

Energy homeostasis and the challenge of obesity

Humans and virtually all species of mammals are endowed with complex control systems that maintain "energy homeostasis" by matching energy intake and expenditure over long periods of time. Maintenance of an adequate energy supply is essential for survival and deficits of energy stores rapidly and powerfully increase hunger, driving a person to seek food and reduce energy expenditure.

The robust efficiency of this energy homeostasis system in preventing energy deficits apparently does not translate to prevention of energy surplus, at least in many humans, as evidenced by the extremely high prevalence of overweight and obesity in our society. Why are these powerful regulators of energy balance so frequently overridden to cause obesity and/or overweight in over 2/3 of U.S. adults? Despite rapid advances in our knowledge over the past several years, we have a long way to go to answer this question.

The extremely high prevalence of obesity, its adverse impact on almost every organ of the body, its enormous economic costs, and its associated stigma have created tremendous demand for effective pharmacological therapies. Unfortunately, none of the drugs currently available provide satisfactory treatment for most patients, especially those who are severely obese. Interventions that focus on diet, exercise and lifestyle modification can be effective in some patients, but the recidivism rate is very high, approaching 90% or more after 1-2 years. The only effective treatment currently available for many obese patients is bariatric surgery, often referred to as "metabolic surgery" since many of the metabolic effects of obesity such as diabetes are often rapidly reversed after surgery. Yet, bariatric surgery is recommended for only a small percentage of obese people.

What is the outlook for better pharmacological management of obesity and its adverse effects? I am optimistic that more effective treatments will be available in the future. Our current understanding of the pathophysiology of obesity and treatment is at about the same stage as hypertension treatment was 50-60 years ago. A major difference, however, is that research tools and technology are becoming available at a much more rapid pace, giving encouragement that effective treatments for obesity won't take another 50 years to develop.

MCOR researchers are making progress toward understanding the pathways that integrate short-term and long-term control of energy homeostasis and mechanisms responsible for the adverse effects of obesity to cause hypertension, diabetes, fatty liver, and other metabolic disorders. However, development of effective therapies for obesity must account not only for the factors that cause obesity and its adverse effects on the body, but also for how excess body fat is defended and why it is so difficult to lose body fat

with diet and exercise. These complex issues will require multidisciplinary basic, clinical, population, and outcomes research that are key strategies for achieving the MCOR mission of *improving lives through discovery, innovation and improved patient care and prevention of obesity and related disorders.*

This newsletter highlights a few activities of the MCOR and UMMC clinical programs during the past several months. A grant from a Center for Biomedical Research Excellence (COBRE) grant from the National Institutes of General Medical Sciences has enabled the MCOR to fund new pilot project grants to investigate the mechanisms by which diabetes adversely affects recovery after a heart attack and potential therapeutic targets for adverse cardiac remodeling after myocardial infarction. These and other projects supported by the COBRE advance our understanding of the pathophysiology of obesity and associated cardiorenal disorders and offer potential new targets for therapeutic interventions.

We are pleased that several faculty members, fellows and students associated with the MCOR were successful in obtaining extramural support for their research and received numerous honors and awards this past year. Some of these are highlighted in this newsletter. We are fortunate to continue receiving support from many sources, including benefactors, the National Institutes of Health, American Heart Association, and other funding agencies. We express our sincere gratitude for this support and to the researchers, healthcare professionals, and others who are working so hard to advance the mission of the MCOR.

We hope that you enjoy reading the newsletter. A more extensive list of papers published, extramural funding and other news can be found on the MCOR website, <https://www.umc.edu/mcor/>. Please contact us if you have any questions or suggestions for how we can better achieve success in our mission.



Dr. John E. Hall

John E. Hall, Ph.D.
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Childhood obesity solution proposals receive awards

With nearly 40 percent of children classified as overweight or obese, Mississippi has among the highest childhood obesity rates in the nation. Given the challenges for both children and adults to maintain weight loss, preventing weight gain during youth and adolescence is an important step in achieving lifelong health.

To this end, the MCOR solicited proposals for projects that represent innovative approaches for curbing childhood obesity in the state. Recognizing this work requires a trans-disciplinary approach, all researchers affiliated with the University of Mississippi or the University of Mississippi Medical Center were invited to apply.



Roseman

The 21 proposals submitted represented both campuses. Following peer review, two proposals were selected to receive funding for pilot projects. The award recipients, Dr. Mary Roseman and Dr. Melinda Valliant, both serve as faculty members in the Department of Nutrition and Hospitality Management at the University of Mississippi. Their proposals for school-based initiatives offer novel strategies and creative insights that address the unique challenges to ensuring health for Mississippi's children.

Roseman's primary research focuses on consumer behavior in multiple phases of critical health issues related to diet, such as obesity, healthy/nutritious eating behaviors and food safety. She addresses such topics as healthy menus in schools; nutrition programs and interventions; and dietary behaviors of adolescents.



Valliant

Roseman's "Eating Good Food" pilot project focuses on the eating behaviors of middle school children, particularly their participation in the National School Lunch Program. By providing a training program for U.S. Department of Agriculture Child Nutrition Program directors, managers and staff employees, the project has a goal of increasing schools' capacity to serve and market high-quality, healthy food in accordance with the USDA's NSLP requirements. The project also addresses students' satisfaction and parents' perceptions of school meals to improve participation in the NSLP.

A board-certified specialist in sports dietetics, Valliant serves as co-director of the Center for Health and Sports Performance at the University of Mississippi. She has worked as the consulting sports dietitian for Ole Miss Athletics for 10 years and has served as the coordinator for sports nutrition for three years. Her research primarily focuses on best practices in sports medicine, particularly related to the health and safety of athletes. She also has led several community-based projects encouraging physical activity and healthy eating among children.

Her "Healthy Eating" pilot project seeks to provide Mississippi schools with an engaging, culturally sensitive nutrition education program. Through the pilot project, Valliant will work with experts in nutrition and curriculum development to develop lesson plans and classroom resources that will allow teachers to incorporate messages about healthy eating into their existing curricula.

Both pilot projects will be implemented in North Mississippi schools during the next two years, with the expectation that the tools developed through the projects can eventually be shared throughout the state. ■

Marathon, TFA partnership strengthen educational equity

Dr. Debbie Minor represented the MCOR while completing the annual Mississippi River Marathon. The only marathon in the Mississippi Delta, the race was created to positively impact health and education in the region.

All proceeds from the race benefit Teach for America, a nonprofit organization with a mission to "enlist, develop and mobilize our nation's most promising future leaders to grow and strengthen the movement for educational equity and excellence."

TFA works to accomplish this mission by recruiting and training recent graduates from top universities across the country who commit to teaching in underserved school districts for at least two years. TFA established its partnership with Mississippi in 1991; currently, 195 corps members work in the state.



Minor

The MCOR has partnered with TFA as part of the center's Mississippi Delta Health, Wellness and Education Initiative. Through the initiative, TFA will provide health education resources and training opportunities for teachers and will partner with other community-based organizations to extend their health education efforts beyond the classroom.

By developing new partnerships and strengthening its capacity for community outreach, TFA's initiative will have a sustainable influence on health and education in the areas in which they serve.

Registration for the 2019 Mississippi River Marathon begins in mid-May. The race is certified by the USA Track and Field and is a qualifier for the Boston Marathon. The MCOR and TFA partnership provides an opportunity to generate enthusiasm about nutrition and physical activity in the classroom and the community. ■

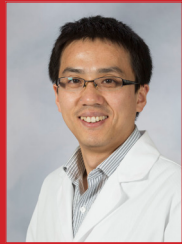


COBRE funds new pilot project grants

The Center for Biomedical Research Excellence grant from the National Institute of General Medical Sciences is a five-year grant to develop mentoring and education programs, infrastructure and core facilities that foster excellence in basic, clinical and population research in obesity, cardiorenal and metabolic diseases. The COBRE currently supports several research core facilities and the research of 10 investigators in six different departments. Last year, three new researchers were awarded COBRE pilot grants; two of the researchers are profiled below.

Dr. Yonggang Ma, assistant professor of physiology and biophysics, is investigating how the innate immune response and extracellular matrix turnover regulate cardiac remodeling after myocardial infarction. The ultimate goal is to find novel intervention targets to improve MI patient outcomes.

MI-induced heart failure is a leading cause of morbidity and mortality in the U.S. More than 1 million Americans each year are diagnosed with MI; about 250,000 of them will progress to develop heart failure associated with adverse cardiac remodeling. While in-hospital survival rates have greatly improved during the last three decades due to coronary artery reperfusion and other therapeutic strategies, five-year survival rates for HF remain at ~50 percent. Elucidating the mechanisms of adverse remodeling of the left ventricle post-MI may identify potential targets to prevent, slow or even reverse the development and progression of HF.



Ma

Ma's group has recently found that matrix metalloproteinase (MMP)-28, an ECM-degrading enzyme, plays a biphasic role in cardiac remodeling post-MI. Early post-MI MMP-28 serves a signaling molecule to inducing pro-inflammatory macrophage M1 polarization and is detrimental; at a later stage, MMP-28 triggers a pro-reparative response by inducing anti-inflammatory M2 polarization and activating fibroblasts, which is beneficial. Ma strives to elucidate the underlying molecular mechanisms and develop a translational protocol that minimizes unfavorable pro-inflammatory actions and maximizes favorable pro-reparative actions.

This project is designed to assess whether MMP-28 can function as a signaling molecule to regulate inflammation and reparative response in addition to degrading ECM substrates.

Dr. Romain Harmancey, assistant professor of physiology and biophysics, conducts research to understand why type 2 diabetic patients, who represent 95 percent of the diabetes population, recover less well

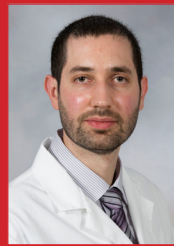
from a heart attack when compared to non-diabetic patients. Specifically, he is investigating how resistance to the hormone insulin affects the heart's ability to convert food substrates into the energy it uses for its pumping function.

More than 29 million Americans have diabetes, an amount that is expected to nearly double during the next two decades. Diabetic individuals are at increased risk for developing heart disease and account for more than 280,000 heart attacks annually. In addition to increasing the incidence of myocardial infarction, diabetes also is associated with a two-to-fourfold increase in cardiac morbidity and mortality following hospitalization and revascularization.

Harmancey's research has found that after interruption of its blood flow, the insulin-resistant heart has impaired capability to use long-chain fatty acids, the most prominent source of fat-derived energy in the body. His research has also found that insulin resistance causes mitochondria, the energy factories of the cells, to lose almost 50 percent of one of their protein components known as uncoupling protein 3.

His laboratory is now working with rats that have been genetically engineered to introduce a frameshift mutation in the gene encoding UCP3 to test whether partial loss of this protein is responsible for the inability of heart mitochondria to generate energy from long-chain fatty acids after a heart attack. Harmancey believes that providing shorter fatty acids may help mitochondria produce more energy from fat in spite of the loss of this protein, and may therefore improve recovery of the heart's pumping function after myocardial infarction.

The long-term goal of Harmancey's research is to reduce health disparities between diabetic and non-diabetic patients facing a heart attack. More precisely, he expects to demonstrate that a simple metabolic intervention can be used as an adjuvant therapy to current surgical interventions used to reestablish blood flow in patients suffering from a heart attack. He hopes that improving the recovery of the pumping function of the heart will benefit patients by decreasing the time they spend in the hospital after being treated for a heart attack, and that it will improve their quality of life and survival in the long term. ■



Harmancey

Summer institute engages interactive learning among faculty

The 2017 Community-Engaged Research Summer Institute took place July 10-14 at the University of Southern Mississippi's Trent Lott Center in Hattiesburg. The institute welcomed 11 participants from five Mississippi universities and included a workshop/seminar-type format with presenter-participant discussions and interactive learning. Junior faculty members from all major Mississippi universities were encouraged to apply.

The institute included presentations on many aspects of planning and conducting community-engaged research related to obesity along with individual and group activities focused on developing proposals for a community-engaged, obesity-focused research project. One-to-two institute participants will be selected to submit a proposal to the MCCTR Pilot Projects Program.

Participants included:

- Dr. Caroline Compretta, Department of Preventive Medicine, UMMC
- Dr. David Dolbow, School of Kinesiology, USM
- Dr. Danielle Fastring, Department of Public Health, USM
- Dr. Whitney Herring, Department of Pediatrics, UMMC
- Dr. Sarah Jones, Department of Pediatrics, UMMC
- Dr. Margaret Ralston, Department of Sociology, Mississippi State University
- Dr. Martha Ravola, Department of Human Sciences, Alcorn State University
- Carolann Risley, School of Graduate Studies in the Health Sciences, School of Medicine, UMMC
- Dr. Meagen Rosenthal, Department of Pharmacy Administration, University of Mississippi
- Dr. Alicia Stapp, Department of Teacher Education, University of Mississippi
- Monica White, School of Nursing, UMMC

Kinesiologist receives MCCTR Pilot Project Program support

The MCCTR Pilot Projects Program supports clinical, translational and population-based obesity-focused research projects that can become the basis for competitive extramural funding applications.

Key considerations in awarding support are the likelihood of attracting extramural funding, evidence of a path toward an independent research career for the applicant and the probability that the research program will lead to improved management of obesity and its complications.

The program is designed to promote multi-institutional and multi-disciplinary collaboration and to ensure equitable and productive distribution of research support across MCCTR partner institutions UMMC, Tougaloo College and the University of Southern Mississippi.

One Pilot Project was awarded to Dr. David Dolbow, assistant professor of kinesiology at the University of Southern Mississippi: "Electrically Induced Cycling and Nutritional Counseling for Counteracting Obesity after SCI"

Five UMMC faculty earn MCCTR investigator development awards

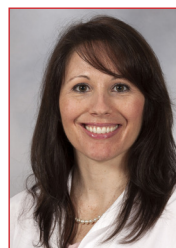
The Mississippi Center for Clinical and Translational Research's Investigator Development Program:

- Provides structured mentorship, protected time and research support to promote the development of junior faculty to establish independent careers in obesity-focused research;
- Seeks to increase the number and diversity of junior faculty members pursuing clinical, translational and population research in obesity and related disorders; and
- Supports the development of junior faculty exploring racial disparities in obesity and related disorders in Mississippi.

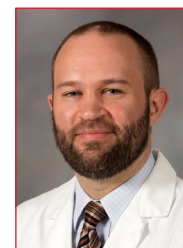
Each of the IDP recipients received a Pilot Project. In the first funding cycle, five IDP awards were issued, including four to UMMC faculty.

- Dr. Abigail Gamble, assistant professor of preventive medicine: "Exploring Exercise Behavior in Pregnant and Postpartum Adolescents in Mississippi"
- Dr. Matthew Kutcher, assistant professor of surgery: "Obesity-associated Hypercoagulability in Trauma Patients"
- Dr. Andrew Smith, assistant professor of radiology: "Comparative Effectiveness of Noninvasive Tests for Staging Chronic Liver Disease"
- Dr. Sarah Sterling, assistant professor of emergency medicine: "The Chronic State of Obesity and the Acute Response to Sepsis"

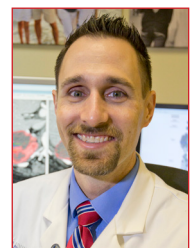
- Dr. Susan Mayfield-Johnson, assistant professor in the Department of Public Health, University of Southern Mississippi: "Effectiveness of a Community Health Worker Heart Disease Reduction Program in Mississippi"



Gamble



Kutcher



Smith

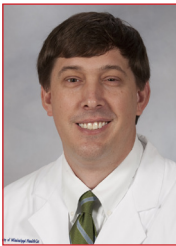


Sterling



Mayfield-Johnson

Dr. Michael Hall, assistant professor of medicine and assistant professor of physiology and biophysics, was elected as a 2016 Fellow of the American Heart Association's Council on Hypertension. This fellowship recognizes outstanding and sustained scientific contributions in hypertension and cardiovascular disease and volunteer leadership and service to the American Heart Association.



Hall

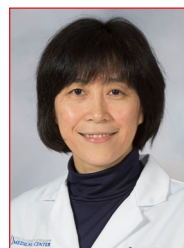
Hall also received a Junior Faculty Research Travel Award to attend the Southern Society for Clinical Investigation's Southern Regional Meeting.

Dr. Andrew Smith, associate professor of radiology, received the First Place Award at the Mississippi New Venture Challenge sponsored by Innovate Mississippi.

Dr. Eric George, assistant professor of physiology and biophysics, received the 2016 Early Career Advocacy Fellowship from the American Physiological Society.



George



Fan

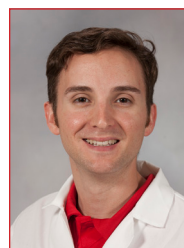
Dr. Fan Fan, assistant professor of pharmacology and toxicology, received the National Institutes of Health/ National Institute of Environmental Health Sciences travel award to attend the 16th International Winter Eicosanoid Conference.

Fan also received the 2016 PLOS Early Career Travel Award to attend the sixth International Conference on Vascular Dementia.

Dr. Michael Garrett, professor of pharmacology and toxicology, was recognized as the 2016 American Physiological Society Star Reviewer.



Garrett



Spradley

Dr. Frank Spradley, instructor in surgery and instructor in physiology and biophysics, received the 2016 Regulatory, Integrative and Comparative Trainee Abstract Award, and the Water and Electrolyte, Homeostasis/American Journal of Physiology Award.

Spradley also received the 2016 Research Career Enhancement Award from the American Physiological Society.

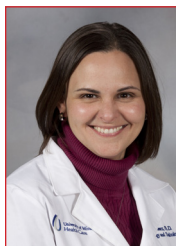
Dr. Barbara Alexander, professor of physiology and biophysics, was recognized by the Journal of Hypertension as its 2016 Top Reviewer.



Alexander

MCOR investigators receive extramural grants

Dr. Jennifer Sasser, assistant professor of pharmacology and toxicology, received an NIH-R01 award, "Mechanisms of Cardiorenal Disease following Preeclampsia."



Sasser

Dr. Eric George, assistant professor of physiology and biophysics, received a Grant-In-Aid from the American Heart Association, "A Novel Therapy for Preeclampsia."

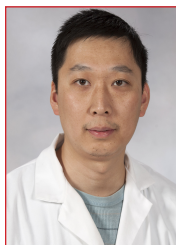
George also received an NIH-R01 award, "A Novel Therapy For Preeclampsia."

Dr. Frank Spradley, instructor in surgery, received an NIH-K99 award, "Effect of Obesity on Antiangiogenic and Inflammatory Mechanisms Mediating Hypertension During Pregnancy."

Dr. Jan Williams, assistant professor of pharmacology and toxicology, received an NIH-R01 award, "Mechanisms Involved in the Early Development of Renal Disease Associated with Prepubertal Obesity."



Williams



Wang

Dr. Zhen Wang, instructor in physiology and biophysics, received an NIH-K99 award, "Synergistic Interactions of Hypertension and Diabetes in Promoting Kidney Injury."

Dr. Michael Ryan, **Dr. Heather Drummond**, **Dr. Babette LaMarca** and **Dr. Joey Granger** received an NIH R01 award, "Placental Ischemia, Hypertension and Hemodynamics."



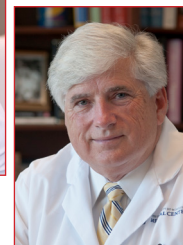
Ryan



Drummond



LaMarca



Granger

MCOR Faculty earn Research Award Ceremony recognition

The Excellence in Research Awards Program at UMMC recognizes investigators who have been successful in attracting extramural funding for their research programs. The following MCOR faculty received awards at the annual ceremony Nov. 9, 2016.

Platinum Medallion - \$5 million received in extramural funding

Dr. Merry L. Lindsey, professor of physiology and biophysics

Dr. James G. Wilson, professor of physiology and biophysics

Gold Medallion - \$1 million received in extramural funding

Dr. Ji Li, associate professor of physiology and biophysics

Dr. Jan Williams, assistant professor of pharmacology and toxicology

Dr. Jussara do Carmo, assistant professor of physiology and biophysics

Silver Medallion - \$500,000 received in extramural funding

Dr. Jennifer M. Sasser, assistant professor of pharmacology and toxicology

Dr. Romain Harmancey, assistant professor of physiology and biophysics

Dr. Bettina M. Beech, associate vice chancellor of population health, professor of pediatrics, professor of family medicine and executive director of the Myrlie Evers-Williams Institute for the Elimination of Health Disparities

Early Career Investigator Awards

Dr. Michael E. Hall, assistant professor of medicine

Dr. Jennifer M. Sasser, assistant professor of pharmacology and toxicology

Selected recent publications by MCOR Investigators

- Alexander BT. The Impact of Nutritional Insults during Fetal Life on Blood Pressure. *J Nutr Sci Vitaminol (Tokyo)*. 2015;61 Suppl:S5-6.
- Chade AR, Hall JE. Role of the Renal Microcirculation in Progression of Chronic Kidney Injury in Obesity. *Am J Nephrol*. 2016; 44:354-367. PMID: PMC5117364.
- Harvey TW, Engel JE, Chade AR. Vascular Endothelial Growth Factor and Podocyte Protection in Chronic Hypoxia: Effects of Endothelin-A Receptor Antagonism. *Am J Nephrol*. 2016;43:74-84. PMID: PMC4828273.
- Ma Y. LRP5: A novel anti-inflammatory macrophage marker that positively regulates migration and phagocytosis. *J Mol Cell Cardiol*. 2016; 91:61-62.
- Dasinger JH, Alexander BT. Gender differences in developmental programming of cardiovascular diseases. *Clin Sci (Lond)*. 2016;130:337-348. PMID: PMC4912835
- Taylor EB, Ryan MJ. Understanding mechanisms of hypertension in systemic lupus erythematosus. *Ther Adv Cardiovasc Dis*. 2016. PMID: PMC5065379
- Spradley FT, Tan AY, Joo WS, Daniels G, Kussie P, Karumanchi SA, Granger JP. Placental growth factor administration abolishes placental ischemia-induced hypertension. *Hypertension*. 2016; 67:740-747. PMID: PMC4786447
- Stec DE, Juncos LA, Granger JP. Renal intramedullary infusion of tempol normalizes the blood pressure response to intrarenal blockade of heme oxygenase-1 in angiotensin II-dependent hypertension. *J Am Soc Hypertens*. 2016; 10:346-351. PMID: PMC4829442
- Roman RJ, Fan F, Zhuo JL. Intrarenal renin-angiotensin system: Locally synthesized or taken up via endocytosis? *Hypertension*. 2016; 67:831-833. PMID: PMC4833086.
- Sun W, Quan N, Wang L, Yang H, Chu D, Liu Q, Zhao X, Leng J, Li J. Cardiac-Specific Deletion of the Pdha1 Gene Sensitizes Heart to Toxicological Actions of Ischemic Stress. *Toxicol Sci*. 2016; 151:193-203. PMID: PMC4914805.
- Wang X, Johnson AC, Sasser JM, Williams JM, Solberg Woods LC, Garrett MR. Spontaneous one-kidney rats are more susceptible to develop hypertension by DOCA-NaCl and subsequent kidney injury compared with uninephrectomized rats. *Am J Physiol Renal Physiol*. 2016; 310:F1054-F1064. PMID: PMC5002061
- Ryan MJ, Coleman TT, Sasser JM, Pittman KM, Hankins MW, Stec DE. Vascular smooth muscle-specific deletion of the leptin receptor attenuates leptin-induced alterations in vascular relaxation. *Am J Physiol Regul Integr Comp Physiol*. 2016; 310:R960-R967. PMID: PMC4896083.
- Yang H, Sun W, Quan N, Wang L, Chu D, Cates C, Liu Q, Zheng Y, Li J. Cardio protective actions of Notch1 against myocardial infarction via LKB1-dependent AMPK signaling pathway. *Biochem Pharmacol*. 2016; 108:47-57. PMID: PMC4959604.
- Hall ME, Wang W, Okhmina V, Agarwal M, Hall JE, Dreisbach AW, Juncos LA, Winniford MD, Payne TJ, Robertson RM, Bhatnagar A, Young BA. Cigarette smoking and chronic kidney disease in African Americans in the Jackson Heart Study. *J Am Heart Assoc*. 2016; 5. PMID: PMC4937270.
- Chade AR, Tullos NA, Harvey TW, Mahdi F, Bidwell GL 3rd. Renal therapeutic angiogenesis using a bioengineered polymer-stabilized vascular endothelial growth factor construct. *J Am Soc Nephrol*. 2016; 27:1741-1752. PMID: PMC4884109.
- Dasinger JH, Intapad S, Rudsenske BR, Davis GK, Newsome AD, Alexander BT. Chronic Blockade of the Androgen Receptor Abolishes Age-Dependent Increases in Blood Pressure in Female Growth-Restricted Rats. *Hypertension*. 2016; 67:1281-1290. PMID: PMC4865435.
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How to help the MCOR achieve its mission

Although UMMC has made a strong commitment to developing and sustaining MCOR research and prevention efforts, external funding is required to fully realize MCOR's potential. The MCOR program is mainly funded by extramural sources, including gifts from generous donors and NIH grants. All funds donated to MCOR help advance obesity research, prevention and treatment.

Donations may be made online at umc.edu/givenow. Select "UMMC Options" and then select the "Mississippi Center for Obesity Research" fund.

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