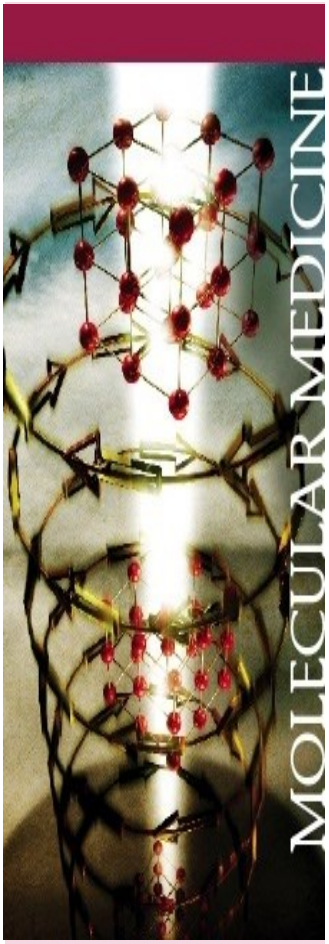

CENTER FOR
MOLECULAR MEDICINE AND GENETICS

Spring 2023/Summer 2023

Dr. Kezhong Zhang recently discovered CREBH-C, a new hepatokine that helps control triglyceride levels

CREBH, a stress-sensing protein tethered to the cell's endoplasmic reticulum, was discovered more than 10 years ago by Dr. Kezhong Zhang, PhD (Professor of Molecular Medicine and Genetics and of Biochemistry, Microbiology and Immunology). Recently, he and his colleagues made the surprising discovery that CREBH can be processed to release a fragment from the carboxy terminus (CREBH-C) that acts as a secreted liver hormone (a hepatokine) that regulates an enzyme called lipoprotein lipase. Lipoprotein lipase is the enzyme that primarily clears triglycerides from plasma. How it functions and how its function is regulated are of major importance in seeking to control elevated triglyceride levels and associated metabolic disorders. CREBH-C production is stimulated by fasting or hepatic stress.

The new work is part of Dr. Zhang's long-time focus on the cellular stress responses originating from the endoplasmic reticulum and/or mitochondria, which are associated with metabolic diseases, autoimmune diseases, and cancer. He will specifically study the role of CREBH-C in regulating lipid metabolism in the whole body. CREBH, as noted above, is a protein factor localized to the ER-membrane that is stress-inducible and implicated in lipid metabolism. It is cleaved into two fragments, one of which,

Zhang

Zhang Spotlight continued on Page 3

Ischemia-reperfusion Injury: from the Lab to the Clinic

A new study to gauge the effectiveness of infrared light therapy in preventing ischemia-reperfusion injury is getting underway under the direction of Dr. Maik Hüttemann, PhD (Professor of Molecular Medicine and Genetics and of Biochemistry, Microbiology, and Immunology). The study is based on previous basic research by Hüttemann showing that the damage caused after relieving a blood flow interruption such as is found in ischemic stroke or cardiac arrest is produced by the hyperactivity of the terminal enzyme of the electron transport chain, cytochrome *c* oxidase (COX), which promotes damaging free radical species (ROS), and that there are wavelengths of infrared light that can reduce COX activity and thereby protect against this ROS damage.

Paradoxically, as oxygen delivery is restored, mitochondria become hyperactive, and thus ROS production increases exponentially, causing cellular dysfunction and death. For example, during a stroke, when a blood clot prevents oxygen from entering brain tissue, the only way to restore oxygen delivery and save the tissue is to remove the blood clot. "What wasn't understood for so long," Hüttemann says, "is that when you open up the blood vessel to do this [remove the blood clot], it creates additional damage in the

Hüttemann

Hüttemann Spotlight continued on Page 2

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Hüttemann Spotlight (cont.)

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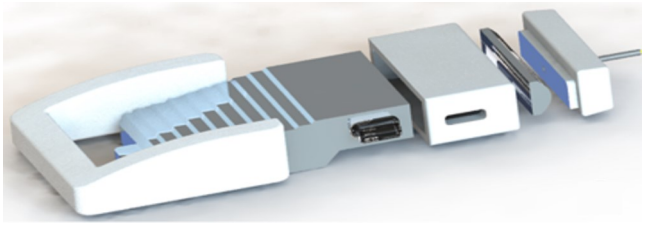
form of reperfusion damage."

Hüttemann studies mitochondrial regulation under stress, specifically the regulation of cytochrome c oxidase and cytochrome c, which are key components in mitochondrial oxidative phosphorylation—Mitochondria function to produce the energy used to power all processes in the body. ROS, also called free radicals, are a byproduct of this energy production process, and the overproduction of ROS is implicated in cell dysfunction and death. COX is found to be key in the absorption of infrared light, which affects the regulation of mitochondrial function and ROS production.

Hüttemann started working on noninvasively preventing ischemia-reperfusion injury through the usage of infrared light in 2006 when he received an initial grant from the Wilson Foundation. With this grant, he and his collaborators identified wavelengths of infrared light (750 nm and 950 nm) that inhibit mitochondrial function. Hüttemann explains that "typically, other literature has focused on and shown that infrared light *activates* mitochondrial function at wavelengths of 810 nm." Their discovery identified wavelengths of infrared light with an inhibitory effect on mitochondrial function.

Building on these findings, Hüttemann and Dr. Thomas Sanderson (Associate Professor of Emergency Medicine and Molecular & Integrative Physiology, University of Michigan) developed the technology to apply inhibitory wavelengths of infrared light to ischemic tissue during reperfusion to prevent injury. Small and large animal testing has been successfully conducted on rats and pigs. The work was so encouraging that Hüttemann and Sanderson founded a startup company, Mitovation, to advance this technology. The success of the large animal work with pigs led them to apply for an NIH U44 grant to carry out a clinical trial. This $6.5 million grant was just awarded, and with it, Hüttemann is building a medical device emitting infrared light for a trial at the Children's Hospital of Michigan. The device will distribute infrared light over a large, controlled area to ensure the patient's safety.

Hüttemann credits this project's success and progress to his team's persistence and the support he has received over the years. He would like to recognize the efforts and contributions of his colleagues and collaborators, particularly Sanderson, Dr. Dennis Goebel, PhD (Associate Professor of Ophthalmology, Visual and Anatomical Sciences), Dr. Moh Malek, PhD (Professor, Physical Therapy Program), and Dr. Kathleen Meert, MD (Clinical Professor, Pediatrics), and their lab members. "From the initial grant awarded by the Wilson Foundation to the continued institutional support provided by WSU, this technology has received a great deal of support," says Hüttemann, noting that he and his collaborators are "incredibly motivated in making a difference for patients."



Above: "exploded view" of the infrared light waveguide technology

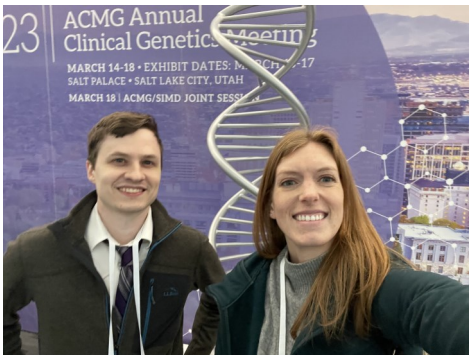
Student Highlights

NIH Fellowship Award

Shreya Nirmalan, a second-year student in the MGG MD-PhD program in the labs of Drs. Francesca Luca and Roger Pique-Regi, received a new four year F30 NIH fellowship entitled "The Interplay of Host Genetic Variation and the Gut Microbiome in Crohn's Disease." The highly competitive F30 award supports promising doctoral candidates who will perform dissertation research and training for an MD-PhD.

Nirmalan

Beyond the Classroom



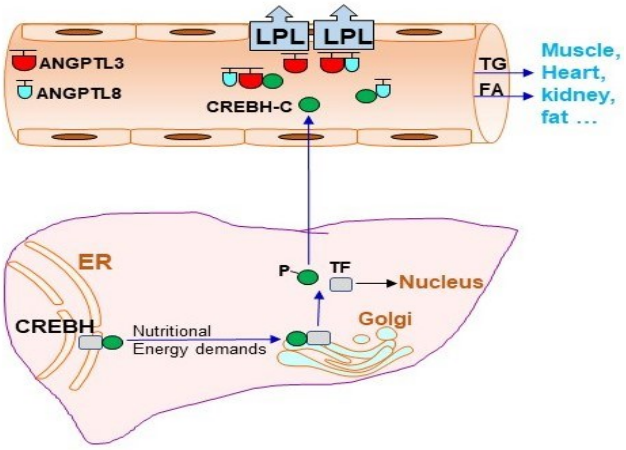
Baughan and McCarthy-Leo

Scott Baughan and Claire McCarthy-Leo, from the lab of Dr. Michael Tainsky, PhD (Professor of Oncology and of Molecular Medicine and Genetics), presented data of their research at the ACMG Annual Clinical Genetics Meeting in Salt Lake City, Utah.

K. Zhang Spotlight (cont.)

From Page 1

from the amino terminus end of the protein, is sent to the nucleus as a transcription factor for enzymes acting in lipid and glucose metabolism. The other fragment derived from CREBH is the CREBH-C protein that is secreted as a hepatokine. For example, during exercise or fasting, CREBH can be activated to release CREBH-C to increase lipid metabolization to provide energy to the muscles exerting energy. This hormone functions to prevent hyperlipidemia, a condition caused by overnutrition or genetic susceptibility. “With this hormone, hyperlipidemia can be significantly attenuated,” said Dr. Zhang, thus having “very promising potential in the treatment of cardiovascular and metabolic disorders.”



A hepatokine derived from the ER protein CREBH promotes plasma triglyceride clearance and counteracts hyperlipidemia

The CREBH-C work is funded by a renewal of Dr. Zhang's grant from the NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases). The CREBH project has been continuously funded by the NIH for the past 15 years and is his fourth successful NIH R01 grant in the last two years.

Dr. Zhang's collaborators on this project include another Center faculty member, Dr. Ren Zhang, PhD (no relation), (Associate Professor of Molecular Medicine and Genetics and of Internal Medicine), whose interest in lipid metabolism catalyzed the collaboration. Dr. R. Zhang is a co-investigator on the new NIH grant as well as a coauthor on the recent publication describing the identification of CREBH-C (https://pubmed.ncbi.nlm.nih.gov/36649378/).

Racial Disparities in Cancer Genetics

Carmany

A new study to determine whether patient race affects healthcare quality as viewed through a genetic counseling perspective is just getting underway as a collaboration involving Center faculty member Erin Carmany. The study, " Cancer health disparities and genetic counseling encounters (CHANGE)," aims to compare and contrast the nature of genetic counseling encounters and patient-centered outcomes between Black and White patients in a genetic counseling clinical setting. This study will include recruitment at genetic counseling clinics in Richmond, Virginia, and Karmanos Cancer Institute in Detroit.

Carmany (Associate Professor of Molecular Medicine and Genetics and Associate Director of Genetic Counseling Master's Program) is part of a collaboration that was recently awarded an R01 grant from the National Cancer Institute and included researchers at Virginia Commonwealth University (Principal Investigators: Nao Hagiwara, PhD and John Quillin, PhD, CGC) and WSU/Karmanos Cancer Institute (Co-Investigator: Susan Eggly, PhD). Carmany and Eggly are overseeing patient and provider recruitment and data collection in Detroit.

"We are going to be conducting a mixed-methods study, looking at both qualitative and quantitative data analyses," says Carmany. Patients with either a personal or family history of cancer referred for genetic counseling will be surveyed prior to their initial appointment for their perceptions of racial discrimination, general trust in genetic counseling providers, and satisfaction with the healthcare provided by the health system. This approach is expected to allow a robust and comprehensive collection of data, important for investigating a complex issue like racial healthcare disparities.

Following the initial survey, patient genetic counseling sessions will be recorded and then analyzed for provider communication style and overall patient-provider communication by studying non-verbal and verbal markers of communication. A post-visit survey will be given to both provider and patient to measure what they call the therapeutic alliance – the cooperative and positive relationship between a healthcare provider and patient. Additionally, the patient post-visit survey will include measures of provider-specific trust, provider-specific satisfaction, and patient empowerment (whether the patient felt in control of the situation and was able to take appropriate actions given their current circumstances).

Carmany Spotlight (cont.)

From Page 3

The implications of this study are important at both a global and national level as healthcare providers, including genetic counselors, seek to bridge gaps in healthcare for their diverse patient populations. Carmany said this study could provide further information on the extent of healthcare disparities in genetic counseling between Black and White patients and provide insight into the drivers of those disparities and their impacts on patient-centered outcomes. "We are seeing differences in our patient populations," she said. "It's important to understand why these differences are present.

"Because genetic counseling is such a communication-based field, it is important to evaluate how provider communication styles differ and of the values promoted by the WSU School of Medicine and will contribute to the broader discussion of healthcare disparities," Carmany added.

Paul Morse

MD - PhD candidate at CMMG

Paul Morse, an MD-PhD student working with Dr. Maik Hüttemann at CMMG, defended his dissertation, "The Endogenous Regulation and Exogenous Manipulation of Mitochondrial Activity: Cytochrome *c* and Cytochrome *c* Oxidase" on January 30, 2023.

Currently, there are about 6,000 MD-PhD students in the U.S., and Paul Morse is one of those few. Morse was deeply engaged with research during his undergraduate years at GVSU and sees that as a positive and formative experience. Enrolling in an integrated MD-PhD program has allowed him to pursue both medical school and research, and develop a unique skill set that would be beneficial to his future patients. Morse hopes to use these skills in the future and "mix clinical practice and research together… and keep that scientific mindset going forward."

Morse's dissertation comprised his work regarding the mitochondrial coupling mechanism and manipulation of this mechanism. This research has broad implications for various diseases associated with mitochondrial dysfunction, and finding novel therapies to manipulate mitochondrial function is of great interest.

Morse

Pursuing both a medical degree and a PhD is certainly a difficult but rewarding path to pursue, and is a path with many small setbacks and accomplishments. A common misconception about research is that researchers know everything there is to know, and that could not be far from the truth. An important aspect of research is being flexible and problem-solving along the way. Morse explains that over his past few years on this path, one of the accomplishments he is most proud of would be transitioning from an unsure student into a researcher confident in his abilities. "I learned when to pull the plug… it was a valuable experience learning when to say no," says Morse. Learning how to best focus his energy has been very fruitful to Paul as he finished his PhD with several successful projects. "I feel very accomplished bringing so many different projects to completion." The support system he developed while working in this lab with Dr. Hüttemann also helped shape him into the researcher he is now. "He's [Dr. Hüttemann] a very hands-on mentor…he always encouraged me to think and was willing to let me be wrong about things," explains Morse. Mentorship is key to developing independent and successful future researchers, and Dr. Hüttemann taught Morse the various aspects of running a lab, from writing NIH grants to running and interpreting experiments." He [Dr. Hüttemann] really just wanted me to think about things," says Morse, emphasizing the importance of thinking critically and developing a scientific mindset during his time at CMMG.

Although he will start from the ground up again as he re-enters medical school this coming year, he is confident that the skills he has learned will help him succeed in this part of his journey. "I've had a broader education and have got exposure to a lot of different techniques and ideas." As for future professional goals, Morse hopes to apply for a research residency after medical school and gain exposure to a different field of study. When asked how he would advise future PhD students, Morse emphasized the importance of having a strong support system because "… it's hard even when it goes well" while pursuing such a strenuous path. Most importantly, choosing a mentor who is willing to go a long way to support and teach you is imperative as a graduate student. "It's all about having good mentors, people who are ready to take a chance on you."

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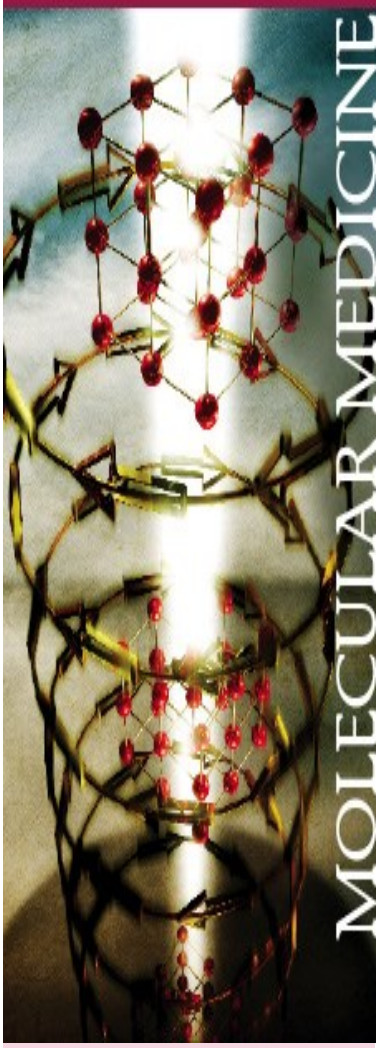

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