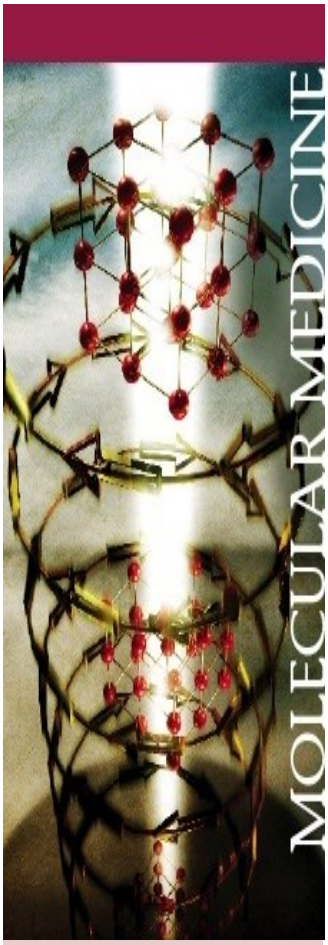
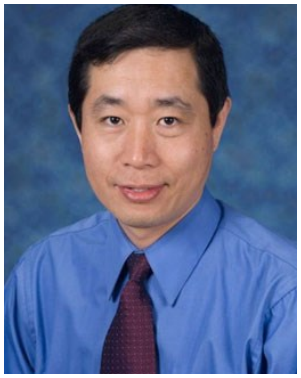


CENTER FOR
MOLECULAR MEDICINE AND GENETICS

December 2017

Dr. Zhang's studies of liver-specific stress sensors reveal metabolic disorders link

Kezhong Zhang, PhD, Professor of Molecular Medicine and Genetics and of Microbiology, Immunology, and Biochemistry, focuses on intracellular stress signaling in inflammation and metabolism. He came to the Center from the University of Michigan in 2008 and has been making key research discoveries ever since.



Dr. Kezhong Zhang

His group defined the mechanisms and functions of CREBH and IRE1α as key regulators of hepatic lipid homeostasis under pathophysiological stress conditions. In particular, he says, "we discovered that CREBH is a multifaceted transcriptional regulator that can be activated by distinct stress signals or circadian cues to regulate multiple, even functionally opposite, metabolic pathways." Disrupted sleep cycles play a role in stress factors that lead to disease.

More generally, he says, "My research interest is focused on molecular mechanisms and physiological roles of endoplasmic reticulum (ER) stress signaling and inflammatory responses in cellular metabolism and that are associated with metabolic disease, autoimmune disease, and cancer." His lab investigates stress response, inflammation, and metabolism that are linked to metabolic disorders, such as non-alcoholic steatohepatitis (NASH), obesity, and type-2 diabetes.

As he describes, "In the course of studying the physiological ER stress response, we discovered a novel, liver-specific stress sensor called CREBH that modulates inflammation and energy metabolism associated with metabolic disorders. We also revealed the molecular mechanisms and physiological roles for the primary transducer of the Unfolded Protein Response (UPR), IRE1α, in B cell differentiation and function, in hepatic steatosis (fatty liver disease), and in macrophage inflammation."

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Inside this issue:

Dr. Ghosh builds biostatistics expertise at WSU

Samiran Ghosh, PhD, Associate Professor of Family Medicine and Public Health Sciences and of Molecular Medicine and Genetics, is a biostatistician who has pioneered the field at Wayne State. When Dr. Ghosh arrived here in 2012 the University had no biostatistics department or staff devoted to that discipline.

Now it does and Dr. Ghosh serves as Director of Biostatistics in the Biostatistics and Epidemiology Research Design (BERD) core. He is currently a member of several research groups around campus as well as Principal Investigator of a PCORI (Patient-Centered Outcomes Research Institute) grant. As a biostatistician, he designs, analyzes, and interprets data for studies, primarily in health and medicine. "Statistics play an integral role, especially in human studies, to ensure things are done correctly," he says, and points out that the collected data is crucial to securing grants. It has also proven helpful in securing funding more quickly; in one case it took approximately one year for the go-ahead, something which he likens to practically being a miracle.

Dr. Samiran Ghosh

"Appropriate statistical design is the cornerstone of successful clinical research, and the biostatistician plays an integral role in this development," he explains. "Wayne State is possibly one of the few large medical schools which does not have a biostatistics department or division. This shortage forces investigators to go outside of WSU to other institutions for this expertise." That can obviously prove disadvantageous, and he is determined to remedy that.

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Dr. Feldman seamlessly juggles three roles as a physician, educator, and researcher

Gerald Feldman, MD, PhD, Professor of Molecular Medicine and Genetics, of Pediatrics, and of Pathology, serves the Center and Wayne State and the Detroit Medical Center in a threefold manner: medical genetics laboratory directorship/ patient care, and education. He teaches the principles of medical genetics to medical and genetic counseling students and to medical genetics residents and fellows.

Dr. Gerald Feldman

He also is in the last leg of a six-year term with the American College of Medical Genetics (ACMG), including 2 years as President, where he led efforts to develop a policy that defined "the scope of practice for a medical geneticist." Previous policies were in need of revision, Dr. Feldman explained. In addition, Dr. Feldman helped revise the ACMG's policy on direct-to-consumer genetic testing, which recommended that a genetics health professional (such as a clinical geneticist or genetic counselor) be available to help the consumer interpret and understand both the technology and the test results as well as how they might use the results in their health care management. Dr. Feldman explained that direct-to-consumer genetic testing offerings do not simply focus on ancestry, but also on health-related information – for example, whether an individual is more prone to develop certain cancers or to be at risk to develop Alzheimer's disease. The ACMG also recommended that the consumer be aware of the need for informed consent and understand privacy matters such as what happens to the consumer's DNA sample after testing is completed. Advocacy for patient-related genetic services, including adequate reimbursement for laboratory testing and genetic consultations, was another area that ACMG addressed during his tenure as president.

Gene editing is another interest of Dr. Feldman's. Theoretically one could "correct a mutation in a patient and allow the repaired gene to function normally." However, because there are large ethical and moral concerns raised by such technology, ACMG developed a policy statement on gene editing. The statement strongly encourages further discussion and debate of the issues involved. As part of the ACMG's press release this year, Dr. Feldman was quoted as stating: *"ACMG is excited about the vast potential for genome editing that will benefit patients with rare genetic disorders, not to mention other conditions such as cancer. We are aware that there are clinical trials already ongoing in treatment of cancer and others likely to be launched in the near future, including for genetic conditions. Our goal in this statement is to draw attention to the opportunities for treatment of genetic conditions, some of the challenges that are being actively addressed, and the ongoing concern about even greater challenges associated with germline, as opposed to somatic, genome editing. We look forward to facilitating in any way we can the rapid and safe transfer of this important technology to clinical application."*

In addition to his leadership stint at ACMG, Dr. Feldman is a professor of Molecular Medicine and Genetics, of Pathology, and of Pediatrics at the University's School of Medicine, and the Division Director for Clinical Genetics at the Center. He also serves as Director of Clinical Genetics Services and medical director for the Division of Laboratory Genetics and Molecular Pathology, Detroit Medical Center-University Laboratories.

Dr. Feldman's research focuses on the use of molecular technologies in the diagnosis of genetic diseases. He is also interested in the treatment of patients with inborn errors of metabolism diagnosed through newborn screening and in educational programs related to medical genetics residency and fellowship training.

His work in clinical genetics pertains in particular to genetics services and newborn screening. Newborn screening refers to screening infants after birth for known genetic disorders – so-called inborn errors of metabolism – so that they can be treated to prevent the damage that would occur if untreated. Such screening is currently his primary concentration in clinical genetics, specifically "disorders that affect enzymes in various metabolic processes." Phenylketonuria (PKU) is one such genetic disorder. He and his team have recently published a study which documented the challenges that patients and families have in adhering to the PKU dietary management recommendations required for optimal treatment. In addition to PKU, nearly 50 other inborn errors of metabolism are also screened for in Michigan. The Children's Hospital of Michigan's Metabolic Clinic, of which Dr. Feldman is the Program Director, is responsible for managing all patients diagnosed with one of those inborn errors of metabolism for the entire state of Michigan.

Dr. Feldman's office is in Scott Hall, Room 2375.

Dr. Feldman is on the last leg of a six-year term with the American College of Medical Genetics (ACMG), including 2 years as President, where he led efforts to develop a policy that defined "the scope of practice for a medical geneticist." While there, he also helped revise the ACMG's policy on direct-to-consumer genetic testing.

New to the Center: Dr. Tiffany Cook

Tiffany Cook, PhD, Associate Professor of Molecular Medicine and Genetics and of Ophthalmology, joined the Center in August of 2015. Dr. Cook came to Wayne State from Cincinnati Children's Hospital Medical Center. There she developed an internationally-recognized research program on nervous system development.

Dr. Tiffany Cook

At Wayne State, she has begun to complement these studies by addressing how the mature nervous system functions and ages. With the broad questions of how the nervous system develops but declines over time, Dr. Cook's studies subsume a diverse spectrum of areas including differentiation and maintenance of neuronal vs non-neuronal cell fates, glial support mechanisms, cell-specific transcriptional regulatory mechanisms, and cell-cell interactions involved in sensory system development and function.

As an experimental model, the common fruit fly *Drosophila* has been instrumental in Dr. Cook's efforts. The work in her lab and many others established that the tiny eye of this animal can inform on human retinal degenerative disease processes. Some of her work in this area has appeared in leading journals such as *Science* and *Nature Genetics*. Dr. Cook's laboratory collaborates with human geneticists to identify and study new genes associated with retinal degeneration.

In addition to understanding how neurons form and function, Dr. Cook has begun to explore a second cell type, glia. So named because they were long thought to be the glue that holds the nervous system together, glia are the caretakers of neurons. This work is the topic of one of Dr. Cook's most recent papers, published in *PLoS Genetics* in May, "Multifunctional glial support by Semper cells in the Drosophila retina."

"An important finding from this paper," Dr. Cook says, "is that we can genetically separate the role of glia in promoting neuron structure vs function, processes that are typically thought to be inseparable."

"Perhaps even more importantly, she adds, "the factors we have identified in these events - Pax2 and Prox1 - are linked to two common diseases associated with vision loss - renal coloboma and diabetes. By following up on the function of these factors, we expect to gain a better understanding of these disease states."

Glia have been found to do much more than originally thought. "Defects in glia are tied to almost every neurodegenerative disease out there," Dr. Cook says. "We're just starting to find this out and what they do."

"The longterm goal is to activate glial repair to help patients suffering from neurodegeneration. Glia research may eventually help to develop drugs for curing or slowing down disease progression. Right now, our work is on the eye, but our findings could apply to other diseases too."

What drew Dr. Cook to the Center was its "strong program in metabolism and genomics – two areas my research was leading me towards. In addition, there is outstanding eye research across the Wayne State campus, allowing for great synergy. It therefore made a lot of sense to join Wayne State."

Dr. Cook's office is located at 3206 Scott Hall. Visit her online bio at www.genetics.wayne.edu/tiffany-cook.

Dr. Samiran Ghosh - Continued from Pg. 1

"My long-term goal is to change this culture. This task is quite challenging and often involves substantial effort from my part to convince researchers to think the other way around. At Wayne State, I am not only sustaining my own statistical methods research by my group, but also performing as an educator to fulfill this unmet need of biostatistics resources."

To formalize the procedure, he's assumed the role of director of BERD core. "I consider my effort in this direction as pioneering," he says.

As principal investigator for the PCORI grant – titled "Developing Bayesian Methods for Non-inferiority Trial in Comparative Effectiveness Research" – Dr. Ghosh explains that this is likely the only biostatistical methods grant secured for the University in some time as well as the first PCORI contract for Wayne State.

The goal of the research "... is to improve clinical trial methods by incorporating patient opinion in the trial design itself using Bayesian methodology."

In the proposal abstract, Dr. Ghosh's team addresses multiple treatment options, and how "comparative effectiveness research is gaining importance for better and informed health care decisions," adding that, "design and analysis of an effectiveness trial is more complex than that of an efficacy trial."

Several treatment options may offer many benefits as well as flexibility to patients. It also means that informed care decisions can be challenging. When the advantages of an experimental treatment are not readily apparent, be it because of factors of cost, administration methods, etc., weighed against the level of effectiveness – the very nature of CER – then non-inferiority design is vital.

"This may lead to not only reduction in sample size requirements but also may increase patient satisfaction, leading to improved overall trial success," Dr. Ghosh explains.

With human subjects in patient-centric research, a biostatistical core is crucial for correct collection and analysis of data according to Dr. Ghosh. That focus should prove invaluable in securing other grants as well, he explains; in addition to helping design studies, the core can help the investigator stay a step ahead, both in terms of supplying needed data as well as remedying potential pitfalls.

Dr. Ghosh explained that PCORI trials have been limited due to a number of factors, including "lack of understanding about the role and impact of prior information, lack of methodological development, and unavailability of easy-to-use software to design and conduct such analysis." His proposal addresses the "refinement of design-specific analytics methods" and seeks to "set new standards where Bayesian design for CER can be used via NI trial." The result, he concludes, "will be more efficient, ethical and can incorporate prior information from multiple and possibly heter-

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Kalita wins prestigious AHA fellowship on first try

Cynthia Kalita is a student in the Center's Molecular Genetics and Genomics PhD program who was awarded a fellowship from the American Heart Association in January, 2017. She is co-advised by Francesca Luca, PhD and Roger Pique-Regi, PhD, both Assistant Professors of Molecular Medicine and Genetics and of Obstetrics and Gynecology.

Cynthia Kalita

"I was super excited when I found out, since it was my first submission," Kalita says. "I just figured it would require revisions before even having a chance of being awarded."

Dr. Francesca Luca shares Kalita's excitement. "I was really impressed by the outcome," she says. "I was prepared to receive helpful reviews, but a score outside the fundable range. In fact, I had warned Cindy, when we were preparing the application, that it may take up to three submissions to get funded."

Dr. Luca, when she was a post-doctoral fellow at the University of Chicago, knew students who had won AHA fellowships. "However, they were all members of well-established laboratories. Cindy is the first student in our group to apply for a fellowship and, even if we are well funded (with National Institutes of Health and AHA grants), both I and Dr. Roger Pique-Regi were Assistant Professors for less than five years when Cindy applied for the fellowship. I think that, given the circumstances, it wasn't obvious for Cindy to receive the fellowship at the first try. We are very proud that she is one of the few students who has been selected for this very prestigious fellowship program."

Kalita first became interested in genetics while taking biology in the eighth grade. "The idea that there was a master code that determined what people look like, how they form, the diseases they would get, that was just amazing to me."

Kalita arrived at Wayne State after earning a Bachelor's degree in Biotechnology in 2010 from the State University of New York School of Environmental Science and Forestry.

In her undergraduate studies, Kalita researched spruce defensin genes, which were thought to be capable of transferring blight resistance to the American Chestnut. From there she worked in industry at Kodak, Arch Chemicals, and Dow Chemical. While at Dow she decided to pursue a higher degree.

"I was looking at universities in Michigan with strong genetics research going on," Kalita says. "I chose Wayne State's MGG PhD program because of the high level of research and the range of research topics going on. This program also has a strong emphasis on translational work."

Kalita says she would like to discover the DNA variants that indicate functional effects or disease risk.

Her AHA fellowship dovetails nicely with her thesis. "Overall my thesis project is being developed towards an integration of results from genome-wide association studies of complex traits with newly developed functional annotations in relevant tissues. Cardiovascular diseases and the vascular endothelium were already part of my broader thesis project. The AHA fellowship is now giving me the opportunity to focus more on cardiovascular health. Part of my research project focuses on developing a high throughput reporter assay to investigate the function of non-coding regulatory variants in different cell types and environmental contexts. For the AHA project, I am focusing on HUVECs (human vascular endothelial cells, a cell type important for modeling vascular function) and I plan to treat them with compounds that reflect common cardiovascular disease risk factors."

Kalita enjoys the blend of computational and experimental work the study affords. "I came by this project because our lab had some pretty extensive computational predictions of functional variants for which we wanted to perform experimental validation. This project is great for testing the effect on gene expression of thousands of variants at once."

That Kalita won the fellowship was no surprise to Dr. Luca. "Cindy has incredible time-management and multi-tasking skills. In the first two years of her PhD she was able to efficiently work in parallel on two independent research projects, while also attending classes. The field of functional genomics is characterized by frequent switches from 'bench to desk' to perform data generation and data analysis. Cindy is extremely good at these transitions and is not afraid to try new approaches both in the lab and on the computer."

Once she has her doctorate, Kalita intends to continue with her research. "As a first step, I will soon start to apply for post-doctoral positions to continue developing into an independent scientist."

Dr. Samiran Ghosh - Continued from Pg. 3

ogeneous sources in a robust fashion."

In these studies, patient preference is accounted for. Ultimately if the drug works and if the patient likes the cost, the administration method, or reduced side effects, to cite some potential examples, then it's a success. "Even if (the drug) works, if the patient doesn't like it, and will not take it, then the drug doesn't work," Dr. Ghosh explains. Hence, the potential his methodology provides for a more successful trial.

In addition to the PCORI grant work, Dr. Ghosh is involved in several other studies, including for the Center for Urban Responses to Environmental Stressors (CURES), a P30 grant from the National Institute of Environmental Health Sciences (NIEHS). "I played a vital role from 2013, when our P30 got funded for the first time for three years (2014-2017), and I played a major role in its recent renewal (2017-2022)," he said.

Dr. Ghosh is also working on Scale-it-Up. "This is a multi-institution National Institutes of Health (NIH) grant concerning prevention of HIV among adolescents through increased medication adherence. I played the key role of biostatistician." Furthermore, his biostatistics expertise is playing a role in three other R01 level projects.

Dr. Ghosh's offices are located in Room 1128 of the new Integrated Biosciences Center (aka the IBio building) at 6135 Woodward Ave. and in the Center in Room 3325 of Gordon Scott Hall.

Dr. Kezhong Zhang - Continued from Pg. 1

Dr. Zhang's research has resulted in 98 scientific publications, including those published in high-profile journals such as *Cell*, *Nature*, and *Science*.

"We also revealed," he says, "that CREBH and PPARα form a transcriptional complex to potently regulate lipolysis, fatty acid oxidation, and ketogenesis upon energy demands. CREBH deficiency leads to profound NASH and hyperlipidemia."

Furthermore, Dr. Zhang discovered that the liver is a major target organ of inhalation exposure to fine airborne particulate matter ($PM_{2.5}$) and is responsible for air pollution-induced NAFLD and type-2 diabetes.

Dr. Zhang's lab has undertaken a wide range of topics, for which he has secured 11 extramural research grants from the National Institutes of Health, the Department of Defense, and the American Heart Association, totaling more than $10 million in research funding. In the next five years, his research programs will receive support from six NIH R01 awards. In addition, Dr. Zhang mentors both graduate and undergraduate students, as well as junior faculty members. The specific research projects his lab is conducting are summarized below:

Regulation of Hepatic Steatosis and Energy Metabolism by Stress-inducible, Circadian-regulated Transcriptional Activators. Fatty liver disease is considered a precursor or manifestation of cardiovascular and metabolic disease. "We are investigating the activation of CREBH by metabolic stress signals or physiological circadian cues in the liver and its pathophysiologic roles in the non-alcoholic fatty liver disease (NAFLD), obesity, and atherosclerosis models," Dr. Zhang says, "we demonstrated that activated CREBH functions as a key metabolic regulator of lipid homeostasis by regulating hepatic lipogenesis, fatty acid oxidation, lipolysis, and ketogenesis." The findings by the Zhang lab may help mold new approaches to prevent and treat human NAFLD and related cardiovascular and metabolic disease.

Roles and Mechanisms for the UPR Transducer IRE1α in Autoimmune Diseases. "UPR signaling mediated through IRE1α, triggered by environmental or pathophysiological stressors, interacts with toll-like receptor (TLR)-mediated inflammatory response and act in synergy to promote production of pro-inflammatory cytokines in macrophages." The inflammatory UPR plays a key role in the onset of inflammatory arthritis. "Currently, we are dissecting the molecular network governing the inflammatory UPR signaling in macrophage inflammation and testing the potential of targeting this novel signaling pathway by specific IRE1α inhibitors for arthritis and lupus therapies," Dr. Zhang says.

Airborne Particulate Matter-induced Inflammatory Stress Response and Its Effects on Non-alcoholic Steatohepatitis (NASH) and Type-2 diabetes. Studies have shown links between inhaled airborne particulate matter (PM) and cardiovascular and metabolic diseases, though the underlying mechanism is unclear. Dr. Zhang's team, collaborating with a research group at Ohio State University, has found that exposure to PM smaller than 2.5 μm, ($PM_{2.5}$) leads to inflammatory stress in lung and liver tissues of animal models, and that the $PM_{2.5}$ exposure leads to NASH and type-2 diabetes. "Our findings not only demonstrated that sub-chronic exposure to airborne $PM_{2.5}$ represents a significant "hit" that triggers NASH and impairs glucose metabolism, but also defined a type-2 diabetes model triggered by environmental stress but independent of obesity. "The related studies have important implications in the prevention and treatment of air pollution-induced systemic diseases," he says.

Roles of Endoplasmic Reticulum Lipid-raft Proteins and ER Stress Sensors in Breast Cancer Malignancy Maintenance and Therapy Resistance. Cancer cells must adapt to oncogenic stressors such as DNA damage and proteotoxic, metabolic and oxidative stresses. Dr. Zhang's team identified that the endoplasmic reticulum (ER) lipid raft associated 2 (ERLIN2) gene is amplified and over-expressed in the aggressive forms of breast cancer cells. ERLIN2 helps cancer cells to adapt to cancer-related cellular stress. **"**Using human breast cancer lines as well as animal models," Dr. Zhang says, "we are investigating the molecular mechanism for the role of ERLIN2 or IRE1α in maintaining stress- and apoptosis-resistant phenotypes of human breast cancer cells. We are also testing whether inhibition of ERLIN2 or IRE1α activity can enhance the effectiveness of the conventional anti-cancer drugs in aggressive breast cancers."

Dr. Zhang's office is in Scott Hall, Room 3202.

Faculty and trainee accomplishments

2017 WSU School of Medicine award recipients:

College Teaching Award:

— **Erin Carmany, MS, CGC**: Assistant Professor of Molecular Medicine & Genetics

— **Angela Trepanier, MS, CGC**: Associate Professor of Molecular Medicine & Genetics

— **Ren Zhang, PhD**: Assistant Professor of Molecular Medicine & Genetics, and of Internal Medicine

— **Kezhong Zhang, PhD**: Professor of Molecular Medicine & Genetics, and of Microbiology, Immunology, and Biochemistry

— **Tiffany Cook, PhD**: Associate Professor of Molecular Medicine & Genetics, and of Ophthalmology

Research Excellence Awards:

— **Leonard Lipovich, PhD**: Associate Professor of Molecular Medicine & Genetics, and of Neurology

— **Roger Pique-Regi, PhD**: Assistant Professor of Molecular Medicine & Genetics, and of Obstetrics & Gynecology

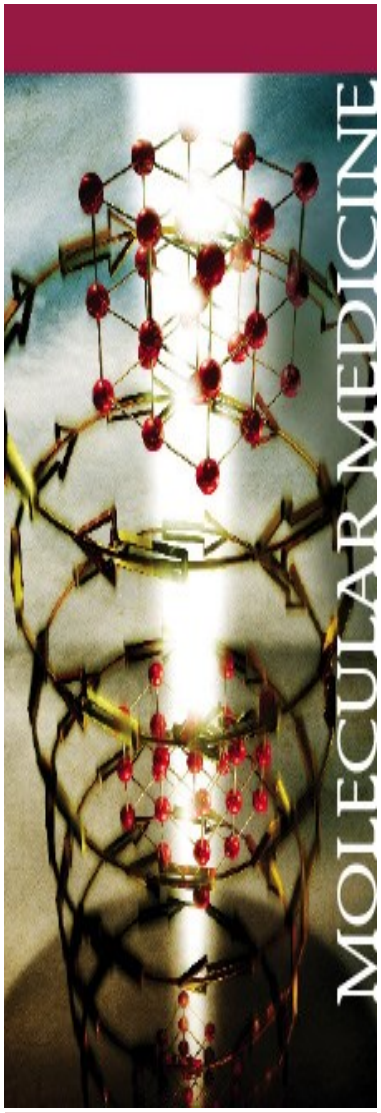
Maik Hüttemann, PhD won 'Best Short Oral Presentation' at the 8th World Congress on Targeting Mitochondria, held in Berlin from October 23-24th, 2017. His talk was titled "Modulation of cytochrome C oxidase activity with specific near-infrared light wavelengths attenuates brain ischemia/reperfusion injury"

Francesca Luca, PhD and **Roger Pique-Regi, PhD,** along with other WSU faculty, submitted a proposal for a Presidential Sesquicentennial Symposium Series that will be co-sponsored by Genomics@Wayne, CURES, the School of Social Work, and RoBUST. The proposal was accepted and the symposium will take place on September 14, 2018.

Vanesa Ramseyer, PhD was awarded an NIH diversity supplement on April 1, 2017. Dr. Ramseyer is a post-doctoral fellow in the Granneman Laboratory.

Emilio Mottillo, PhD was awarded an NIH K99 award on July 1, 2017. Dr. Motillo is a post-doctoral fellow in the Granneman Laboratory.

Bhanu Jena, PhD received the "Award of Honorary Scientist" following his November keynote lecture in Bucharest at the *130th anniversary of Victor Babes National Institute of Romania*, sponsored by the Romanian National Academy.



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