucose utilization in mice and reversing abnormalities of fuel metabolism. If these findings can be shown to be operative in human subjects, this would offer a very effective adjunctive therapy for type 2 diabetes.

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



Bioinformatics and Statistical Genetics

Bioinformatics Laboratory

Faculty – Andrey Ptitsyn, Ph.D.

Focus

To develop various theoretical and applied aspects of biomedical science with an emphasis on high-performance computation, supercomputer and algorithm development.

ANDREY PTITSYN, PH.D.
Assistant Professor

Current Projects

Among my current interests in computer science research, one is the development of a high-performance parallel version of unsupervised clustering application. The algorithms developed at PBRC using *FOREL* concept and *Natural Classification* approach demonstrate very promising results and an ability to scale to as many as a few hundred CPUs. I am also interested in the development of a high-performance bioinformatics API for grid and multi-core computation.

We retain contacts with South African National Bioinformatics Institute and continue development of high-performance algorithms for detection of matching sequence fragments, EST clustering and genome assembly. Recently we began implementation of the new multi-stage sifting algorithm, which combines negative oligonucleotide pre-selection based on Barrows-Wheeler transformation and modernized CLU algorithm for match verification. The algorithm is developed for scalable parallel computation.

We have advanced the interest in computational analysis of gene expression

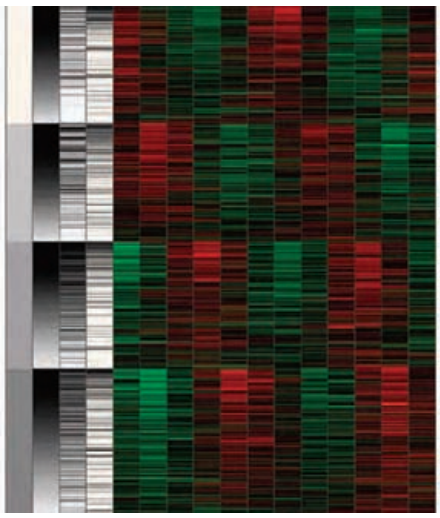


Figure 1: *Summary of the microarray analysis of circadian periodicity and phase in murine liver. The Roman numerals represent the grouping of all expressed genes based on the calculated circadian phase, displayed in circadian time. The gray shades of first 3 columns display the p-value ranging from 0 (black) to white (1). After phase assignment in each of four phase classes the non-randomness of periodic pattern is assessed by 3 different algorithms: Permutation test developed at PBRC (P), Autocorrelation (aC) and Fisher's g-test (F). When sorted by permutation test (P) p-value other algorithms generally agree with the permutation test selection, but offer less sensitivity. Out of over 22,000 genes, presented on this heat map over 25% are expressed with circadian periodicity above p<0.05 cutoff.*

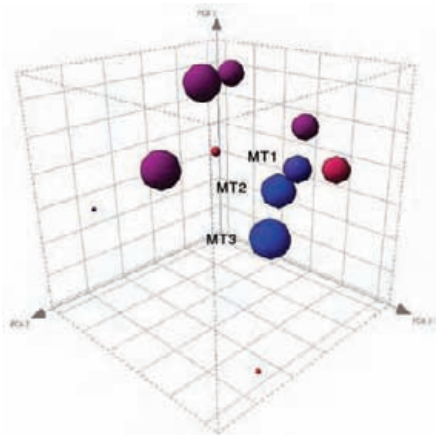


Figure 2: *Classification of microarray fingerprints of primary and metastatic prostate tumors. Clusters MT2 and MT3 contain metastatic tumors. Cluster MT1 contains both primary and metastatic tumors. Other clusters contain only primary tumors.*

patterns in connection with metabolic disorders (diabetes, obesity). Our recent studies have revealed novel molecular mechanisms of insulin resistance in skeletal muscle, which opens new avenues for personalized early diagnostics and treatment of Type 2 diabetes.

Another area of special interest is analysis of periodic patterns in gene expression. Our recent studies in collaboration with Dr. Jeff Gimble and his laboratory indicate a remarkable, though largely neglected, impact on the overall energy balance of a diurnal oscillation of gene expression in the peripheral organs (Fig.1). To analyze extensive data sets generated at PBRC we produced computationally effective implementations of well-established algorithms for identification of periodic patterns in gene expression. We have also developed a new algorithm that is particularly effective on short time series. This study has the potential to radically alter the way biological pathways are perceived and modeled.

One of my current research projects is related to prostate cancer. Using machine learning algorithms we have been able to identify classes of prostate cancer associated with metastatic progression. Our preliminary studies indicate a dramatic decrease of variability in metastatic compared to primary tumors, which suggests that a limited number of biological pathways are implicated (Fig.2). The next step in this development is to trace the specific biomarkers associated with metastatic potential in multiple independent data sets stored in public databases. We hope this will reveal the molecular mechanisms of metastatic cancer and allow the development of an early diagnostic technique.

Research in this laboratory is supported by grants from the Louisiana Health Excellence fund, the National Institutes of Health and the LSU/Tulane COBRE-CEIDR Program of the National Center for Research Resources.

DIABETES

Diabetes and Nutrition Laboratory

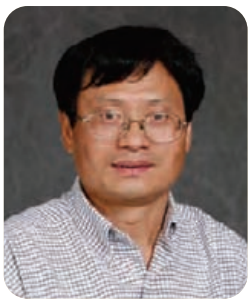
Faculty – William T. Cefalu, M.D., Zhong Wang, M.D.

Research Team – Xiaotuan Liu, Ph.D., Ann Coulter, Ph.D., Jianhua Qin, B.S., Xian Zhang, B.S., Xin Ye, B.S.

Focus

The primary mission of our laboratory is to study the cellular mechanisms contributing to the development of insulin resistance in humans. In addition, our goal is to evaluate the clinical effect and mechanism of action by which dietary factors modulate insulin resistance.

WILLIAM T. CEFALU, M.D.
Douglas L. Manship
Professor of Diabetes



ZHONG WANG, M.D.
Instructor

Current Projects

Insulin resistance is a condition in which a normal or elevated level of insulin produces an abnormal response, particularly as it relates to glucose disposal. Insulin resistance exists in pre-diabetic and obese states, is a key pathophysiologic feature of type 2 diabetes and is strongly associated with coexisting cardiovascular risk factors and accelerated atherosclerosis. As a consequence, one of the most desirable goals of treatment 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 lifestyle changes in humans with type 2 diabetes over a long period of time. Therefore, understanding the mechanisms of insulin resistance and designing strategies to improve insulin resistance by pharmacologic or nutritional supplementation represent a very attractive approach to the treatment of type 2 diabetes, and serves as a major goal of our laboratory. In particular, the lab has been evaluating dietary supplementation with chromium. It is trace mineral proposed as a nutritional intervention to improve resistance, but whose mechanism of action is not specifically known. We have demonstrated in animal models that supplementation of the diet with higher levels of chromium may modulate intracellular pathways of glucose metabolism and improve comorbidities associated with insulin resistance. In addition, we have provided evidence that the effect of chromium is more predictive if used in a specific phenotype. Specifically, studies suggest that lean, insulin sensitive animal models do not increase their insulin sensitivity when given chromium, yet obese animals with insulin resistance respond well. This clinical effect was also correlated with specific biochemical signals in the tissues as chromium enhanced PI-3 Kinase activity, an intracellular signal of insulin action, and decreased activity of a specific phosphatase, e.g. PTP1B, responsible for diminishing the intracellular signals. Taken together, these data suggest that a specific phenotype, i.e. obesity, is responsible for an abnormality in the intra-cellular insulin signaling cascade that appears to be overcome with chromium supplementation.

On a clinical level, the question remains as to the mechanism by which hyperinsulinism, insulin resistance, and/or obesity, modulates chromium metabolism and/or excretion. This is a very relevant

area of human investigation and is currently being addressed in long-term human trials. The objective of these clinical trials is to evaluate for a specific effect of chromium supplementation on insulin action by conducting randomized clinical trials in subjects with Type 2 diabetes. These trials utilize "gold standard" techniques to assess insulin action, i.e. hyperinsulinemic, euglycemic clamps combined with adipose and skeletal muscle biopsies that are obtained to study mechanisms. The tissue obtained from the biopsies are being evaluated in the lab for content of proteins involved in insulin action, gene expression of proteins, and specific kinase activities. Evidence obtained thus far from the human trials have demonstrated that chromium supplementation may improve insulin resistance, decrease glucose levels and attenuate weight gain noted from traditional therapies. In particular, we have noted that individuals with Type 2 diabetes whose diets were supplemented with higher doses of chromium had less weight gain, less increase in percent body fat, and less accumulation of visceral fat in the abdominal area compared to individuals with Type 2 diabetes who were randomized to placebo. The specific mechanism by which this occurs is not known, but suggests that chromium may alter some aspect of the energy balance equation for either dietary intake or caloric expenditure. These parameters are being assessed in ancillary human studies. The Lab is collaborating with other investigators at PBRC to perform detailed dietary intake and assessment studies, comprehensive energy expenditure evaluations with use of 24 hour metabolic chambers, and assessing measures of skeletal muscle fatty acid oxidation.

The 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 provide 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 dracunculus L*) referred to as PMI-5011, may increase insulin action *in vivo* and have identified several novel intracellular pathways that may explain the effect. The overall objective of this project is to examine the role of a specific botanical, PMI-5011, on insulin action *in vivo* and to elucidate potential cellular mechanism(s) of action. To accomplish this goal, the lab is conducting both *in vitro* and *in vivo* experiments with PMI-5011 and its bioactive components that are designed to assess insulin sensitivity and pathways of glucose metabolism with whole-body, cellular, and molecular approaches. We hypothesize that in both animal models and in subjects with the metabolic syndrome, dietary supplementation with PMI-5011 will improve whole-body insulin-mediated glucose uptake (i.e. insulin sensitivity) by increasing non-oxidative glucose disposal. This increase in whole body glucose

disposal will be due to enhanced cellular signaling through the insulin receptor and modulation of genes regulating glucose and lipid metabolism in skeletal muscle.

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

JIANPING YE, M.D.
Associate professor

Antioxidant and Gene Regulation Lab

Faculty – Jianping Ye, M.D., Zhanguo Gao, Ph.D.
Research Team – Qing He, Ph.D., Jun Yin, Ph.D., Zhonghai Chen, Ph.D., Jin-hua Yan, M.D., GangYu, M.S., Wei Tseng, B.S., Xin Ye, B.S.

FOCUS

We try to understand the cellular and molecular mechanisms of insulin resistance with long-term goal of identification of novel therapeutic targets for type 2 diabetes.

Current Investigations

Our study suggests that insulin signal pathway is subjected to a negative feedback regulation. The molecules involved in the feedback regulation include serine kinases, such as JNK, mTOR, GSK-3B, S6K, and Akt. FFAs and inflammation mediators are able to activate one or more of these kinases in the feedback loop to induce insulin resistance. This conclusion is supported by our observations published in the past few years, which include: (a) JNK and IKK was able to phosphorylate IRS-1 at Ser307/31; (b) Aspirin was able to protect IRS-1 function by inhibiting multiple serine kinases including JNK, IKK, Akt, and mTOR; (c) FFAs, such as palmitic and lenoleic acids, were able to activate IKK/NF-kB; (d) FFAs inhibited insulin signal transduction through IRS-1 serine phosphorylation by IKK and JNK. In the latest study, we demonstrated that NF-kB inhibited the transcriptional activity of PPAR through transcriptional cofactors. Current studies are designed to understand the molecular mechanism of crosstalk of insulin and inflammation pathway, and fatty acid signaling pathways, and with signaling pathway of bioactive botanicals. Our hypothesis is summarized in Figure 1. Following are some focuses in our research:

1. Regulation of IKK (Inhibitor kappaB kinase) and JNK by FFAs.
2. Regulation of PPARgamma and IRS-1 by IKK and MAPK (mitogen-activated protein kinases).
3. Regulation of IKK, and MAPK by bioactive botanicals.

We believe that adipocytes serve as a sensor as well as a regulator of nutrients/energy balance. Functional failure of adipocytes is a result of oversupply of nutrients/energy. When energy is oversupplied in the body, adipocytes undergo changes to adapt to the oversupply. When the degree of oversupply exceeds the capacity of compensation in adipose tissue, adipocytes will suffer functional failure, which is characterized by changes in adipopkine profile and development of insulin resistance. Insulin resistance in adipocyte is an early event of systemic insulin resistance.

To understand insulin resistance, we are focusing on adipocytes and trying to

ZHANGUO GAO, PH.D.
Instructor

understand how adipocyte failure happens. In the study, two questions are asked: (1) How chronic inflammation is induced in adipose in obese condition. In this regard, the signal pathway of fatty acids is investigated in adipocytes. (2) Whether the serine kinases (IKK, MAPKs, and PKCs) play a role in translation of fatty acid signal into functional failure in adipocytes. To this end, inhibition of IRS-1 and PPARgamma function by these kinases is under investigation. A variety of molecular, cellular and animal models are used in the study. Free fatty acids (palmitic and linoleic acids) and inflammatory cytokines (TNF-alpha) are used to induce insulin resistance in adipocytes. Dietary obese C57BL/6J mice, JNK1-/- mice, PKCtheta-/- mice, ob/ob mice, SIRT1-/- mice and p50-/- mice are used to investigate the crosstalk among the signaling pathways. Integration of signal transduction and transcriptional regulation is one of the focuses in mechanistic study. Transcriptional cofactors are studied for the crosstalk of NF-kB and PPARgamma. Molecular strategies, such as RNAi (RNA interference), ChIP (chromatin immunoprecipitation), and gene knockout, are used in the study.

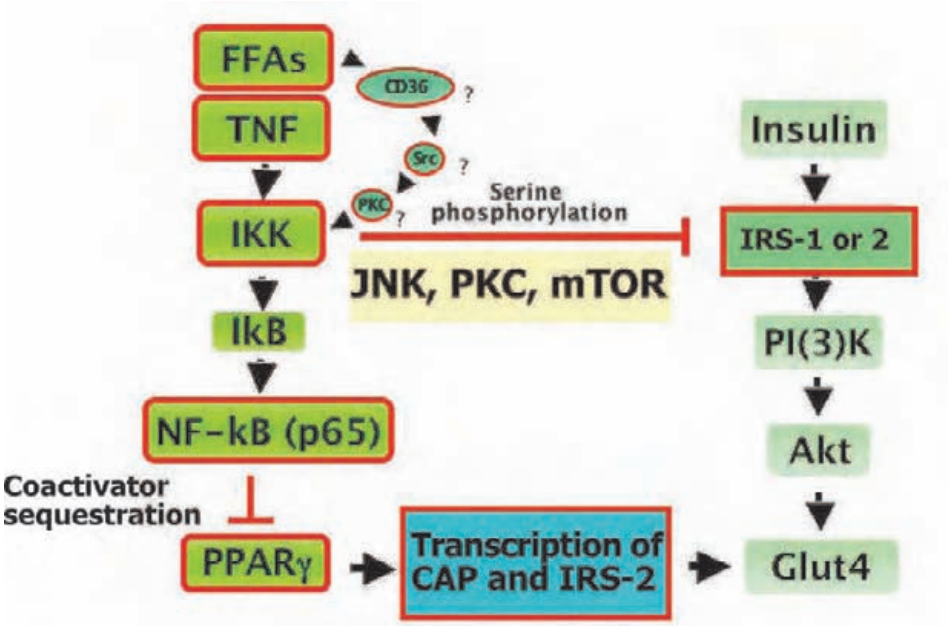


Figure. *Mechanisms of FFA and Inflammation-mediated alteration of Insulin Signaling in Adipocytes. FFAs lead to IKK activation probably through a pathway like FFAs/CD36/Src /PKC, and IKK inhibits IRS-1 function through serine phosphorylation that may require cooperation of IKK with other kinases including JNK, PKC and mTOR. NF-kB inhibits PPAR function through competition for the transcriptional coactivators and this probably leads to suppression of the gene transcription of CAP and IRS-2. CAP and IRS-2 are signaling molecules in PI(3)k-independent and -dependent signaling pathways for insulin-induced GLUT4 translocation.*

Another aspect of our research is related to the cellular and molecular mechanisms of a Chinese herbal medicine SLH. This medicine is a botanical product and has an insulin-sensitizing effect. We will identify the molecular target and the bioactive components of this medicine.

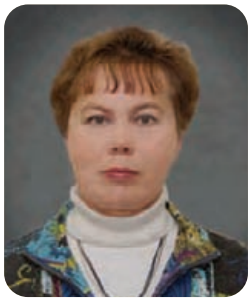
Research in this laboratory is supported by grants from the National Institutes of Health and American Diabetes Association.

Mechanisms of Diabetes Complications Laboratory

Faculty – Irina G.Obrosova, Ph.D.

Focus

To understand the pathogenesis of diabetes complications, especially neuropathy.



IRINA G. OBROSOVA, PH.D.
Associate Professor

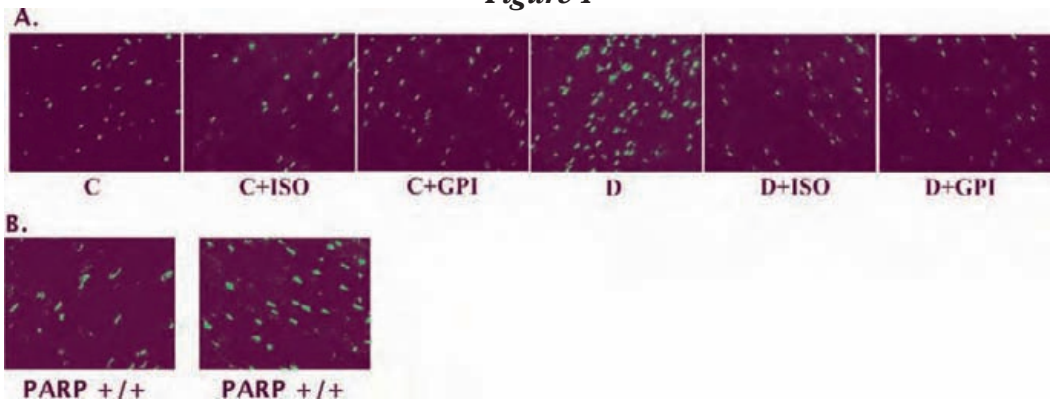
Current Projects

My laboratory is investigating oxidative-nitrosative stress and its downstream effectors and their role in the pathogenesis of diabetes complications primarily diabetic neuropathy. Lately, we have concentrated on several novel mechanisms that could potentially be involved in diabetic neuropathy and diabetic neuropathic pain.

Using two structurally diverse poly(ADP-ribose) polymerase (PARP) inhibitors and PARP-knockout mice, we obtained convincing data in support of the role for PARP activation in diabetic neuropathic pain and abnormal sensory responses. In particular, pharmacological inhibition of PARP partially corrected thermal, mechanical and chemically-induced hyperalgesia and tactile allodynia in streptozotocin-diabetic rats. Diabetic PARP-/- mice have been protected from both thermal algesia and tactile allodynia that were clearly manifest in diabetic PARP+/+ mice. Immunofluorescent microscopy confirmed the presence of PARP activation in peripheral nerves of both diabetic rats (Fig.1, A) and diabetic PARP+/+ mice (Fig.1, B), and such activation has been blunted by PARP inhibitors.

Our studies generated a new animal model of peripheral neuropathy associated with impaired glucose tolerance. Female mice fed for 4 months with high-fat diet had impaired glucose tolerance test and 2.5-fold elevated free fatty acid concentrations, in the absence of fasting hyperglycemia, and developed motor and sensory nerve conduction deficits, thermal hypoalgesia and tactile allodynia. This model will be used to explore the effect of caloric restriction and other nutritional approaches on neuropathy associated with obesity and initial phase of type 2 diabetes. Whereas evidence for the important role of arachidonic acid metabolism in diabetic neuropathy is emerging, the contribution

Figure 1



of lipoxygenases, and, in particular, 12/15-lipoxygenase (LO) remains unexplored. Using STZ-diabetic (model of Type 1 diabetes) and high-fat fed (model of Type 2 diabetes) LO-/- mice and as well as pharmacological LO inhibition, we produced novel findings suggesting the important role of this pathway in diabetes-associated motor and sensory nerve conduction deficits and tactile allodynia. 12/15-LO expression was increased in the diabetic sciatic nerve and high glucose-exposed human Schwann cells. LO overexpression contributed to high glucose-induced activation of three major subfamilies of MAP kinases.

Our immunohistochemical studies with endothelial (isolectin) and Schwann cell (S-100) markers localized 12/15-LO in both endothelial and Schwann cells of the peripheral nervez. Studies of the role for 12/15-LO in diabetic neuropathy are in progress.

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

Clinical Research Unit Reports

Clinical Research at the Center is organized around four areas, each of which has multiple investigators and laboratories. This section contains reports from each research unit as outlined in the following list.

Clinical Physiology and Metabolism

- Stable Isotopes and Energy Expenditure
  J. Rood
- Energy Metabolism
  E. Ravussin, L. deJonge, S. Smith
- Lipoproteins
  M. Lefevre

Epidemiology and Public Health

- Nutritional Epidemiology
  C. Champagne, D. Ryan, B. Kennedy
- Clinical Epidemiology
  R. Horswell
- Chronic Disease Epidemiology and Health Delivery
  D. Harsha

Clinical Trials

- Pharmacology-based clinical trials
  F. Greenway, G. Bray, W. Cefalu, K. Elliott, A. Gupta, J. Rood, D. Ryan, S. Smith
- Diet, Physical Activity and Behavior modification Trials
  G. Bray, C. Champagne, J. DeLany, F. Greenway, D. Harsha, B. Kennedy, M. Lefevre, C. Martin, M. Most, R. Newton, T. Rankinen, J. Rood, D. Ryan, S. Smith, S. Redmann, D. Williamson

Health Psychology

- Behavioral Approaches for the Prevention and Treatment of Obesity
  D. Williamson, C. Martin, R. Newton, T. Stewart
- Behavioral Medicine
  P. Brantley, V. Meyers, H. Roy
- Women's Health Eating Behavior and Smoking Cessation Program
  P. Geiselman

CLINICAL PHYSIOLOGY AND METABOLISM

Stable Isotopes and Energy Expenditure

JENNIFER ROOD, PH.D.
Associate Professor

Faculty – Jennifer C. Rood, Ph.D., DABCC, FACB, Jim Delany, Ph.D., Lauri Byerley, Ph.D. (adjunct)

Research Team – Bruce Toth, M.A., Evest Broussard,B.S., Sunny Brogan, B.S., Leigh Anne Wade, B.S., Paige McCowan, B.S., Eric Gravois, Emily Gilliam, Annie Lewis, B.S., Lettie Harkins, B.S., George Jezek, B.S., Calista Daigle, B.S.

Focus

The Stable Isotope laboratory provides services in two areas: measurement of energy expenditure and tracers for metabolic studies.

Current Projects

Several projects were completed during the past two years that involved measurements of total body water, energy expenditure, amino acid metabolism and carbohydrate metabolism.

In order to enhance our capabilities related to energy expenditure, a Finnigan Delta XP isotope ratio mass spectrometer (IRMS) was purchased. This complements the three existing IRMSs in the laboratory. The Delta XP is equipped with two peripheral devices (and H device and a gas bench) that allow for automated analysis of samples for deuterium and oxygen 18.

An example of the studies performed in the past two years is the Pikes Peak Altitude Study. The stable isotope laboratory collaborated with the United States Army Research Institute of Environmental Medicine's Altitude Section to study a group of subjects at Pikes Peak, CO. The experiment was designed to test the following hypotheses:

1) determine if increased daily levels of activity and prolonged antioxidant supplementation will affect the incidence, severity, and duration of acute mountain sickness (AMS), markers of oxidative stress and immunity, and variables associated with acclimatization and
2) evaluate the effect of prolonged antioxidant supplementation on indicators of immune function and oxidative stress, symptoms of AMS, and ventilatory acclimatization in volunteers exposed to altitude
3) determine if carbohydrate supplementation during prolonged exercise at altitude will result in improved exercise performance. Six soldiers were administered doubly labeled water for the determination of energy expenditure and water turnover.

	Regression Analysis			
Subject	TBW, kg	kO	kD	EE, kcal/d
17	46.3	0.1891	0.1529	5915
29	72.0	0.1149	0.1152	5581
31	54.6	0.1318	0.0861	6045

The study was divided into two sections – a sea level phase in Palo Alto, CA and an altitude phase (4,300 m) at Pikes Peak, CO. Doubly Labeled Water and total daily energy expenditure were calculated. Total body water (TBW) by

Oxygen-18 dilution, the O-18 and deuterium dilution spaces (kO and kD), and energy expenditure (EE) by regression are presented below. Daily energy expenditures were quite high, about 6000 kcal/d.

The laboratory is currently re-organizing to increase its human and physical measures for the pursuit of advanced tracer and metabolic studies.

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

Energy Metabolism

Faculty – Eric Ravussin, Ph.D., Lilian de Jonge, Ph.D., Steve Smith, M.D.

Research Team –Tuong Nguyen, B.S., Carole Traoret, M.Sc., Henry Anderson

Focus

The research in the Energy Metabolism Laboratory is focused on exploring the inter-individual variability in energy metabolism in stable conditions and in response to changes in environmental conditions.

Current Projects

We have shown evidence in a group of young lean men that the adaptability of substrate oxidation to an increase in dietary fat intake varies largely between individuals but is quite consistent within a person. During 2004-2005 we expended the investigation in a group of 78 young adults with a large range of percentage body fat in the ADAPT study. Dr. Steve Smith was the Principal Investigator on this study. The data of this study are in the process of being analyzed.

Other studies in the field of energy metabolism include the impact of caloric restriction on energy metabolism. The CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) study, of which Dr Eric Ravussin is the Principal Investigator, focuses on this issue. The first phase of this study, which involved exploring the effects of 6 months of caloric restriction in 48 healthy overweight men and women, has recently been completed. We measure 24 hour energy expenditure in our metabolic chambers and resting metabolic rate (RMR) using our metabolic carts. The second phase of this study, involving 2 years of caloric restriction, is now being prepared.

We have also been looking at the effects of menopause on energy metabolism in a subset of women who participated in a large longitudinal study, originally headed by Dr. Jennifer Lovejoy, but now by Dr Steve Smith. We measured 24-hour energy expenditure and substrate oxidation in a metabolic chamber before the onset of menopause and four years later. Since a large percentage of the women were not yet post-menopausal at that time point we are now repeating the measurement at 6 years after the baseline.

All above mentioned studies involved measurement of 24H energy expenditure in our metabolic chambers. In addition to the assessment of the effects of environmental changes on energy metabolism, we are also interested in exploring the effect of potential thermogenic compounds. We have participated in a total of 26 trials over the

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

Steve Smith, M.D.
Associate Professor

Lilian de Jonge, Ph.D.
Instructor

last two years. The compounds tested included both pharmaceutical and herbal substances. The majority of those studies were performed using the metabolic carts for the assessment of the acute effects of the compound on energy expenditure and/or substrate oxidation. However, we performed two of the trials in the metabolic chambers, and in early 2006, we will start a trial measuring the effects of chromium picolinate on energy metabolism in patients with type 2 diabetes.

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

Lipoproteins Laboratory

Michael Lefevre, Ph.D.
Professor

Faculty – Michael Lefevre, Ph.D.
Research Team – Xiaoying Zhang, M.D., Hyeung-Rak Kim, Ph.D. (adjunct), Sunita Gupta, M.S., Angie White, B.S., Bong-Gi Lee (adjunct), Catharine Wolfe
Collaborators – Tuomo Rankinen, Ph.D., Marlene Most, Ph.D., David Harsha, Ph.D., George Argyropoulos, Ph.D., Steven Smith, M.D., James DeLany, Ph.D., Jennifer Rood, Ph.D., Betty Kennedy, Ph.D., Yolanda Robertson, Melody McNicholl, Lisa Miller, Connie Murla, Fatemeh Malekian, Doris Hoffpauir, Lettie Simon, William Assaf, Michelle Burton

Focus

The focus of this laboratory is to further the understanding of the interrelationships between diet composition, genetic predisposition and the progression of cardiovascular disease (CVD).

Current Projects

Within the context of our focus, three goals are currently being pursued: 1) defining the impact of macro- and micro-nutrient dietary composition on risk factors for CVD, with a specific emphasis on lipid and lipoprotein risk factors; 2) identifying genetic, anthropometric, and other factors which contribute to the substantial variations in CVD risk factor response to dietary manipulation; and 3) examining the effects of phytochemical dietary components on health. In support of these goals, the laboratory is currently involved in several specific areas of investigation.

The *Gene-Environment Trial on REsponse in African-Americans to Diet Intervention (GET-READI for Heart Health)* study examines individual CVD risk factor responsiveness to a diet known to favorably lower plasma cholesterol and blood pressure. On a population basis, moderation of both lipid profiles and blood pressure can be accomplished readily with a prudent diet. However, it is well known that CVD risk factor response to diet varies widely across the population, presumably as a result of both genetic and non-genetic influences. In this controlled feeding study, extensive assessments of baseline behavioral characteristics, anthropometric features, metabolic factors, and genetic characteristics (candidate gene analyses), will allow us to identify both genetic and non-genetic factors that predispose to response (or the lack of) to dietary interventions. The results of this investigation are expected to provide important information on the link between

a healthy diet, genetic makeup and underlying biological mechanisms. This information will help guide the design of future dietary and lifestyle interventions to combat CVD.

There is an increasing recognition that trace components in the diet may impact risk for cardiovascular disease. With respect to dietary fats and oils, emphasis has traditionally been placed on the role of their fatty acid composition to modify lipid risk factors for CVD. However, many plant oils contain additional minor components that may prove to be important in modifying CVD risk factors. In collaboration with Dr. Richard Ostlund (Principal Investigator) at Washington University in St. Louis, we are testing the hypothesis that minor components in vegetable oils play a significant role in altering plasma cholesterol levels.

Employing a series of controlled dietary trials, the study will specifically examine the effects of a variety of components in vegetable oil on cholesterol absorption and metabolism. This new research area has the potential to provide an additional independent dietary approach to lower plasma cholesterol beyond that afforded by current recommendations to reduce calories, saturated fat and cholesterol content.

The laboratory has recently completed a program that sought to systematically investigate the health benefits of functional foods from economically important, phytonutrient-rich Mid-South crops. This work was undertaken by a consortium between the University of Arkansas (lead institution), USDA-ARS Rice Research Unit; USDA-ARS South Central Agricultural Research Laboratory; Louisiana State University and the Pennington Biomedical Research Center. Bioactive compounds in concentrated extracts derived from selected crops (watermelons, red grapes, and spinach) were identified and their potential to affect metabolic processes relevant to chronic diseases was assessed. This was achieved through the use of animal models and cell culture and relied upon gene expression, proteomic, and cell signaling technologies.

While interesting data are available from all three crop extracts, work with anthocyanins derived from a unique red grape variety (in which both the skin and flesh are pigmented) has advanced the furthest. Both microarray and proteomic analysis of liver and heart tissue revealed that grape anthocyanins affected metabolic pathways governing carbohydrate and fat metabolism/disposition. Follow-up work in tissue culture confirmed effects on gene expression and demonstrated additional effects on insulin signaling. These effects are being followed-up in this laboratory as one of three major projects in the recently awarded Botanical Research Center grant.

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

EPIDEMIOLOGY AND PUBLIC HEALTH

Nutritional Epidemiology

CATHERINE M. CHAMPAGNE, PH.D.
Professor

Faculty –Catherine M. Champagne, Ph.D., RD, LDN, FADA, Donna Ryan, M.D., Betty M. Kennedy, Ph.D.

Research Team –H. Raymond Allen, Ph.D., Marlene Afton, B.S., Michelle Begnaud, RD, LDN, Courtney Brock, RD, LDN, Barbara Cerniauskas, RD, LDN, CDE, Lindsay Coates, B.S., Laura Decuir, RD, LDN, Gina Frazier, RD, LDN, Katherine Lastor, RD, LDN, Erma Levy, MPH, RD, LDN, Kate Melder, B.S., Lisa Miller, RD, LDN, Dawn Turner, B.S., Dana Vieselmeyer, MPH, RD, LDN

Focus

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

BETTY M. KENNEDY, PH.D.
Instructor

Current Projects

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

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

Previous findings indicated that Delta residents consumed diets inferior in nutrient content and quality of food servings compared to the US population. In all 3 states, pilot interventions were put into place with the investigators partnering with communities. In Louisiana, Franklin Parish was the designated pilot community. Prior to working in Franklin Parish, two pilot projects known as SHOP (Shiloh Healthy Obedience Project) and the "Rolling Store," providing access to fresh fruits and vegetables and addressing weight control in African American areas of Baton Rouge.

The Franklin NIRI piloted an intervention called PUSH (People United to Sustain Health) which focused on weight loss and improving diet by incorporating more fruits and vegetables. A larger PUSH project is currently underway with more individuals in Franklin Parish.

Dietary Counseling Activities

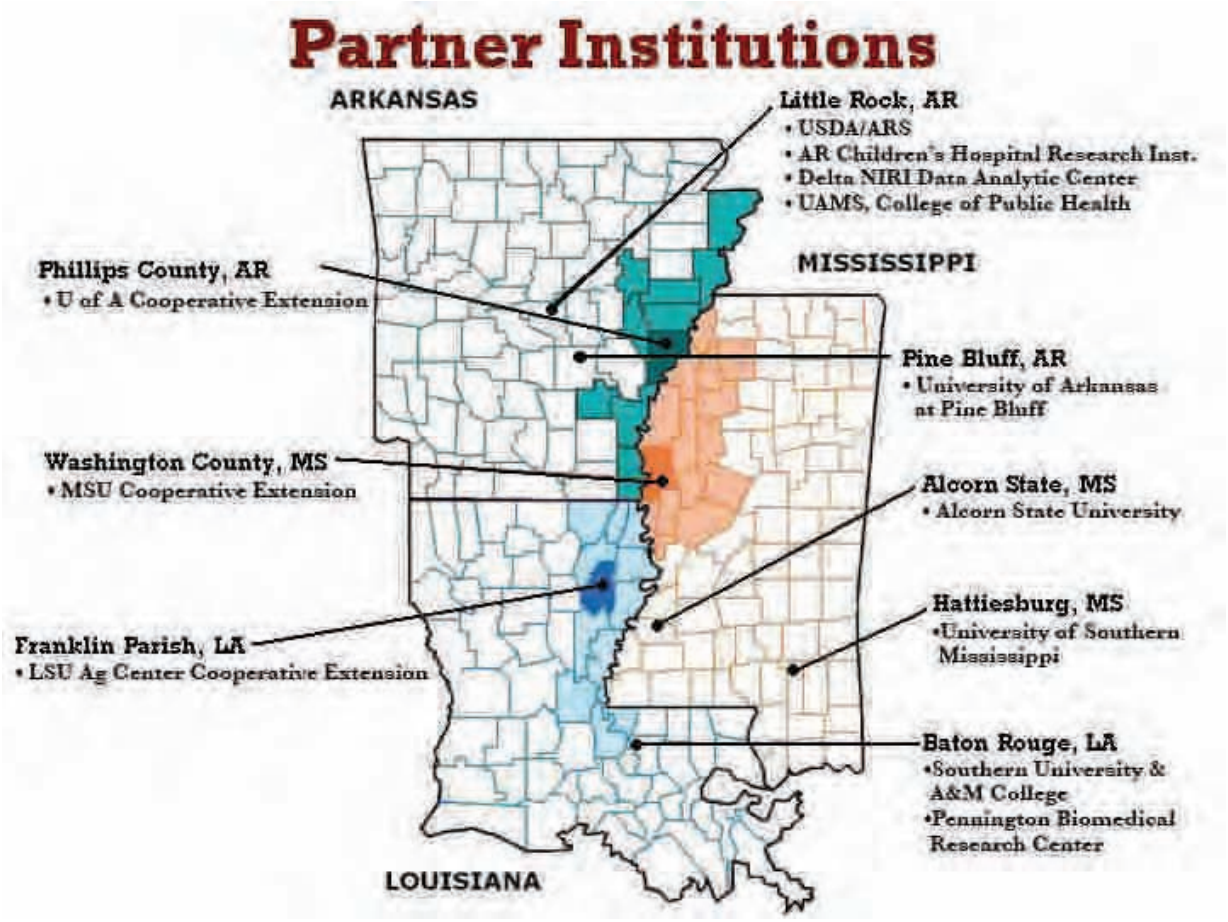
A number of projects at the Pennington Biomedical Research Center involve dietary counseling efforts. The Diabetes Prevention Project Outcomes Study (DPPOS) is following individuals from DPP who have successfully made lifestyle changes. The Look AHEAD trial focuses on lifestyle changes in a population 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 trial utilizes four different diet treatments varying in protein and fat to scientifically test these diets for weight loss

effects. Subjects are asked to follow structured meal plans or exchange options in order to adhere to the dietary targets. The research dietitians/interventionists play a key role in working with these participants by conducting both group and individual sessions utilizing nutrition information and behavior change messages.

Soldier Nutritional Epidemiology

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

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



Clinical Epidemiology

Faculty – Ronald Horswell, Ph.D.
Research Team – Shannon McNabb, M.A., Jay Besse

Focus

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

Ron Horswell, Ph.D.
Associate Professor

Current Projects

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

One project, done with collaborators (Jolene Johnson, Charles Wascom, Fred Cerise) at the Earl K. Long Medical Center in Baton Rouge, estimated the effect of a pharmacy support program on diabetes patients' HbA1c levels. The pharmacy program facilitates acquisition of diabetes oral medications for those unable to afford them. Its effect on the average program user was estimated to be an absolute reduction in HbA1c of 0.64%, although the effect was closer to an absolute 1.00% reduction among those who took full advantage of the program. The effect size also varied with number of medication refills, as shown in Figure 1. These effect sizes are clinically important.

Another recent project conducted with LSU HCSD cardiologists (Kathy Hebert, Lee Arcement) examined the relationship of anemia to survival time among systolic heart failure patients. Within the study's patient population (LSU HCSD heart failure patients), survival modeling found anemia to be independently associated with increased mortality risk among men, but not among women. However, while this association of anemia with survival has been found by us and others, the nature of anemia's role in heart failure outcomes remains ambiguous.

Over the next year, a major emphasis will be on creation of population-based patient registries covering one or more chronic disease areas, such as heart failure and diabetes. Successfully establishing these registries will increase the number of data elements available for use in identifying factors related to clinical outcomes.

Research in this unit is supported by a grant from the Agency for Healthcare Research and Quality.

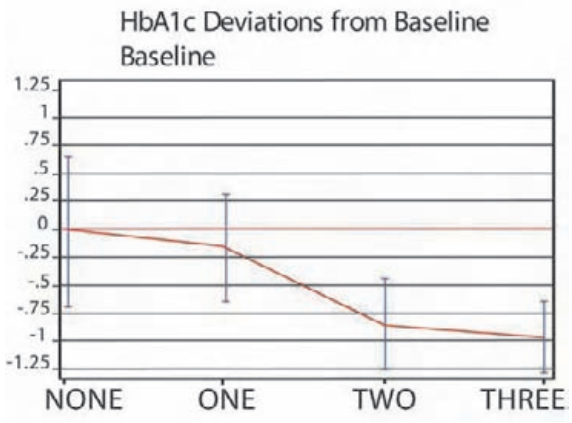


Figure 1

Chronic Disease Epidemiology and Health Delivery

Faculty – David W. Harsha, Ph.D.

Focus

The implementation of efficacy studies in behavioral interventions for cardiovascular disease, overweight, and metabolic syndrome, and the study of effectiveness of proven behavioral strategies in real world populations.

Current Projects

Our Research goals focus on two areas of health promotion. The first is the implementation of efficacy studies in behavioral interventions for cardiovascular disease, overweight, and metabolic syndrome. Past research has indicated dietary, physical activity, and other lifestyle factors to be related to risk for these conditions. Improved behavioral techniques for addressing them would be of great public health benefit.

The second is the study of effectiveness of proven behavioral strategies in real world populations. Of particular interest are programs designed to deliver these interventions to low-income, substantially minority, small town and rural populations regionally and ultimately nationally.

Future Directions

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

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

CLINICAL TRIALS

Pharmacology-Based Clinical Trials

Faculty – Frank Greenway, M.D., George A. Bray, M.D., William Cefalu, M.D., Ph.D., Kevin Elliott, Ph.D., Alok Gupta, M.D., Jennifer Rood, Ph.D., Donna Ryan, M.D., Steve Smith, M.D.

Adjunct Faculty – David Baker, DVM, Drake Bellanger, M.D., Lauri Byerley, Ph.D., Brian Despinesse, M.D., Daniel DiLorenzo, M.D., Ph.D., M.B.A., Karen Elkind-Hirsch, Ph.D., Stewart Gordon, M.D., Maren Hegsted, Ph.D., Sylvia Heidingsfelder, M.D., Michael Jazwinski, M.D., Jolene Johnson, M.D., Zhijun Liu, Ph.D., Jennifer Lovejoy, Ph.D., Louis Martin, M.D., Pamela Martin, Ph.D., John Paige, M.D., William Raum, M.D., Ph.D., David Roane, Ph.D., Heli Roy, Ph.D., Gary Sander, M.D., Lars Sjostrom, M.D., Ph.D., Melinda Sothern, Ph.D., Kaj Stenloff, M.D., Ph.D., Michael Welsch, Ph.D., Eugene Woltering, M.D.

Research Team – Yolanda Robertson, N.P., Anne Chatellier, R.N., Allison Strate, R.N., Andrew Roberts, B.S., Brandi Armond, LPN, Chrystal Duncan, LPN, Dawn Rachal, B.S., Diane Crow, LPN, Elizabeth Cadarette, B.S., Heidi Kilburn, B.S., Jana Ihrig, R.N., Kristi Rau. B.S., Liz Barber, R.N., Marisa Smith, B.S., Melody McNichol, B.S., Natalie Currier, R.D., Patricia Pinsonat, R.N., Patti Smith, B.S., Sara Schoen, R.D., Susan Mancuso, R.N., Susan Thomas, R.D., Tiffany Hudnall, R.N., Jennifer Perrault, Elizabeth Tucker, B.S., Mary Beth Burnett, Melissa Lingle, B.S., Janet Fahr, B.S., Carmella McKneely, Betsy Bernhard, B.S., Brenda Dahmer, B.S., Grace Bella, B.S., Jan Day, B.S., Annette Hutchison, B.S., Beatrice Winkler, M.S., Charles Sides, RPh., Claire Hazlett, RPh., Lura Reed, Linda Guy

David W. Harsha, Ph.D.
Associate Professor

Frank Greenway, M.D.
Professor

Alok Gupta, M.D.
Assistant Professor

Focus

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

Current Projects

Pharmaceutical trials range from testing new drug concepts to trials to determine the proper dose (phase II trials) to large trials for drug approval (phase III trials). One proof of concept trial evaluated the ability of two drugs approved for other purposes to cause weight loss. Using drugs already approved expedites the time-consuming and expensive drug approval process. One phase II drug trial sought to discover the proper dose of a hormone to help overweight people eat less fat. Center researchers studied this hormone extensively in animals; positive results eventually led to a human clinical trial.

One of the phase III studies tested rimonabant, a drug now being considered by the FDA for approval as a new obesity drug. Rimonabant gives as much weight loss as the present obesity drugs, but improves the risk factors for cardiovascular disease to a greater extent (Figure 1).

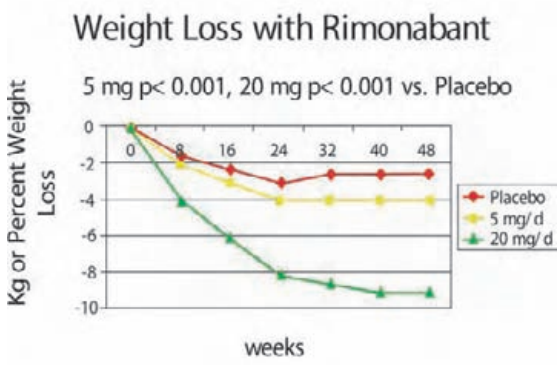


Figure 1

Obesity in the United States is growing rapidly, but most dramatically among adolescents and children. Along with the University of Kentucky, we tested bupropion for the treatment of adolescent obesity. Bupropion is approved to treat depression, to help in smoking cessation, and it promotes weight loss in adults. A drug to treat obesity in adolescents is an unmet need, since no drugs with this indication exist.

Dietary herbal supplements are foods, and studies demonstrating their efficacy are required to support advertising claims. Since ephedra has been withdrawn from the market, no effective supplements exist for the treatment of obesity. One dietary herbal supplement trial is evaluating a fat emulsion known to decrease food intake during a single day of testing. If this dietary herbal supplement also reduces body weight, the public will have access again to an effective supplement for weight reduction.

Angiogenesis, the formation of new blood vessels, is necessary for the growth of fat tissue, and inhibitors of angiogenesis reduce body fat in obese rodents. The Pennington Biomedical Research Center, the LSU-Health Sciences Center and the LSU-Agricultural Center collaborated to identify food plants that inhibit angiogenesis in a human tissue assay. One active food plant ingredient is presently in clinical trials, and another food plant is the subject of an NIH grant submission. A new pathway for stimulating lipolysis in the fat cell was discovered during the screening of food plants using a human fat cell assay.

Pilot studies in humans demonstrated effective lypolysis for one of these plants.

One of the trials testing novel foods for the reduction of obesity-related risk factors was performed in collaboration with a small Louisiana company to test the effects of a health food bar. The health bar, containing Louisiana rice bran, lowered homocysteine in the blood stream and lowered the risk for heart attacks and strokes (Figure 2).

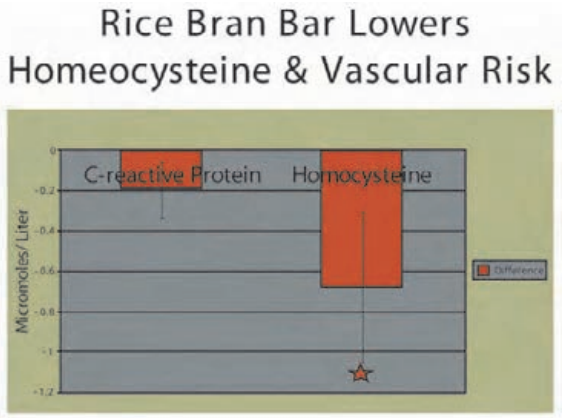


Figure 2

One of our studies of novel devices concerns a small balloon that takes up room in the stomach as a means of reducing food intake. We're investigating the balloon as a possible treatment for obesity. Another device study attempts to identify subjects who will have the greatest weight loss using a stomach pacemaker.

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 and public health in the future.

Research in this unit is supported by grants from multiple public and private grants and/or contracts, including but not limited to GlaxoSmithKline, Eli Lilly, Pfizer and Novartis.

GEORGE A. BRAY, M.D.
Boyd Professor

Diet, Physical Activity and Behavior Modification Trials

Faculty – George A. Bray, M.D.

Research Team – Donna H. Ryan, M.D., Frank L. Greenway, M.D., Steven R. Smith, M.D., Catherine Champagne, Ph.D., Jim DeLany, Ph.D., David Harsha, Ph.D., Betty Kennedy, Ph.D., Michael Lefevre, Ph.D., Corby Martin, Ph.D., Marlene Most, Ph.D., Robert Newton, Ph.D., Tuomo Rankinen, Ph.D., Jennifer Rood, Ph.D., Stephen Redmann, Jr., Ph.D., Donald Williamson, Ph.D., and the Nursing, Dietary and Clinic Staff

DONNA RYAN, M.D.
Professor

FOCUS

This unit focuses on the mechanisms, effects and effectiveness of intentional weight loss and weight management through behavior, diet and activity modification.

Current Projects

- **Diabetes Prevention Program**
- **Look AHEAD Trial**
- **POUNDS Lost Trial**

Each of these large, NIH-funded clinical trials has a significant component involving weight loss, and they have thus been linked together.

Diabetes Prevention Program Outcomes Study

The Diabetes Prevention Program Outcomes Study (DPP) is a multi-center trial that began with the question of whether either weight loss or metformin could delay or prevent the development of diabetes in individuals at high risk for this disease because they had impaired glucose tolerance. Subjects were recruited from 1996 to 1999, and the initial trial was terminated in 2001 because it had become clear that those in the weight reduction lifestyle program had benefited significantly more than in the other groups. Here is a list of some of the lessons that have been learned from this study so far. The first lesson is that the Intensive Lifestyle Program which produced a weight loss of 7% and increased physical activity, reduced the risk of diabetes by 58%. Men and women of several ethnic groups showed a similar response to weight reduction. The second important lesson was that the conversion rate of diabetes was slowed by 31% in participants treated with metformin, a drug that also produced a small but significant 2.5% weight loss. Termination of metformin did not produce a significant short term increase in conversion to diabetes. The conversion to diabetes was slowed even more by the lifestyle intervention that produced a 7% average weight loss after 6 months, and an average of 5.5% by the end of the trial at 2.8 yrs. The principal effect of the lifestyle program was weight loss, with lower dietary fat also producing a significant contribution. Within the lifestyle arm of the trial, increased exercise contributed to reducing participants' conversion to diabetes. An arm of the trial that received troglitzone for an average of 0.9 years, before the drug was withdrawn from the market, had a conversion rate that was similar to lifestyle over the same period. Among those without the metabolic syndrome at baseline, the incidence of the metabolic syndrome at three years was reduced by 41% in the ILS group and 17% in the metformin group. Success in the lifestyle program was higher in individuals with higher initial body weight, lower levels of physical activity and higher self-confidence in their ability to lose weight. Increased insulin secretion and greater insulin sensitivity at baseline were associated with a lower risk of diabetes and improved more in the lifestyle intervention group. The prevalence of hypertension and dyslipidemia increased with time in the subjects with impaired glucose tolerance. Lifestyle intervention reduced risk factors, including hypertension, low HDL and small dense LDL. Urinary incontinence was lower among the lifestyle intervention group. Participants in the intensive lifestyle group had greater reductions in CRP (inflammatory marker) and TPA (fibrinolysis marker) than placebo; metformin also produced a smaller but also statistically significant effect. Metformin produced a small but significant increase in two tests of liver function (AST and ALT). Female DPP participants showed a positive correlation between leptin and obesity across ethnic groups which was not affected by androgen levels. Depression scores at baseline were

significantly worse in women, in minority groups and those with less education. During the first year the depression scores improved more in those in the intensive lifestyle group. Activity of the autonomic nervous based on variable RR intervals is improved in the lifestyle intervention group that lost weight. Finally, fasting plasma glucose has a sensitivity of less than 60% for diagnosing diabetes compared to an oral glucose tolerance test. As time progresses with this trial there will be many more important lessons about people with diabetes and how to prevent this problem.

Study of the Health Effects of Weight Loss in Diabetics - The Look AHEAD (Action of Health in Diabetes) Trial

The Look AHEAD (Action for Health in Diabetes) trial is a 16-center randomized clinical trial in overweight and obese patients with type 2 diabetes designed to evaluate the long-term effects (up to 11.5 years) of an intensive weight loss intervention on the time to incidence for major cardiovascular events. The baseline metabolic characteristics of this population will provide a gauge for the likelihood of reaching this goal. Of the 5415 patients who were randomized, 61.3% were white, 15.6% African-American, 13.2% Hispanic, 5.1 % Native Americans, and 1.0% Asian-American. Average age at entry was 59.0 ± 6.8 years (mean ± SD). Of the participants, 60.0% were women, 32.6% were <45 years of age, and 16% >65-75 years of age. Of the women, 81.8% were postmenopausal. The duration of diabetes was 6.8 y. The group was well educated with nearly 80% completing high school and more than 45% with an income > $ 60,000/yr. HgbA1 at baseline was 7.28%; more than 25% had HgbA1 < 6.5% and less than 25% had HgbA1 > 8.5%. The mean fasting glucose at entry was just over 150 mg/dL. An average of 15.0 % of participants were taking insulin, 25% a TZD and 45% a sulfonylurea. Other medications included statins (41%), niacin (1%), ACE inhibitors (41%), calcium channel blockers (16.5%), beta-blockers (17.5%) and diuretics (18.5%). Antidepressants were used by 16.5% of participants. 13.2% had a history of cardiovascular disease; this was more than twice as high in men. Average TC was 190 mg/dL, LDL Chol 112 mg/dL, HDL Chol 43 mg/dL and TG 182 mg/dL Women had higher TC, LDL-C and HDL-C but lower TG than men. Blood pressure averages 128/70 mmHg. Only 4.3% were current smokers. More women than men were in the never smoking category. Overall, BMI averaged 37± 5.0 kg/m2 at baseline, and was similar in all groups except Asians where none of the men and only 21% of the women had a BMI > 35 kg/m2. More than 75% had a BMI > 30 kg/m2. Among the women >25% of women (Hispanic 20% and Asian 9%) had a BMI > 40 kg/m2 and among the men > 18% had a BMI < 40 kg/m2 except (Hispanic 16%, American Indian 13% and 0% Asian). This population also had central adiposity as shown by the waist circumference of 116 cm. The Look AHEAD project has successfully recruited a type 2 diabetic cohort for long-term evaluation of the lifestyle intervention.

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

The trial called Prevention of Obesity Using Novel Dietary Strategies (POUNDS LOST) is a trial conducted at the Harvard School of Public Health and the Pennington Biomedical Research Center. Recent investigations have focused on manipulating the macronutrient content of the diet (increasing the proportion of energy derived from fat and/or protein and decreasing the proportion derived from carbohydrate) as an alternative to the low-fat, high-carbohydrate, weight-loss diet. The hypothesis that lower-carbohydrate diets may be effective for weight loss, although well promoted in the popular press, has not been systematically investigated in free-living individuals, particularly with long-term follow-up beyond 3-6 months. This trial will be a well-controlled, clinical study of the relative effectiveness of diets varying in fat, protein and carbohydrate for weight loss and its long-term maintenance in free-living overweight men and women who receive a standardized behavior and exercise program. The primary specific aim of this study is to compare four diets, differing in fat, carbohydrate and protein composition, on weight-loss and its long-term maintenance. 800 overweight or obese people will be randomized among four diets: (1) low-fat, average protein; (2) low-fat, high protein; (3) moderate fat, average protein; (4) moderate fat, high protein. The low-fat, average protein diet will be the reference diet to which the other three dietary approaches will be compared. Change in total body weight after 24 months will be the primary outcome variable. Change in total body fat, measured by dual-energy x-ray absorptiometry (DXA), visceral fat, measured by CT, and waist circumference are secondary outcomes related to the primary aim. Our hypothesis is that an intensive behavioral program to teach and foster an energy-restricted low-fat diet will succeed in long-term treatment of obesity after 2 years. An alternative hypothesis is that reduction in energy intake and weight loss can be best achieved by reducing intake of all macronutrients and leaving unchanged the usual moderate content of dietary fat. This hypothesis has support from several recent trials that found either no difference in weight loss with low-fat vs moderate-fat diets, or even long-term superiority of moderate-fat diets. Long-term adherence may be related to enhanced diet satisfaction. Primary Specific Aim 1b tests the hypothesis that an intensive behavioral program to teach and foster an energy-restricted moderate-fat diet will be as successful or more so than a low-fat diet in long-term treatment of obesity after two years. A high protein may improve weight loss by reducing glucose and insulin responses to meals resulting in a more stable postprandial response, by increasing satiety, and by causing a greater thermic effect. Limited data from weight loss trials suggest improved weight loss with high protein. Primary Specific Aim 1c tests the hypothesis that high protein (25% energy) substituted for carbohydrate will improve weight loss in the context of either a low-fat or a moderate-fat diet after two years.

The proposed trial has four diet groups: low-fat and average-protein, low-fat and high-protein, moderate-fat and average-protein, and moderate-fat and high-protein. The moderate-fat and high-protein will replace carbohydrate. Primary Specific Aim 1d will determine which of these four diets has the most success in weight loss after two years. The low-fat, average protein diet will be the reference diet to which the other three dietary approaches will be compared. The efficacy of the specific diets will be determined during the first six months when weight loss tends to be maximal, and effectiveness for maintenance of weight loss over a two-year period. We hypothesize that diets higher in protein will be more effective for sustained weight loss regardless of fat content. The investigators do not have a consensus view on whether low-fat or moderate-fat will produce better long-term weight loss, as discussed in Section B. Thus, the trial has overt "equipoise" as to this controversial issue. We will also test the hypothesis that, compared to diets higher in fat or protein, adherence to a low fat, high carbohydrate diet is hampered due to reduced palatability and diet satisfaction. We will explore this hypothesis by comparing the changes in variable analogue scale measures of hunger, satiation, and fullness as well as measures of quality of life. Another hypothesis that high baseline insulin, higher baseline RQ and lower VO2 max will predict lesser weight loss and more weight regain during maintenance. This hypothesis is based on clinical studies showing a relation of higher RQ, higher insulin and lower VO2 max with weight regain and lower fat oxidation. A last hypothesis will determine the long-term effects of the protein, fat, and carbohydrate content of weight-loss diets on risk factors for cardiovascular disease, including blood pressure, plasma lipids, and insulin sensitivity.

As of November 1, 2005, all 800 individuals had been enrolled into this trial with 200 allocated randomly to each of four arms.

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

DONALD WILLIAMSON, PH.D.
John Stauffer McIlhenny
Professor in Nutrition

HEALTH PSYCHOLOGY

Behavioral Approaches for the Prevention and Treatment of Obesity

Faculty – Donald Williamson, Ph.D., Corby Martin, Ph.D., Robert Newton Jr., Ph.D., Tiffany Stewart, Ph.D.

Research Team – Steve Anton, Ph.D., Amy Bachand, M.A., Ray Allen, Ph.D., Archana Acharya, M.S., Robin Barnes, Danielle Bellotte, Leah Blaize, Catherine Blappert, Carolyn Brinkley, MBA, Sandra Coulon, Kenyatta Esters, MNS, MPA, Chris Goff, Helen Guay, MA, RD, Hongmei Han, M.Ap.Stat., Kelly Lefleur, MS, LDN, RD, Eric Leblanc, Leslie Lewis, MPH, LDN, RD, Sean Marshall, David Martin, Sandra May, MS, LDN, RD, Sridhar Pallapotu, M.S., Shelly Prince MS, LDN, RD, Heather Walden, M.S.

CORBY MARTIN, 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.

Current Projects

The *Wise Mind* study tested the efficacy of an environmental approach for the prevention of weight gain in children enrolled in grades 2 through 6 at five schools. The study began in the fall of 2003 and the participants have now completed the intervention that was tested over 18 months. The primary aim of *Wise Mind* was to test whether a primary prevention program that targets weight gain prevention (Healthy Eating and Exercise; HEE) was more efficacious in comparison to an active control group that targets prevention of substance abuse (Alcohol/Drug/Tobacco prevention; ADT). After 1.5 years of intervention, participants with a BMI %tile < 50 gained, on average, +2.48 BMI %tile. In contrast, students between the 50th and 85th BMI %tile lost -1.13 BMI %tile and students with a BMI > 85th %tile lost -1.09 BMI %tile. The BMI differences for children above and below the 50th %tile were statistically significant. These findings suggest that both prevention programs were associated with prevention of inappropriate weight gain, but the program that specifically targeted weight gain prevention yielded effects that were comparable to those of the active control group.

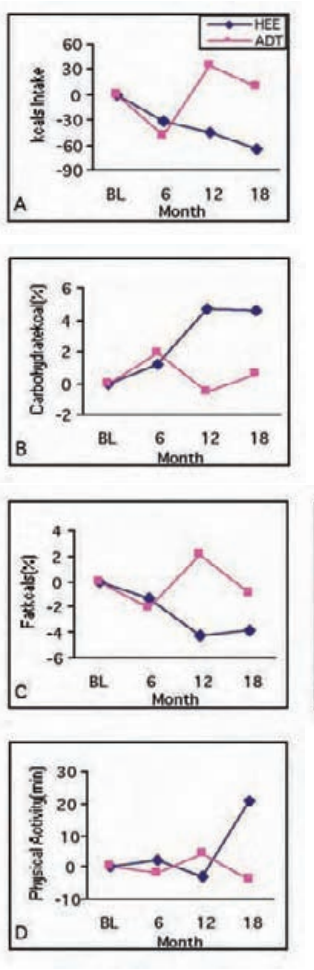


Figure 1 A *Food consumption (kcals) change for each treatment over time; B) Changes in carbohydrate intake (% of total kcal) for each treatment arm over time; C) Changes in fat intake (% of total kcal) for each treatment arm over time; D) Physical activity changes associated with each treatment arm over time.*

One feature of the *Wise Mind* study was the modification of food preparation and service of foods in the school cafeteria. Figure 1 summarizes the findings that are derived from the digital photography method. Figure 1A shows that after 1.5 years, total caloric intake of students in the HEE weight gain prevention program was reduced, while the caloric intake of students in the control arm, ADT, increased. Figure 1B illustrates that carbohydrate intake (% of total calories) for the HEE students increased, but the carbohydrate intake of students in the control (ADT) arm did not change over the 18 months of the study. The opposite pattern was observed for dietary fat (Figure 1C), with students in the HEE schools eating significantly less fat during Months 12 and 18 and no changes in fat intake for the students in the ADT schools. Of significance is the fact that the dietary fat intake of the HEE approached the recommendation that children should consume a diet of no more than 30% fat. Figure 1D illustrates changes in self-reported physical activity. Minutes of physical activity by the HEE group increased by Month 18, which was significantly higher than the physical activity of the ADT group, which did not change from baseline.

The *LA Health* study represents the joint efforts of National Institutes of Health, USDA, the Louisiana State University Board of Regents, and the Pennington Biomedical Research Center to address the childhood obesity problem. Beginning in September 2006, this research study will test the efficacy of two school-

based prevention programs (combination of primary and secondary prevention and primary prevention alone) that are designed to prevent weight gain in children initially enrolled in grades 4 to 6 over a three-year period. The study is based on the results of two pilot prevention studies and collaborates with an ongoing U.S. Department of Education (USDE) project, LA GEAR UP. The LA Health project is the first statewide obesity prevention program that has been developed by the Pennington Biomedical Research Center.

A study conducted for the Department of Defense (DoD), *Military Health Behaviors: Promotion of Healthy Weight and Fitness in Career Personnel,* was initiated in May 2003. This research study has three primary aims: (1) development of a computerized database that can record and track results of the Army Physical Fitness tests and body weight/fatness measurements across time, (2) development of an environmental/internet-based intervention to promote healthy weight and physical fitness, and (3) tests of efficacy for weight management and consumer satisfaction with the environmental/internet-based intervention in a single population, i.e., soldiers at Fort Bragg, N.C. During Phase 1 of this study a prototype for the computerized database was established and the architectural design of the internet-based intervention was developed. Phase 2 has also been completed, and consists of three steps: (1) beta testing of the computerized database, (2) development of the environmental/internet-based intervention, and (3) collection of baseline data for the program evaluation of the next phase. We are currently in Phase 3, during which the program evaluation will be completed. This phase will include two steps: (1) implementation of the environmental/internet-based intervention and (2) collection of data for two years.

Another DoD sponsored study, *Weight Measurements and Standards for Soldiers*, will be conducted with Reservists assigned to the 94th Regional Readiness Command in New England. The primary focus of this 3 year study is to: 1) implement a computerized database to track the fatness and physical performance of Reservists assigned to the 94th RRC, 2) provide the 94th RRC with an environmental /internet based intervention to increase health risk communication and promote healthy body weight /fatness and physical performance, 3) monitor the fatness and physical performance of the Reservists for 2 years following a 1 year baseline period to evaluate the efficacy of the intervention, and 4) evaluate consumer satisfaction with the intervention.

The Eating Behavior Laboratory is a state-of-the art laboratory for objectively measuring eating behavior in humans. This lab completed five industry-sponsored projects that tested the efficacy of foods, medications, herbal products, and behavior modification tools for reducing food intake. These studies provide controlled evidence supporting the use of these strategies for modifying eating behavior.

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

ROBERT NEWTON JR., PH.D.
Instructor

TIFFANY STEWART, PH.D.
Instructor

Behavioral Medicine

Faculty – Phillip J. Brantley, Ph.D., Pamela Davis Martin, Ph.D. (adjunct), Valerie H. Myers, Ph.D., Heli Roy, Ph.D. (adjunct)
Research Team – Geralyn Datz, Ph.D.,Glenn N. Jones, Ph.D., Brooke Barbera, Shannon Blackstone, Jamie Bodenlos, Margaret Cowles, Lisa DePasquelle, Garreth Dutton, Karen Grothe, Jenny Palcic, Dawn Rachal, Patti Smith, LeKeisha Tatman, Dorothy Whitehead

Phillip J. Brantley, Ph.D.
Professor

Focus

Understanding 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.

Current Projects

The Behavioral Medicine Laboratory has two primary research sites, one at the Pennington Biomedical Research Center and the other at Earl K. Long Medical Center in Baton Rouge. Research has demonstrated that behavioral interventions promoting healthy eating habits and increased physical activity result in weight loss and improved health outcomes. Our clinical unit continues this line of research by conducting studies to: (1) determine if behavioral techniques demonstrating effectiveness in traditional clinical trials can be successfully translated and applied to real world settings such as primary care clinics (2) examine whether behavioral techniques can be successfully adapted for diverse and underrepresented populations who typically experience minimal success with traditional behavioral programs (e.g., African American women), (3) develop innovative techniques to prevent weight regain in individuals who have lost weight, and (4) isolate factors associated with maintenance of weight loss.

A major factor contributing to the rise in obesity is weight regain after initial weight loss. Research has shown that short-term weight loss can be reasonably attained, however weight regain is extremely common. National guidelines emphasize the need for behavioral approaches to achieve reduced energy intake through improved dietary choices and increased energy expenditure through physical activity. Many of these reports acknowledge the difficulty of sustaining long-term weight loss, and suggest that weight loss programs include a prolonged weight maintenance component. Despite this recommendation, little data are reported on the needed content, structure, and mode of delivery for successful maintenance programs.

The Weight Loss Maintenance (WLM) trial is an ongoing multicenter randomized trial comparing alternative strategies for maintaining long-term weight loss in participants who lost weight in a group based lifestyle change program (Phase I). Our unit at the Pennington Biomedical Research Center is one of four clinical sites participating in the study. Other sites include: Duke University Medical Center, Johns Hopkins Medical Center and Kaiser Permanente Center for Health Research in Portland, Oregon. Adults were eligible if they were overweight/obese and on medications for hypertension and/or

dyslipidemia. During the initial weight loss phase, 1,685 participants entered a state of the art, behavior-change program consisting of weekly group sessions promoting calorie reduction, increased physical activity, and a low-fat eating style based on the DASH diet (Dietary Approaches to Stop Hypertension). Individuals who successfully lost 4 kg or greater were randomly assigned to one of three conditions: (1) a Personal Contact intervention that provided monthly contacts primarily via telephone; (2) an Interactive Technology intervention that provided frequent contacts through a state-of-the-art interactive Web-based program, or (3) a Self-Directed control group. All participants have completed Phase I, and intervention and monitoring for Phase II are underway. The primary outcome for the study is weight change from the end of the initial weight loss program to the end of the 30-month weight maintenance intervention period.

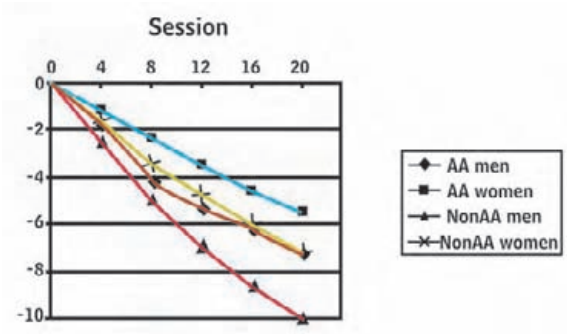


Figure 2 *Weight Loss maintenance Trial Phase 1 Mean Weight Loss.*

Of the phase I participants randomized to Phase II, 44% are African American (AA) and 67% are female. Mean (SD) weight change at the end of Phase I was -6.2 kg (5.1), and 63% lost greater than the 4 kg required for Phase II eligibility. Mean (sd) weight loss varied by sex-race subgroups: AA-men (-5.8 kg/4.8); non-AA-men (-8.8 kg/6.4); AA-women (-4.5 kg/4.3); and non-AA-women (-6.2 kg/4.5) (Fig. 1). All subgroups achieved clinically significant weight loss, although average weight loss was lower among African Americans and women. Data from Phase I suggest that the WLM trial has successfully recruited a large and diverse population, and that most individuals achieved substantial and clinically relevant weight loss.

Additional studies have attempted to translate methods proven efficacious in controlled clinical trials to primary care medical settings. The Primary Care Office Management of Obesity (PCOMO) study examined two types of physician directed behavioral weight loss interventions designed to prevent weight gain and promote weight loss in low-income women attending primary care medical clinics. Training physicians to use the current NIH guidelines for managing overweight and obese patients was successful in preventing weight gain. More extensive physician training along with carefully prepared tailored scripts and handout materials resulted in modest weight loss. Current efforts are examining predictors of treatment success and weight regain. In addition to PCOMO, other primary care studies have examined the use of previously successful clinical trial techniques to promote physical activity in sedentary

HELI ROY, PH.D.
Associate Professor (adj)

VALERIE H. MYERS, PH.D.
Instructor

adults and to enhance medical adherence in patients with diabetes.

Finally, the Behavioral Medicine Laboratory has made significant contributions (i.e., staff training, intervention development) to the Louisiana Obese Subjects Study (LOSS; Donna H. Ryan, M.D., Principal Investigator). This five-year pragmatic clinical trial will compare two methods of medical management for obese participants enrolled in the Louisiana state employees health insurance program (Louisiana Office of Group Benefits).

Research in the unit is supported by grants from the National Institutes of Health, the Louisiana Department of Health and Hospitals and the Louisiana Office of Group Benefits.

PAULA J. GEISELMAN, PH.D.
Associate Professor

Women's Health Eating Behavior and Smoking Cessation Program

Faculty – Paula J. Geiselman, Ph.D.,
Research Team – Megan Apperson, Amanda Manning, Michael Businelle, and Kelly Keeton

FOCUS

To study the robust role of fat and other macronutrient intake and fat preferences in the control of appetite and body weight in pre- and post-menopausal women following smoking cessation.

Current Projects

STOP I (Smoking Treatment/ Obesity Prevention): Development of an Individually Tailored, Multidisciplinary, Dietary Control and Exercise, Weight Management and Smoking Cessation Program for Weight Concerned Women

STOP II (Smoking Treatment/ Obesity Prevention): Obesity Prevention after Smoking Cessation in Menopause.

A reason that many women begin and continue to smoke is to control appetite and reduce body weight, and women are more likely than men to report using smoking as a weight-control strategy. Women get more weight control benefits from smoking and suffer more postcessation weight gain than men. Furthermore, middle-aged women gain more weight postcessation than do young women.

One of the primary nicotine withdrawal symptoms differentiating men and women is increased appetite in women. Although increased food intake has been implicated in postcessation weight gain, the issue of effects of smoking and smoking cessation on specific macronutrient intakes is not yet resolved. There have been no studies that have tested macronutrient self-selection in a validated and reliable paradigm that significantly and systematically varies macronutrient content in a wide spectrum of foods in which fat is commonly consumed in the American diet.

The specific aims of the STOP program are as follows. **Aim 1 -** To assess specific macronutrient intake (fat, sugar, complex carbohydrates, and protein) and total caloric intake in pre- and post-menopausal women at baseline while still smoking and at regular intervals following smoking cessation. Pre-menopausal women were tested in the late luteal phase. There are no published studies that have tested the interrelationships among these variables, nor have any studies tested food choices in smokers in a validated, reliable

macronutrient self-selection paradigm. (We are using the Geiselman Macronutrient Self-Selection Paradigm © [MSSP] and the Geiselman Food Preference Questionnaire © [FPQ] to test this specific aim. **Aim 2 -** To compare the relative effectiveness of an empirically validated smoking cessation program followed by either 1) a group cessation maintenance program with standard exercise advice and food pyramid instructions for healthy eating, or 2) an individually tailored dietary control and exercise weight management program in women, assessed by weight change and drop out rates following completion of the smoking cessation program.

Results showed that abstinence rates were significantly higher among the women randomized to the individually tailored intervention than among those assigned to the group intervention. Differences between conditions in postcessation weight gain were not significant. However the postcessation weight gain that did occur was significantly associated with subsequent smoking relapse in the group condition only.

Results also suggest that both pre- and post-menopausal women who quit smoking increase their intake of high fat/high sugar (HF/HS) foods (Figure 1.). The present results indicate that the postcessation increase in intake cannot be attributed to the fat content of these foods independent of the other macronutrient content, nor can this effect be generalized to all high fat/high carbohydrate foods. This is concluded because women did not show a postcessation increase in their intake of high fat foods that are high in either complex carbohydrate (HF/HCCHOO) or protein (HF/HP). Further, the increased intake of high fat/high sugar foods is apparently not due specifically to the sugar content of the foods. This is concluded because the women tended to show a postcessation decrease in intake of high sugar foods that did not have a high fat content. Hence, it may be concluded that women who quit smoking tend to increase their intake specifically of high fat/high sugar foods. Foods that are high in both sugar and fat content may be especially conducive to hyperphagia and weight gain and, therefore, may contribute to the weight gain that is often observed in women postcessation.

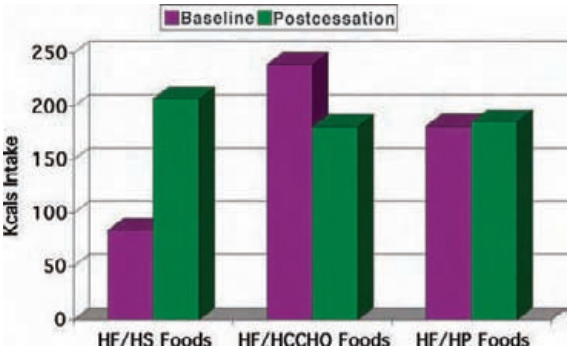


Figure 2 *Baseline and postcessation intake (kcals) of high-fat/high-sugar (HF/HS), high-fat/high-complex-carbohydrate (HF/HCCHO), and high-fat/high-protein (HF/HP) foods in premenopausal women in the late luteal phase of the menstrual cycle.*

Research in this unit is supported by grants from the National Institutes of Health, and the Bristol-Myers Squibb Foundations.

CORE SERVICES

Animal Metabolic and Behavioral Core

Gregory Holmes, Ph.D., Leslie McLaughlin DMV, Ph.D.

The newly established Comparative Behavior and Metabolic Core brings together several existing systems for the non-invasive assaying of metabolism, body composition and activity in rodents.

Central to the Core are the Columbus Instruments Inc. OxyMax (tm) indirect calorimeters for the 24/7 measurement of energy expenditure and substrate oxidation. The original Oxymax system is capable of recording metabolism of up to 16 mice or rats. The recently upgraded Oxymax CLAMS (Comprehensive Laboratory Animal Monitoring System) is dedicated to the minute-by-minute monitoring of up to 16 mice. The CLAMS system provides faster (3X) rate of data acquisition combined with greater sensitivity of oxygen and carbon dioxide sensors. The CLAMS system also monitors feeding bouts, volume of food intake and animal activity. Both metabolic units are enclosed in temperature-controlled units that can regulate the ambient temperature of the individual animal chambers.

The Comparative Behavior and Metabolic Core also includes a Bruker Minispec mq NMR and MiniMitter 96-unit computer automated running wheels. The Minispec is a dedicated benchtop NMR instrument for whole body fat and lean tissue analysis for live mice, other small animals and tissue samples. The running wheels provide long-duration, home-cage activity data for mice.

Leslie McLaughlin,
DMV, Ph.D.

Biostatistics and Data Management Core

Stephen M. Redmann, Jr., Ph.D., Ronald Horswell, Ph.D., Julia Volaufova, Ph.D. (adjunct), Lynn R. LaMotte, Ph.D. (adjunct), Anthony Alfonso, M.Ap.Stat., Connie Murla, B.S., Aimee Stewart, B.S., Jessica Arnold, M.S., Richard Heap, B.S.

As the name implies, the Biostatistics and Data Management Core has two primary functions. Through collaboration with Center scientists, our biostatisticians provide statistical support for clinical and

STEPHEN M. REDMANN, JR., PH.D.
Assistant Professor

non-clinical studies conducted at the Center. And, our data management team, consisting of systems analysts and applications programmers, is responsible for implementation and maintenance of the Central Clinical Database, the institution's primary archive of clinical research data.

Biostatistical functions of the Core include general statistical consultation, experimental design consultation, sample size determination and power analyses, data analysis and interpretation, and reporting of results of clinical studies. In addition, our biostatisticians pursue independent research in statistical theory and methods related to the planning and conduct of clinical trials.

The database management team's responsibilities center on the prime mission of creating and maintaining the unified central database for clinical data at PBRC. In addition, our programmers are charged with development of the specialized applications that are used to collect clinical data from diverse sources throughout the institution. Also, this group has responsibility for the continuing development of CDA, an application that provides authorized users a web-based portal to the clinical database.

Cell Culture Core

Carola Leuschner, Ph.D., Janice Keener

The cell culture core provides opportunity for the use of equipment specifically applied to cell culture needs. The cell cultures can originate from humans or animal sources and serve as models for human diseases like cancer, obesity, diabetes, coronary artery disease, neurological diseases, as well as providing access to stem cell research.

The cell culture core offers an introduction and if required expertise in handling various cell cultures including the accessibility for cell cultures as model systems for research projects. Scientists using the cell culture core are trained in handling of biohazards, sterile techniques and receive assistance in setting up cell cultures, including basic skills required for cell culture research. The cell culture core is housing a number of equipment items, which are shared among seven laboratories and scientists and include water jacketed incubators, water baths, cryotanks for short and long term storage of cell cultures, laminar flow hoods, and microscopes. The cell culture facility also has refrigerators and freezers for storage of culture media and supplements.

Clinical Chemistry

Jennifer C. Rood, Ph.D., DABCC, FACB, Stacey Roussel, M.T. (ASCP), Stephen Lee, M.T. (ASCP), Sandra Richard, M.T. (ASCP), Carla Kimmel, M.T. (ASCP), Margaret Graves, M.T. (ASCP), Denise Stein, M.T. (ASCP), Elizabeth Soroe, M.T. (ASCP), Jamie Tuminello, M.T. (ASCP), Dale Achord, M.T. (ASCP), Josephine Cushenberry, Carlo Milo, Donald Lewis, Lisa Jones, Sunni Page, Valery Berrigan, Sharon Thomas

The mission of the Clinical Chemistry Core is to develop innovative methodology, provide accurate and timely tests results and foster a climate of personal and professional achievement. The Core performs more than 250 different clinical

assays to support clinical trials, basic researchers, the U.S. Army Institute of Environmental Medicine, and contracting clients. During 2004, more than 246,000 assays were performed. There has been tremendous growth in the laboratory during the past year; we performed 625,000 assays in 2005. Two new medical technologists, two research specialists, and a specimen courier were added to support the additional workload.

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 participated in the Centers for Disease Control and Prevention National Heart, Lung, and Blood Institute lipid standardization program. All medical technologists and phlebotomists are licensed by the Louisiana State Board of Medical Examiners. In addition, all of the lab's medical technology staff are registered by the American Society of Clinical Pathologists Board of Registry.

A major asset to researchers at the Center is having access to a laboratory that is continually developing and implementing new methodologies. New assays developed during 2004-2005 include the following: atrial naturetic peptide, microalbumin, enterostatin, 22 cytokines, insulin like growth factor binding protein 1, insulin like growth factor binding protein 3, tartrate resistant acid phosphatase, intact n terminal propeptide of type I procollagen, bone specific alkaline phosphatase, and C-terminal telopeptide of Type I collagen.

The laboratory recently purchased three new instruments that will allow the Center to be at the forefront of clinical medicine. The instruments include a Beckman Coulter DXC600 PRO automated chemistry analyzer, an ACL 8000 coagulation instrument and an Array 360 CE protein analyzer.

Comparative Biology Core

Barry Robert, D.V.M., Ph.D., DACLAM, Cindy Kloster, B.S., RVT, RLATG, Linda Chase, RLAT, Deborah Minor, ALAT, R. Faye Louviere, ALAT, Cynthia Angelloz, Genevieve Bazer, Hsin Hsin Hsu, Namiger Ozoral, Emily Wilson, Jennifer Garidel, Monique Simmons, and Tracy Brown.

The Comparative Biology Core's mission is to provide superior animal housing space, complete animal husbandry and veterinary care services, training, and technical support for Pennington Biomedical Research Center scientists using animal models. The attending veterinarian, a registered veterinary technician, and laboratory animal care technicians staff the Core. The Core is a 38,000-square-foot centralized service facility that includes laboratory animal housing, receiving and quarantine facilities, animal procedural, behavioral testing and surgical laboratories, and a diet preparatory area.

The Core is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. This accreditation represents the "gold standard" for laboratory animal

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

care and use, underscoring the Center's commitment to the highest quality laboratory animal program. The Core unconditionally endorses and complies with the NIH *Public Health Service Policy on Humane Care and Use of Laboratory Animals, The Guide for the Care and Use of Laboratory Animals*, and the *USDA Animal Welfare Act and Regulations.* These documents carefully delineate our responsibility for the proper care, use, and treatment of all laboratory animals. Furthermore, the Center's Institutional Animal Care and Use Committee composed of scientists, a veterinarian, and a community member, must review and approve the care and use of all laboratory animals at the Center.

As part of our commitment to excellence in animal care and use, we are dedicated to providing training opportunities to the research staff and Core personnel. Core staff presents an animal care and use orientation program for all new research employees using laboratory animals and offer specific technical training in laboratory animal biomethodology for scientists and their staff members. For Core personnel, an on-going training program based on the American Association of Laboratory Animal Care's Laboratory Animal Technician series is administered in Comparative Biology to assure that our staff is following all applicable regulations and providing the highest standards of care to our laboratory animals.

Dietary Assessment and Food Analysis Core

Catherine M. Champagne, Ph.D., RD, H. Raymond Allen, Ph.D., Eric A. LeBlanc, B.S., Dawn R. Turner, B.S., Mary Marlene Afton, B.S., Lindsay L. Coates, B.S., Katherine Melder, B.S.

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 (2005). Primary datasets used are from USDA. The total count of foods and recipes contained within the MENu food composition files numbers 19,516, from the following data sources:

- Release 16 of the USDA Nutrient Database for Standard Reference (March, 2003).
- The 1994-1996, 1998 USDA Survey Database which is used to conduct the Continuing Survey of Food Intakes by Individuals *(U.S. Department of Agriculture, Agricultural Research Service. 2000. Continuing Survey of Food Intakes by Individuals 1994-96, 1998, CD-ROM).*
- 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. In 2004 and 2005, approximately 67,000 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 we are using scannable questionnaires with results exported as an electronic file, and about 1,400 food frequencies were processed during the last two years.

Genomics Core

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

DNA Sequencing, Real-Time PCR, Robots, Agilent Bioanalyzer, Microarray Hybridization, Development of Future Core Services, Consultation and Training

Susan Newman, B.S., Katrina Carter, M.S., Robert Koza, Ph.D.

Bioinformatics

Andre Ptitsyn, Ph.D.

The Genomics Core Facility (GCF) provides DNA sequencing, DNA fragment analysis, qualitative and quantitative analysis of DNA and RT–PCR and RNA samples, quantitative PCR, Microarray Services, hybridization, and scanning, robotics, and bioinformatics services. Individual and small group training and consultation services are offered for sequence analysis, real-time PCR, and microarray analysis. The GCF laboratory services are available to any researcher. The goal of the GCF is to provide high quality service at low cost to facilitate research. Use of the Genomics Core Facility services are scheduled on a first come, first serve basis. The wait time for instrument use is rarely more than one day and is frequently shorter.

The core laboratory is approximately 900 square feet. Two ancillary laboratories house microarray hybridization, scanning, and microarray spotting instrumentation.

The laboratory is equipped with two sixteen capillary genetic analyzers, an Applied Biosystems 3130 and a 3100. These instruments perform DNA sequencing and fragment analysis. They will accommodate 96 well and 384 well format sample plates. Four Applied Biosystems 7900HT Sequence Detection Systems equipped with 96 well, 384 well, and low density array blocks are available for quantitative PCR. An Applied Biosystems 1700 microarray system is available for researchers who wish to use a commercial microarray system. The microarray facility produces high-density microarrays from mouse (Operon, 16,463 probe oligonucleotide library) and human

(Compugen, 18,861 probe oligonucleotide library) as well as several cDNA libraries generated by scientists at the Center. Slides are printed with a GeneMachine OmniGrid Microarrayer equipped with server arm and scanned using a Perkin-Elmer ScanArray 5000. 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. An Agilent 2100 Bioanalyzer is used for DNA and RNA analysis and quantitation. Three computer workstations are used for sequence analysis and alignment, PCR primer design, and quantitative RT-PCR data analysis.

Imaging Core

Steven R. Smith, M.D., Harris Lappin, M.D., Julia St. Amant, RRT - CT; Michelle Neptune, B.S. - DEXA, Kimberly Landry, B.S. - Echocardiography and ultrasonography; Bradley Newcomer, PhD., consulting physicist

1) **BioImaging (structural imaging)** DEXA [Hologic QDR 4500]: body composition/bone mineral density, CT: [in collaboration with the Baton Rouge General Hospital] multi-slice visceral fat measurement, hepatic fat, and skeletal muscle fat MRI: multi-slice visceral fat [operational Jan 2006] Echocardiography
2) ***in situ* Biochemistry and Metabolism (Magnetic Resonance Spectroscopy - MRS)** MRS [current]: ^{1}H intramyocellular lipid, ^{1}H intrahepatic lipid content MRS [planned]: ^{31}P phosphocreatine, ^{1}H myoglobin content, in vivo P/O ratio, ^{31}P ATP turnover rate, ^{13}C TCA cycle)

Background:

Energy metabolism is a fundamental biological process that generates high energy phosphate bonds in the form of ATP from a wide variety of carbon based molecules such as carbohydrates, fatty acids, proteins and ethanol. A complete understanding of the regulation and dysregulation of these key biological processes requires a multi-disciplinary team capable of examining an organism from the whole body to the molecular level. These techniques cannot exist in isolation. The integration of multiple scientific paradigms is essential to the process of unraveling the tissues, organelles and subcellular systems that integrate in space/location and time to generate the physiologic pathways that lead to obesity. Although the environment is often blamed for the current obesity epidemic, there is strong evidence that the environment and the biologic *susceptibility* converge in a single individual to increase energy stores and produce the subsequent disordered metabolism. From this perspective, susceptibility or resistance to an obesogenic environment can occur at many levels but the ultimate result is the partitioning of the 'excess' ATP into fatty acids. Lipid storage in adipose tissue and other organs occurs concomitantly with activation of specific cell signaling pathways and transcription/translation; this leads to

altered cellular structure and function. The ability of an organism to dissipate energy during periods of energy excess is one of many mechanisms the body uses to limit the growth of energy stores.

The 'classic' tools used to precisely measure body composition (DEXA, CT scanning, MR Imaging) and energy metabolism (metabolic carts and whole room calorimetry) are essential to modern clinical investigation. Indeed, as the molecular revolution illuminates novel metabolic pathways, control systems and regulatory molecules, the necessity for accurate measures of adipose tissue mass, adipose tissue distribution actually increases. Also, the precise measurement of small changes in body composition is necessary assess the success or failure of community and behavioral interventions.

Building upon these tools, newer techniques such as magnetic resonance spectroscopy allow for the measurement of cellular energy metabolism; measurements that previously required invasive procedures such as biopsy or arterial-venous cannulation. Magnetic resonance spectroscopy has proven useful not only for imaging tissue structure (e.g. lipid content and blood flow), but when combined with stable isotopic techniques, MRS revealed unanticipated alterations in energy metabolism *in vivo*.

These techniques should not exist in isolation. We envision an integration of these core technologies such that a single pathway could be studied from the molecular/genetic level (cellular imaging) to whole body cellular imaging (MRS) and on to an integrated system (energy metabolism and body composition). The logical next step in these studies is to examine these pathways at the whole body level. By quantifying skeletal muscle mitochondrial ATP production and oxidative phosphorylation in vivo using stable isotopic techniques combined with MRS and whole body energy metabolism, the relevance of a control system to human diseases can be determined. Additional layers of interaction are envisioned by the inclusion of gene - protein studies on skeletal tissue obtained by biopsy. These types of integrated studies allow for the study of the human condition with precise and minimally invasive techniques.

The recent acquisition of a 3T MRI/MRS increases the capabilities of the Clinical BioImaging Core to include the measurement of cellular function, especially energy metabolism without the need for invasive techniques like biopsy.

In-patient Unit

Steven R. Smith, M.D., Corby Martin, Ph.D., Crystal Traylor, R.N., N.P., Kelly Attebury, R.D.

Inpatient Unit: *Amy Braymer, LPN, Valerie Toups, LPN, Lorraine Eames, LPN, Tracey Banks, NP, Rhonda Hilliard, LPN, Kim Crotwell, LPN, Lisa Dalfrey, LPN, Bridget Taylor, LPN, Katrina Prescott, LPN, Celeste Waguespack, RN, Stephanie Tatum, RN, Kristin Hood, RN, Liz Barber, RN, Yolanda Robertson, NP, Kim Landry Ultrasound tech, Michelle Neptun, Research Associate, Erin Wimberly, Administrative assistant*

Inpatient Kitchen: *Floy Anderson, Theresa Williams, Estelle Morrison, Anne Godwin, Elizabeth Eaton*

LORI C. STEIB, BA, MLIS, AHIP
Director
Library and Information Center

The inpatient unit serves the needs of clinical investigators for the conduct of advanced clinical endpoints in clinical study of obesity, diabetes and metabolism. They consist 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
- a large nursing station that includes a remote pharmacy, internet/intranet access and work table
- a psychology data collection area for questionnaire completion
- immediately adjacent facilities: DEXA, echocardiography, ultrasound, 3T MRI/MRS and pulmonary function testing units

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

Library & Information Center

Lori C. Steib, BA, MLIS, AHIP, Marilyn Hammond, BA, MLn

The Library & Information Center offers print and electronic resources and literature assistance to the researchers at the Center. Staffed by a Director, an Assistant Librarian and a Graduate Assistant, the Library & Information Center offers reference and information services, interlibrary loan processing, bibliographic instruction, and access to electronic databases to all Pennington Biomedical Research Center employees.

The Information Center, a member of the National Network of Libraries of Medicine and LOUIS, The Louisiana Library Network, is open twenty-four hours a day, seven days a week. During the last 12-month period, the Information Center processed more than 5,000 requests.

Center employees may access many databases through the PINE intranet service, including: 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 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 Library and Information Center continues to keep pace

with the developing electronic resources and programming technologies, recently implementing a new online catalog system, and planning for electronic document delivery to the desktop of Center employees.

Mass Spectrometry

Jennifer C. Rood, Ph.D., DABCC, FACB, Bruce Toth, M.A., Evest Broussard, B.S., Sunny Brogan, B.S., Leigh Anne Wade, B.S., Paige McCowan, B.S., Eric Gravois, Emily Gilliam

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 hazard to the patient and can be used in infants, children, and young adults. 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. In addition, the Stable Isotope Laboratory has a Hewlett Packard 5988 quadrupole mass spectrometer. This mass spectrometer has a direct insertion probe and GC interface, EI and CI capabilities, and positive or negative ion monitoring, for measurement of any stable isotope labeled (e.g. 2H, 15N, 13C) organic compound. A Finnigan TSQ 7000 mass spectrometer has been installed with a high performance liquid chromatography interface. The GC/MS and the HPLC/MS are used to measure other stable isotopes, such as Carbon-13 and Nitrogen-15 and are being used to examine cholesterol metabolism in studies of cardiovascular disease and glucose, amino acid and fatty acid metabolism in studies of obesity.

Metabolic Chambers Core

Lilian de Jonge, Ph.D. Eric Ravussin, Ph.D., Carole Traoret, M.S., Tuong Nguyen, B.S., Henry Anderson, Ali Baghian

The main goal of the metabolic chambers core is to perform and provide reliable and reproducible assessments of energy expenditure and substrate oxidation in humans. The technique used for these measurements is indirect calorimetry.

Two types of equipment are available at the Pennington Center. Metabolic carts (Deltatrac II metabolic monitors) are used for measurements under resting conditions. The Center has eight of those devices, which are used for the assessment of resting metabolic rate (RMR) and the acute effects of possible thermogenic stimuli such as a meal or pharmaceutical and herbal

compounds. In addition, the metabolic carts are used during insulin clamp studies to calculate glucose oxidation. The carts use the ventilated hood technique which makes comfortable smeasurements over several hours possible. During 2004 and 2005, we performed approximately 1700 measurements for a variety of studies.

For the measurements of energy expenditure and substrate oxidation on a 24-hour basis whole room indirect calorimeters are used. The Center has two metabolic chambers, (10 feet x 12 feet x 8 feet). Because studies include periods of 24 hours up to 7 consecutive days in the chambers, they are designed to provide a pleasant environment to our study participants. During the last few years, the programming of our chambers was updated to allow for minute to minute data output, making the chambers not only useful for the measurements of 24-hour energy metabolism but also for the assessments of acute changes. During 2004 and 2005 we performed close to 450 measurements of 24H energy expenditure for several studies.

MARLENE MOST, PH.D.
Associate Professor

Metabolic Kitchen Core

Marlene Most, Ph.D., R.D., Justin Abadie, Virginia Austin, Ellen Broussard, Errol Broussard, Michelle Burton, M.S., R.D., Gina Castelluccio, B.S., Betty Fisher, Heather Fleming, B.S., Teresa Gipson, Becky Gromer, Jennifer Hofman, B.S., Jennifer Howard, B.S., R.D., Chantelle Jones, B.S., Greta Johnson, B.S., Sharice Leger, B.S., Sayo Mathur, B.S., Gail Meyn, Lisa Miller, B.S., R.D., Hoita Mongi, B.S., Estelle Morrison, Matilda Nelson, Maria Pyburn, B.S., Mary Richard, Dorothy Richardson, Rachel Romaine, B.S., Anita Sawyer, B.S., R.D., Bobbie Smith, B.S., Hillary Smith, B.S., Amiee Talbot, B.S., Terry Taylor, Toyia Watson, B.S., Renita Weathersby

The mission of the Metabolic Kitchen Core is "to support nutritional research by designing, preparing and serving meals with safety, accuracy and consistency that meet study-specific criteria and produce valid scientific results."

The Metabolic Kitchen Core is located on the second floor of the Clinical Research Building. It is divided into four fully equipped individual kitchen areas that are ideal for conducting simultaneously various protocols. One unit is dedicated to the inpatient unit while another is a baking kitchen. In the metabolic kitchen, there also is a tray service area; dish room; and areas for dry, refrigerated and frozen storage in the storeroom, walk-in refrigerator, and walk-in freezer. On-site are additional dry, refrigerated and frozen food storage areas.

Staff includes research dietitians who have the primary responsibility for planning and managing the dietary component of feeding study protocols. Research specialists, food service coordinators, hostesses, and student workers prepare and serve the research-designated diets.

Microscopy Core

Gregory M. Holmes, Ph.D.

The Mission of the Microscopy Core is to provide researchers at the Center with the latest advances in imaging technology. The Microscopy core is located on the fourth floor of the new Basic Science Research Building.

Central to the Core is the Zeiss LSM510-META laser scanning confocal microscope. The LSM510-META uses both a highly efficient optical grating to physically separate the specimen emission into 32 distinct wavelength bands and computer algorhithms to separate mixed signals on a pixel by pixel basis. This permits subtracting autofluorescence and background noise, further enhancing image quality.

The high degree of resolution and efficiency (sensitivity) not only allows for unsurpassed image quality that is essential for capturing fine detail or faint images, but also permits imaging of living cells. In addition to the five standard excitation laser lines, the LSM510-META is fitted with a near infrared laser for multiphoton excitation. Multiphoton laser excitation is less harmful to living tissue than conventional laser excitation, thus permitting live cell confocal applications such as calcium imaging, FRET (Fluorescence Resonance Energy Transfer) and FRAP (Fluorescence Recovery After Photobleaching). The latter techniques allow scientists to resolve the proximity of proteins and structural changes of the molecules within a cell beyond the optical resolution of the microscope. The addition of an incubation chamber to the LSM510-META imaging platform in 2004, permits long-term imaging experiments (on the order of days) of cultured cells.

For standard fluorescent microscopy, the Microscopy Core has a 3i Everest(tm) digital microscopy workstation. Common uses of this workstation include multi-channel fluorescence imaging, Ratiometric imaging, FRET, 3-D deconvolution, time lapse, large format montage, and stereological techniques for unbiased cell counting experiments. Other recent additions to the core include a general purpose Zeiss upright fluorescent microscope imaging station (Spring, 2005), and the purchase (Fall, 2005) of an inverted widefield fluorescent microscope capable of imaging living nervous system slices or cultured cells.

The adjacent Histology facility allows researchers the opportunity to process specimens for microscopy at the Pennington Biomedical Research Center rather than relying upon outside services.

Outpatient Clinic Core

Frank Greenway, M.D., Alok Gupta, M.D.,Yolanda Robertson, N.P., Anne Chatellier, R.N., Allison Strate, R.N., Andrew Roberts, B.S., Brandi Armond, LPN, Chrystal Duncan, LPN, Dawn Rachal, B.S., Diane Crow, LPN, Elizabeth Cadarette, B.S., Heidi Kilburn, B.S., Jana Ihrig, R.N., Kristi Rau. B.S., Liz Barber, R.N., Marisa Smith, B.S., Melody McNichol, B.S., Natalie Currier, R.D., Patricia Pinsonat, R.N., Patti Smith, B.S., Sara Schoen, R.D., Susan Mancuso, R.N., Susan Thomas, R.D., Tiffany Hudnall, R.N., Jennifer Perrault, Elizabeth Tucker, B.S., Mary Beth Burnett, Melissa Lingle, B.S., Janet Fahr, B.S., Carmella McKneely, Betsy Bernhard, B.S., Brenda Dahmer, B.S., Grace Bella, B.S., Jan Day, B.S., Annette Hutchison, B.S., Beatrice Winkler, M.S., Charles Sides, RPh., Claire Hazlett, RPh., Lura Reed, Linda Guy

The Outpatient Clinic Core supports clinical trials by recruiting participants, scheduling screenings, and collecting research data. Screening is a three-step process from initial phone screening to determine study eligibility, more extensive screening in the clinic with body measurements and blood sampling to the physical exam for subjects passing these initial screening steps.

The Outpatient Clinical Core is on the first floor of the clinical research building which occupies 16,485 square feet of space plus four trailer annexes housing 22 offices, two conference rooms and ten examination rooms, two of which are new. The core has a conference room, three eating monitors and a phlebotomy laboratory as well as three electrocardiogram rooms, three weight and blood pressure stalls and four interview rooms, all of which are newly created.

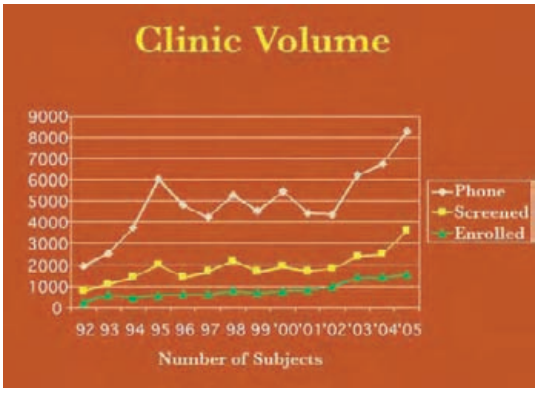


Figure 1 A *The clinic volume has steadily increased since 2002 and is continuing to rise at a rapid rate necessitating expansion of the existing space.*

The Outpatient Clinic employs 40 people: an administrator, a quality assurance specialist, two physicians, a physician assistant, three recruiters, a public relations specialist, ten nurses, seven study coordinators, three dietitians, a medical record librarian with two assistants, five secretarial personnel, a data entry supervisor and two part-time pharmacists. The clinic has access to an eating monitor laboratory to measure food intake and an ultrasound facility to evaluate heart valves and blood vessels.

During 2005 there were 8,500 telephone screenings, 3,500 screening visits and 1,500 subjects randomized into clinical trials. There were 28 clinical trials directed by 12 principal investigators with funding from the federal government (U.S. Department of Agriculture, National Institutes of Health and Department of Defense) and industry (pharmaceutical and food companies). The Outpatient Clinic participates in multi-center trials, and collaborates with industry to develop new products. Most of the studies performed in the Pennington Biomedical Research Center relate to obesity or its associated complications, including diabetes, abnormal cholesterol metabolism, high blood pressure and atherosclerotic vascular disease. The level of activity is growing rapidly, and expansion of the clinical facilities is a priority.

Proteomics Core

Michael Lefevre, Ph.D.; Angie White, B.S.; Amy Gravois, B.S.

The Pennington Biomedical Research Center has developed a state-of-the-art high through-put proteomics facility. The proteomics facility allows researchers to measure the relative abundance of proteins within a cell or tissue, determine the subcellular localization of proteins, examine the extent of protein modification, and identify proteins which are secreted from cells. The technology is built around

high resolution analytical 2-dimensional gel electrophoresis using multiple gel size formats (7 - 18 cm IEF-gels and corresponding SDS-gels) and multiple staining protocols (silver, sypro ruby, western blot with detection). Sensitive imaging techniques coupled with sophisticated imaging and analysis software provides capabilities for spot matching between multiple gels, spot quantitation, the preparation of an annotated "Master Gel", and routine statistical analysis.

The facility also provides state-of-the-art high through-put identification of peptides and proteins. Automated spot picking from preparative 2d-gel electrophoresis and automated in-gel protein digestion, peptide extraction, and MALDI slide spotting facilitates sample preparation for protein identification. A MALDI-TOF mass spectrometer is used to identify proteins through peptide mass fingerprinting. A Q-TOF mass spectrometer is used to verify protein identification through multiple partial peptide sequencing. An integrated data management system provides tracking of all samples through the process, annotation of samples with experimental conditions, and integration with external public proteomic and metabolic databases.

Future capabilities will include isotope coded affinity tag (ICAT) and multi-dimensional chromatography methodologies. Recent projects with the Proteomics Core include: identification of changes in murine liver and heart protein abundance following consumption of bioactive components from foods; identification of changes in adipose-derived adult stem cells following differentiation into adipocytes; analysis of defense related proteins in rice challenged with fungal pathogens; and analysis of proteins in immortalized animal somatic cell lines.

Transgenic and Targeted Mutagenesis Core

Randall Mynatt, Ph.D., Jingying Zhang, Ph.D., Steven Bond, Christine Blackmon

The transgenic facility produces mice for faculty at Pennington Biomedical Research Center as well as investigators at other institutions. The Transgenic Core Facility utilizes pronuclear microinjection and embryonic stem cell technologies to control gene expression in mice. One mission of the core is to 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 Core works closely with users, to provide advice on preparation and purification of transgenes and knockout constructs; offers services in Pronuclear Microinjection of Transgenes and Bacterial Artificial Chromosmes (BAC); development of conditional transgenic mice; injection of embryonic stem cell; cryopreservation on site; and rederivation of fertilized embryos.

RALPH UNDERWOOD
Associate Executive Director for Administration and Finance

Status of Administration and Finance

By all measures, the Pennington Biomedical Research Center continues its history of remarkable growth.

The Center's funding comes from federal grants and cooperative agreements, unrestricted funding through an annual appropriation from the State of Louisiana, private grants and contracts, state research grants, and indirect cost recoveries. During the two years covered by this scientific report, revenues have increased by 40-percent. Total revenues in our most recently completed fiscal year were nearly $45 million.

Federal Grants and Cooperative Agreements

Federal research funding has increased by 44-percent to $17.6 million during the two-year period of this report, and that is particularly gratifying. The majority of this federal funding comes from the National Institutes of Health (NIH), and these NIH awards are made only after an intense and highly competitive review process. Center scientists successfully compete with the best researchers in the land for this funding.

The first federal research agreement received by the Center in 1988 was from the Department of Defense, and this long-standing research relationship continues today through a cooperative agreement with the U.S. Army to fund research in nutrition, exercise and weight control. This relationship with the Defense Department has been, and continues to be, very important to the growth and success of our research center.

The U.S. Department of Agriculture (USDA) has been a long-time supporter of research at the Center as well, and in the past two years we have strengthened that relationship. USDA funding is increasing, and we have realistic hopes that this partnership will grow significantly in the coming years as we develop with USDA scientists a research program in obesity prevention.

State Appropriations

State appropriations have increased by almost 11% to $10.9 million over the past two years. In our most recent fiscal year, state appropriations comprised less than 23% of the Pennington Biomedical Research Center's operating budget, but those dollars are critically important to the Center's ability to attract grant and contract revenues from outside the state. Because of the unrestricted funding provided by the State of Louisiana, the Center's scientists are able to perform pilot studies that result in new grants and contracts, and management is provided 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. This fiscal year, Center scientists will bring in more than $3 of outside research funding for every dollar of state appropriations committed to the Center (Figure 1). If you apply the U.S. Department of Commerce, Bureau of Economic Analysis' economic multiplier factor of 1.89 for research expenditures in the Baton Rouge area, the effect of these outside research dollars on our state's economy this fiscal year alone will be more than $64 million.

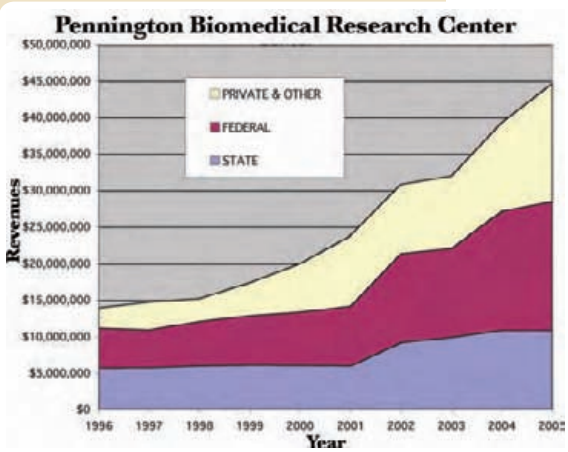


Figure 1

Private Research Grants and Contracts

Private grants and contracts have also shown strong growth. In the past year alone, this source of revenue increased by more than 54-percent to $6 million, and it has increased by 96-percent during the past two years. These revenues 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.

Other Revenues

In the accompanying bar chart (Figure 2), state research grants and indirect cost recoveries have been grouped into "Other Revenues". Over the past two years, this revenue category has increased by more than 50-percent to $10.2 million due primarily to the increase in indirect cost recoveries as a result of increased activity in research grants and contracts.

I am happy to report that the Pennington Biomedical Research Center weathered hurricanes Katrina and Rita without damage, and its research faculty, laboratory personnel, clinical staff, and administrative support groups remain intact and in place. In fact, we are happy to be in a position to accommodate some of our sister campuses of the Louisiana State Univeristy System that were less fortunate. We have provided space to the LSU Health Science Center's Medical School, Dental School, School of Nursing, and School of Allied Health for classes and by providing laboratory space to researchers from the LSU Health Sciences Center in New Orleans and from the University of New Orleans. The work of the Center continues uninterrupted, our researchers continue to be very productive, and we at the Pennington Biomedical Research Center are eager to play our role in bringing economic recovery to Louisiana.

GUY LAVERGNE
Director
Computing Services

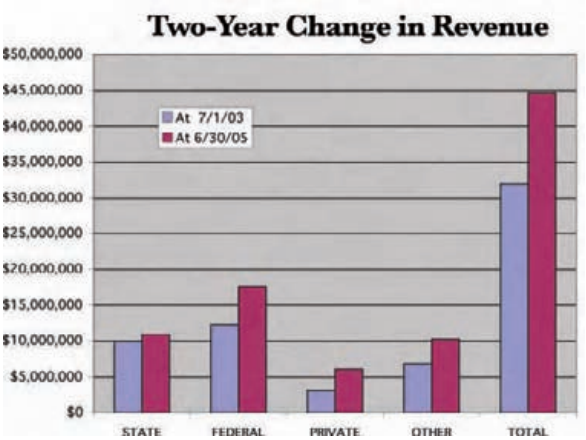


Figure 2

Computing Services

Guy LaVergne, B.S., CCNP, C.S., David Alexander, B.S., Claire Lassalle, B.S., Cherie Gravois B.S., B.A., M.B.A., Barry Buchanan, CNE, Jason Brakel, B.S., Marc DuBos, B.S. MCP, Clint Duffy, B.A., Michael Gelpi, B.S., Jennifer Gonzalez, B.S., Andy Miner, MCSE, Andrew Russell, B.S., Matthew Zylicz, B.S., Brian Buwens, Chetan Chitnis, Erica Cox, Brandon Nye, Jeff Hannaman.

Computing Services' stated mission is ***"To assist the Pennington Biomedical Research Center in the pursuit of its mission by providing exceptional technical support in cutting edge technologies, collaborative tools and customized application development."*** The department does this by focusing on the design, development, implementation, and application of information technologies that will support research and business operations at the Pennington Biomedical Research Center in the furtherance of the Center's goals. Computing Services provides all of the phone, network, server, desktop, and application support for the Center through its three functional groups: Administrative Computing, Technical Support and Education, and Infrastructure. With more than 600 users to support, the department delivers many high-end applications and services utilizing 42 enterprise servers through our fiber optic networks. Users

have access to a robust enterprise network of servers with a storage capacity of more than 2 terabytes and a computational capacity sufficient to support the research and administrative demands of the Center.

Computing Services works to keep abreast of new technological advances and places a high value on opportunities to integrate them into our department's technology offerings in order to increase collaborative opportunities for our faculty and decrease the burden for our administrative staff. By introducing new and novel computing tools and techniques, we are able to enrich the computing environment, thus doing our part to improve overall efficiency and enhance the Center's research activities. One way the department achieves this mission is by placing an emphasis on the technical training of its staff. By seeking to refine the talent that already exists in the department, Computing Services ensures the most competent support possible. The high level of distinction and professionalism achieved by Center scientists serves as an excellent example which Computing Services strives to emulate. We are proud to be associated with the science produced by our institution and gladly welcome the opportunity to serve the Center's research community in its pursuit of excellence.

Facilities Management

Bob McNeese, B.I.E., Marilyn Hughes, B.A.S., Walter Legett, B. Archi., Darryl LeJeune, B.S., Arthur Broussard, Wendy Brown, Barbara Cantrell, Gloria Davis, Walter Farr, Adam Faucheaux, James Hall, Jerrol Jackson, Clinton Jarrett, Cornelius Johnson, Paul Johnson, Sherrie Mabile, Bryan Marks, James Palmer, Zedrick Scott, and Ken Wesley.

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 acquisitions funded by the Pennington Medical Foundation. Presently, department personnel are supervising three construction and renovation projects at the center.
The department faced the challenges of two major hurricanes in 2005, and continues to provide support services to the LSU Health Sciences Center, which was forced to temporarily move its' 1st and 2nd year medical education programs and administrative staff to the Center in September, 2005 in the aftermath of Hurricane Katrina.

Bob McNeese
Director
Facilities Management

Receiving Department

Dwayne Lambert and Joshua Smith

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

Mark Alise
Director
Fiscal Operations

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

Hal Taylor, Scott Bertrand, Willie Bryant, Jason Chambers, Jennifer Heckert, Cori Johnson and Karen Quebedeaux.

The Security Department was reorganized in 2005 when control was transferred from the LSU Police Department to the Pennington Center. Security officers are responsible for the safety and well being of employees and property, and an officer is on duty at the Center at all times. The Security Department issues employee identification cards and parking tags, and regulates and issues temporary cards for contractors, outside technicians, and other visitors. The Department also issues all keys and maintains records that document the assignment of keys. Officers also make rounds monitoring critical plant equipment and recording temperatures of numerous ultra low freezers ensuring that they are in the proper temperature range. Officers respond to all emergencies.

Stores

Richard Caro, Mary Jo Kunsa, Errol Broussard, Hillary Smith, Lindsay Loup, and Justin Doherty.

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. This Auxiliary Eqnterprise operates under the auspices of the LSU Health Science Center.

Fiscal Operations

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

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.

Sponsored Projects

Angie J. Brown, B.S., Gina Larpenter-Billot, B.S., Monica Mougeot, B.S., M.S.

The Office of Sponsored Projects provides a full range of pre- and post award services to faculty, principal investigators, and project directors for grants, clinical trials, and other sponsored research.

Sponsored Projects provides services that include proposal review, budget development, contract development, and negotiation of award terms and conditions. Sponsored Projects also tracks and reports grant and contract awards and current and pending support and locates and targets sources of research funding.

Sponsored Projects assists faculty with locating funding information, initiating and processing proposals, and administering awarded sponsored projects. It also acts as a liaison between investigators and other offices on grant or contract-related matters. It is our goal to remove the administrative burden of sponsored research activity from the faculty in a manner that is both conducive and effective as it relates to the mission of the Center.

Intellectual Property, Legal and Regulatory Affairs

Anne Jarrett, JD, LLM, MBA, MPH, Ph.D. (candidate)

The Director of the Office of Intellectual Property, Legal and Regulatory Affairs (IPLR) reports directly to the Executive Director. The Office of IPLR, which was established in 2003, oversees activities involving economic development, technology transfer, and commercialization of research, as well as activities regarding legal, regulatory and compliance functions.

Technology Transfer and Commercialization

The technology transfer mission of the Office of IPLR is to commercialize the Center's intellectual property - new ideas, inventions and discoveries. This includes obtaining patents and copyrights, seeking licensees and business partners in the U.S. and worldwide to commercialize these technologies, and negotiating and licensing them for the benefit of society, the Center and the inventors. The Office of IPLR strives to provide service oriented assistance - supporting Center researchers and businesses through every step of the technology transfer process. The number of technology disclosures, patent applications, license agreements, joint ventures, new business start-ups, and other economic development activities continues to grow at the Center.

The process of identifying and protecting technology with commercial potential and guiding it toward success requires specialized techniques and skills. The Office of IPLR supplies these skills and coordinates these activities. The Office of IPLR is a resource for Center faculty for material transfer and confidentiality agreements, patenting innovative research and identifying potential partners to develop and/or commercialize Center research. We also serve as a portal for the business community to identify interesting areas of research and to ensure that interested parties are put in touch with the proper laboratories.

Angie J. Brown
Interim Director
Sponsored Projects

Anne Jarrett
Director
Intellectual Property, Legal and Regulatory Affairs

Legal, Compliance and Regulatory Affairs

The Office of IPLR also functions as the compliance office for PBRC and the liaison to other regulatory offices and programs at the Center. The Director of IPLR 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 oversees legal activities for the Pennington Biomedical Research Center.

GENA DOUCET
Director
Human Resources Management

Human Resource Management

Gena Doucet, B.G.S., MBA, Betty Rushing, Becky Guillot, Candace Morgan, Nicole Williams Marjorie Wilson.

The mission of Human Resource Management is 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.

GLEN DUNCAN
Director
Communications

Communications

Glen Duncan, B.S., M.J., M.S., APR; Alan R. Pesch, B.G.S.; Tim Nguyen, B.A., Rhonda Hollen, Emerson Darbonne.

Our mission is simple: *Communications as sophisticated and effective as our research.*

The communications team continues to offer support to our researchers. We have assisted with in-house printing capabilities for full-color posters suitable for scientific poster sessions and with creative and effective website development for various projects and laboratories here at the Center. We worked closely with our Computer Services to introduce individual laboratory websites for our researchers. We are 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, for some specific population studies, communications and media planning as a means of furthering the objectives of the study.

Our primary means of reaching the community at large, at the local, national and international levels, is through timely and engaging news releases. Also, we have instituted a strategy of increasing first-hand knowledge of our community members by re-introducing on-site tours and actively seeking speaking engagements.

The communications team, during the last two years, has brought a greater level and sophistication of measurement to our efforts as a way of determining if we are assisting the Center to reach its goals. We are currently evaluating new means of reaching into our community to determine the effect of our various communications efforts.


HAEMOGLOBIN
Red cells
HCT ratio (PCV)
M.C.V.
M.C.H.
M.C.H.C.
ESR
WHITE CELLS
Neutrophils
Lymphocytes
Monocytes
Eosinophi
Basophil
BLOOD PIC
5.15
.448
86.9 fL
29.0 pg
33.3 g/dL
2 mm/hour
6.16 x10^9/L
54 % 3.33
32 % 1.97
6 % 0.37
6 % 0.37
% 0.12
C, WBC & Pla

Adjunct Faculty

David Baker, Ph.D.	Professor	LSU School of Veterinary Medicine, Dir. of Comparative Biology
Eric D. Bellanger, M.D.	Instructor	Vista Surgical Hospital, Baton Rouge, LA
Peter H. Bennett, MB, FRCP	Professor	NIDDK, NIH, Phoenix, AZ
Leon Bombet, M.D.	Instructor	The Baton Rouge Clinic, Pediatrics, Baton Rouge, LA
Sandra Brown, Ph.D.	Professor	Southern University, Graduate Nursing Program, Baton Rouge, LA
Lauri Byerly, Ph.D.	Professor	UNC, Department of Biology, Charlotte, NC
John T. Caprio, Ph.D.	Professor	LSU, Biological Science Dept.
William Cassidy, M.D.	Asst. Professor	LSUHSC, Dept. of Medicine
Frederick Cerise, M.D.	Asst. Professor	LSUHSC, Dept of Medicine
Steve Clark, Ph.D.	Professor	McNeil Nutritionals/Johnson & Johnson Co.
Deborah A Cohen, M.D., MPH	Professor	Rand Corporation, Santa Moncia, CA
Lisa A. Colvin Cooper, Ph.D., FACSM	Professor	University of Louisiana, Dept. of Kinesiology, Monroe, LA
Brian Despinasse, M.D.	Asst. Professor	LSUMC-N.O. Dept. of Pediatrics, New Orleans, LA
Daniel J. DiLorenzo, M.D.	Asst. Professor	Tulane University, Neurosurgery and Biomedical Engineering Departments, New Orleans, LA
Ronald Eliosoff, M.D.	Asst. Professor	Private practice
Karen Elkind-Hirsch, Ph.D.	Assoc. Professor	Women's Research Inst, Dept. of Reproductive Medicine
Vivian Fonseca, M.D., FRCP	Professor	Tulane University, Dept. of Medicine and Pharmacology
Edward W. Gassie, Ph.D.	Instructor	LSU College of Agriculture, Professor Emeritus
Julia Goerge, J.D.	Instructor	LA. Dept. of Culture, Recreation and Tourism, Office of the Secretary
Stewart Gordon, M.D.	Asst. Professor	LSUHSC, Earl K. Long Hospital, Dept. of Pediatrics
James Greer, Ph.D.	Instructor	LSU, Psychology Department
Jimmy Guidry, M.D.	Asst. Professor	LA Dept. of Health & Hospitals, Office of Public Health
Larry Hebert, M.D.	Professor	Retired
Maren Hegsted, Ph.D.	Professor	LSU, Human Nutrition & Food Division
Sylvia Heidingsfelder, M.D.	Assoc. Professor	LSU Earl K. Long Hospital
Paul Humes, Ph.D.	Professor	LSU Animal Sciences Dept.
Daniel Hwang, Ph.D.	Professor	UC Davis, Western Human Nutrition Research Ctr., Davis, CA
Michal S. Jazwinski, Ph.D.	Professor	LSUHSC, Dept. of Family Medicine, New Orleans, LA

Jolene Johnson, M.D.	Asst. Professor	LSUHSC-N.O., Dept. of Clinical Medicine, Earl K. Long Hospital
Hana Maaria Lakka, Ph.D.	Asst. Professor	University of Kuopio, Finland
Timo Lakka, Ph.D.	Assoc. Professor	University of Kuopio, Finland
Lynn LaMotte, Ph.D.	Professor	LSUHSC, New Orleans, School of Public Health
Monique M. LeBlanc, Ph.D.	Instructor	Louisiana Systemic Initiatives Program
Zhijun Liu, Ph.D.	Assoc. Professor	LSU Agricultural Center, Medicinal Plants Lab
Jennifer Lovejoy, Ph.D.	Professor	Bastyr University, Chair of the Nutrition and Exercise Science Dept., Seattle, WA
Ronald Luftig, Ph.D.	Professor	LSUHSC, Department of Microbiology, Immunology and Parisitology
Pamela Martin, Ph.D.	Professor	Private practice, Behavioral Medicine
Samuel D. McCann, M.D.	Professor	PBRC, Professor Emeritus
Bernestine McGee, Ph.D.	Professor	Southern University, Human Nutrition & Food Dept.
Tipton G. McKnight, M.D.	Instructor	LA Office of Group Benefits Consultant; LA State Police Training Academy Consultant
John T. Paige, M.D.	Professor	LSUHSC, School of Medicine
David Ribnicky, Ph.D.	Professor	Rutgers University, Cook College, Biotech Center
Ilya Raskin, Ph.D.	Professor	Rutgers University, Cook College, Biotech Center
William Raum, M.D., Ph.D.	Assoc. Professor	LSUHSC Dept. of Medicine & Surgery
Edward Richards III, J.D. M.P.H.	Professor	LSU Paul M. Hebert Law Center
David Roane, Ph.D.	Professor	ULM, Dept. of Biology & Kinesiology, Monroe, LA
Heli Roy, Ph.D.	Assoc. Professor	LSU Agricultural Center, School of Human Ecology
Lars Sjostrom, M.D., Ph.D.	Professor	University of Gothenburg, Sweden
Jacqueline Stephens, Ph.D.	Assoc. Professor	LSU, Dept. of Biological Sciences
Maria de Graca Vicente, Ph.D.	Assoc. Professor	LSU, Dept. of Chemistry
Julia Volaufova, Ph.D.	Professor	LSUHSC, School of Public Health
Michael Welsch, Ph.D.	Assoc. Professor	LSU, Dept. of Kinesiology, Robert H. & Patricia A. Hines Endowed Professor in Kinesiology
Eugene Woltering, M.D.	Professor	LSUHSC, School of Medicine, Dept. of Surgery

Professor Emeritus

Samuel M. McCann, M.D., professor emeritus

Dr. McCann received his medical training at the University of Pennsylvania School of Medicine. He was subsequently commissioned a 1st lieutenant and then captain in the U.S. Army, serving in the Medical Corps at Walter Reed Army Medical Center.

Dr. McCann developed a long medical career and research career in neuroendocrinology, leading to membership in the National Academy of Sciences and the American Academy of Arts and Sciences, among many other honors. He arrived at the Center in 1995, where he held the United Companies Chair. He made many important discoveries and was one of the most influential scientists of his generation.

Dr. McCann is the center's first professor emeritus.

Honoris Causa Doctorate

In cooperation with the Louisiana State University Health Science Center, the Pennington Biomedical Research Center granted its first Honoris Causa Doctorate in the Spring of 2005. The first recipient of this degree was Douglas Coleman, Ph.D.

Douglas Coleman, Ph.D.

Douglas Coleman earned his Ph.D. in biochemistry in 1958 from the University of Wisconsin. Until his retirement, Coleman conducted his research at the Jackson Laboratory in Bar Harbor, Maine. His work on what he called the "satiety factor" was a critical in the later discovery of leptin, now known as a major molecular player in the onset of obesity.

Coleman was awarded the 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 30 years ago provided the foundation for the understanding of how our brain interacts with peripheral tissues in order to maintain energy balance.

2004 - 2005
Journal Articles

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OUR FOUNDERS

C.B. "Doc" & Irene Pennington

Our generous founders, C.B. "Doc" and Irene Pennington, displayed great wisdom about the future of health research. The Penningtons donated stock, bonds and oilfield royalties valued at $125 million to Louisiana State University in 1980 to build the Pennington Biomedical Research Center. At the time the gift was given, it was the largest single donation by an individual to a state institution of higher education. With this generous donation, the Pennington Medical Foundation was established with the primary goal of supplying the capital needs of the center.

The Pennington Biomedical Research Foundation was created in 1988 with the Penningtons' encouragement to foster support for the additional needs of the Center from individuals, the community, and the state of Louisiana.

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

– C.B. "Doc" Pennington

Today the two distinct foundations continue to work together to help the Center achieve its mission *"to promote healthier lives through research and education in nutrition and preventive medicine."*

OUR SUPPORTERS

Pennington Medical Foundation

The Pennington Medical Foundation, (PMF) created in 1980 with a generous gift from C.B. "Doc" and Irene Pennington to Louisiana State University, was dedicated to achieving their bold vision to build the biggest and best nutrition research center in the country. Through time, both "Doc" Pennington and the PMF became dedicated to an even greater vision, to create and maintain a world-class center of excellence in research. The result is the Pennington Biomedical Research Center. Today, the Board of Trustees continues to support this vision in the management of an endowment created through the original Pennington donation, and the establishment of guidelines for investments and expenditures. To date, PMF has contributed more than $133 million in total support to the Center, including costs for construction, improvements, equipment, and operating support in both the basic science and clinical research areas.

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A Message from Our Chair...

Dear Friends,

Twenty-five years ago, my grandfather, C.B. "Doc" Pennington, dreamed of creating the "biggest and best" nutrition research center in the United States. His $125 million original gift, establishing the (PMF) in 1980, produced a life-giving legacy that promotes healthier living through research and education in nutrition as well as preventive medicine. Today, the Pennington Biomedical Research Center has vastly exceeded my grandfather's vision and is now recognized as the largest academically based nutrition research center in the world.

On this Silver Anniversary of the Pennington Medical Foundation, the Board of Trustees and I are proud to present the following contributions made during the last two years to the Center, including scientific and construction advances that solidify Pennington's status as an unmatched center of medical discovery.

Achievements highlighted in this report include the Center's Population and Prevention Studies research program, which uses epidemiologic tools to investigate causes of nutritionally related diseases. The program, facilitated by a $5 million, 15,000 square foot expansion of the Center, targets groups of people for health interventions in a wide array of settings such as schools, work-sites, communities, and churches. The goal of this program is to promote health and prevent nutritionally related chronic diseases by epidemiologic research and group-targeted intervention research.

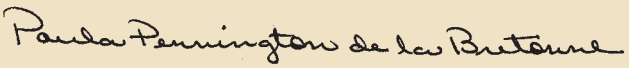
Combining Foundation funds and a U.S. Department of Defense grant, the Center also recently opened a new Bio-imaging laboratory, housing a magnetic resonance spectrometer (MRS), the first of its kind in Louisiana and the only MRS facility in the South dedicated to research applications. Center scientists are using the cutting-edge device to connect and integrate several existing research efforts that are examining aging, diabetes, cancer, obesity and heart disease. This Bio-Imaging Center holds great promise for early detection and treatment of numerous diseases, for providing researchers with detailed information about cellular physiology and function, and for facilitating the goal of personalized medicine.

With an eye toward furthering technology development and growing Louisiana's economy, the Foundation in 2005 became part of the $35 million Louisiana Fund I, which is investing in promising start-up companies based on technologies developed, among others, at the Pennington Biomedical Research Center.

The Fund, a collaboration between the Louisiana Department of Economic Development and the Louisiana State University Research & Technology Foundation, is nurturing development of companies that spring from Louisiana universities, research centers, technology parks, and out-of-state firms that move to Louisiana. Encouraging technology transfer enhances recruitment of internationally known faculty along with producing income from license fees, royalties, and sponsored research generated by the commercialization of knowledge breakthroughs. Investing in such research produces thousands of quality jobs while generating significant new sales for Louisiana businesses.

During the next five years, the Pennington Medical Foundation will remain dedicated to the Pennington Biomedical Research Center's implementation of *Vision 2010*, an ambitious strategic plan that calls for the infusion of $75 million in new dollars. Achieving the Vision 2010 benchmarks will create scores of groundbreaking new research endeavors while assuring the Center's position in the scientific community as a world leader in nutrition and preventive medicine. My grandfather would be proud.

Sincerely,



Paula Pennington de la Bretonne
Chair

Pennington Biomedical Research Foundation

'Changing the health of future generations'

The Pennington Biomedical Research Foundation provides the Center with vital funding for nutrition-based research that aims to prevent premature death from chronic diseases. Our Foundation accepts gifts from individuals, foundations, businesses and industries. The Foundation maintains endowments in the form of one super-chair, nine chairs and three professorships that help the Center to attract and maintain world-renowned senior faculty members. In addition, the PBRF seeks to raise and provide unrestricted support to the Center, helping to bridge the funding gap, and thus providing a margin of excellence. The Foundation is led by an influential board of volunteer leaders comprised of the brightest and most generous business and philanthropic citizens.

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A Message from Our Chair...

JOHN B. NOLAND
Chairman

Dear Friends,

Today the Pennington Biomedical Research Center is the largest academically based nutritional research center in the world and is considered the premier institution of its kind. The Center is at the forefront of medical discovery and education as its researchers strive to understand the causes of obesity, diabetes, cardiovascular disease and some cancers, and then shares those findings with scientists, physicians, other health care practitioners, private industry and the public at large.

An ambitious strategic plan, called Vision 2010, guides the overall growth of the Center's research programs, focusing on disease prevention. Taking its lead from this "road map" for continuing success, the Pennington Biomedical Research Foundation supports the work of the Center by providing vital funding for nutrition-based research that aims to prevent premature death from chronic diseases.

In the past two years, the Foundation has moved forward with leadership from an energetic and focused board of directors. In 2004, Jennifer Winstead, joined the Foundation as its new president and chief executive officer, bringing solid experience in medical research and health care fund development.

Then, in 2005, six new board members with expertise in finance, government, consulting, medical management, and banking joined our team of seasoned directors who have guided our support of the Center for many years. New initiatives bring new relationships and opportunities to tell the Pennington story: the first employee Annual Giving Campaign, Soaring to New Heights balloon festival event, Visiting Scientists Dinners sponsored by Hibernia National Bank, and a new donor recognition program.

The Center is not only a preeminent academic institution but also is a catalyst for spurring economic growth in the state and beyond. For example, for every dollar provided to the institution by the state, the Center earns $3 in grants, contracts and philanthropy, making it one of the best investments ever made by the state of Louisiana. Communicating this message to the public, the business community, state legislators, and potential donors and supporters of the Center is of vital importance.

Generosity abounds in our community as we saw a one million dollar gift from Our Lady of the Lake Foundation to honor the work of Franciscan Missionary of Our Lady, Sr. Marie Edana Corcoran, a beloved pediatric nurse who devoted more than 60 years of service to the Baton Rouge community. The Marie Edana Corcoran Endowed Chair in Pediatric Obesity and Diabetes was formally endowed in the Fall of 2004 when the Board of Regents Eminent Scholars fund matched private donations by providing $1.2 million for this chair and two others: the Peggy M. Pennington Cole Endowed Chair in Maternal Biology, established by the Community Foundation for Southeastern Michigan and the Irene W. and C.B. Pennington Foundation; and the John S. McIlhenny Endowed Chair in Health Wisdom, endowed by the Coypu Foundation Trust.

In January 2005 we celebrated with many donors who joined together to establish the John W. Barton, Sr. Endowed Chair in Genetics and Nutrition. Later in the fall, we received $400,000 in additional matching funds from the Board of Regents for this chair. The Pennington Biomedical Research Center has now received major gifts to endow one super chair, nine chairs and three professorships. For the first time in history, the Center has established naming opportunities, affording donors permanent recognition as supporters of specific research within the Center. Our first named laboratories include: the John S. McIlhenny Laboratory of Botanical Research, established with a gift from the Coypu Foundation Trust; the William Hansel Laboratory of Cancer Prevention, with funding from family members, Loretta and Edward Downey, and a generous matching gift from Dr. Hansel; and the John S. McIlhenny Laboratory of Skeletal Muscle Physiology, established with an additional gift from the Coypu Foundation Trust.

All of these extraordinary gifts signal a confidence in the work of the Center and the ongoing goal and mission of discovery in disease prevention. As we work to change the lives of future generations, understanding and knowledge of the Center's profound research will open doors, one at a time. With this level of commitment and generosity, we are assured continuing success of this great institution

Sincerely,

John B. Noland,
Chairman

Named Laboratories

The Pennington Biomedical Research Foundation is proud to acknowledge and permanently recognize those donors that have made significant gifts to help support the compelling research of the Pennington Biomedical Research Center.

- John S. McIlhenny Laboratory of Botanical Research, established in 2004 with a generous gift from the Coypu Foundation Trust
- William Hansel Laboratory of Cancer Prevention, established in 2005 with gifts from Loretta and Edward Downey, and Dr. William Hansel
- John S. McIlhenny Laboratory of Skeletal Muscle Physiology, established in 2005 with a generous gift from the Coypu Foundation Trust

Dr. William Cefalu (left) with Polly and John Hernandez of the Coypu Foundation Trust inside the new John S. McIlhenny Laboratory of Botanical Research.

Edward and Loretta Downey (left) with Dr. William Hansel outside the new William Hansel Laboratory of Cancer Prevention.

Endowed Chairs and Professorships

We would also like to recognize those donors who have made it possible to attract the most talented researchers through the creation of endowed chairs and professorships.

Pennington Biomedical Research Foundation Chairs & Professorships and Donors

Chair/Professorship	Donor
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John S. McIlhenny Endowed Chair in Health Wisdom	Coypu Foundation Trust
John W. Barton, Sr. Endowed Chair in Genetics and Nutrition	Various donors
Douglas L. Manship Professorship in Diabetes	Douglas L. Manship, Sr.
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George H. Bray Professorship	Various donors

Our Donors

The Pennington Biomedical Research Foundation is proud to acknowledge its donors. These recognized gifts are the cumulative giving of individuals and organizations to the Pennington Biomedical Research Foundation from its inception through December 31, 2005.

Pennington Society ($1,000,000 +)

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