DMRC QUARTERLY

Diabetes and Metabolism Research Center Newsletter

Spring 2023

Greetings from the Director

The Diabetes and Metabolism Research Center has been buzzing with activity and innovation as we go from spring to summer. You will hear more as we prepare to host the 5th Annual Islet Cell Invitational on July 24th, followed by "Dining for Diabetes" Research Education Update on October 19, 2023.

We have also had a successful Internal and External Review of our T32 NIH-funded training grant entitled "Postdoctoral training in Cardiometabolic Science". Drs. Ira Goldberg, Chief of Endocrinology at NYU and Kalyanam Shivkumar, Director of Cardiac Arrhythmia Center & EP Programs, Director & Chief of Interventional Cardiovascular Programs at UCLA were the external reviewers. They provided positive and helpful comments and gave fabulous presentations on "Postprandial Lipemia, Chylomicrons, and Cardiovascular Disease" by Dr. Goldberg and "Internet of the Human Body-Neuroscientific Therapies for Organ Diseases" by Dr. Shivkumar.

A critical goal for the DMRC is to develop a world-class Type 1 Diabetes Research Program that leads fundamental research and translates that research into clinical care leading the way to a cure right here in Central Ohio. We are searching for a lead scientist in Type 1 Diabetes and beta cell biology. This comprehensive bench-to-beside program will link to our outstanding clinical care and clinical trial program in type 1 Diabetes. At present, ~ 20% of patients seen in our Diabetes Multidisciplinary Center of Excellence have Type 1 Diabetes. Our clinical researchers have been part of, or led, clinical trials using the newest technologies for patients with type 1 diabetes. A substantial gift to the Diabetes and Metabolism Research Center Fund can turn our goal into a reality. We are planning a dinner August 16, 2023 if you or family and friends are interested in supporting this important vision. Please contact Ms. Nargis Dzhuraeva, nargis.dzhuraeva@osumc.edu if you would like an invitation.

Warmest wishes for a bright, beautiful, spring!

Willa Hsueh, MD

Director, Diabetes and Metabolism Research Center

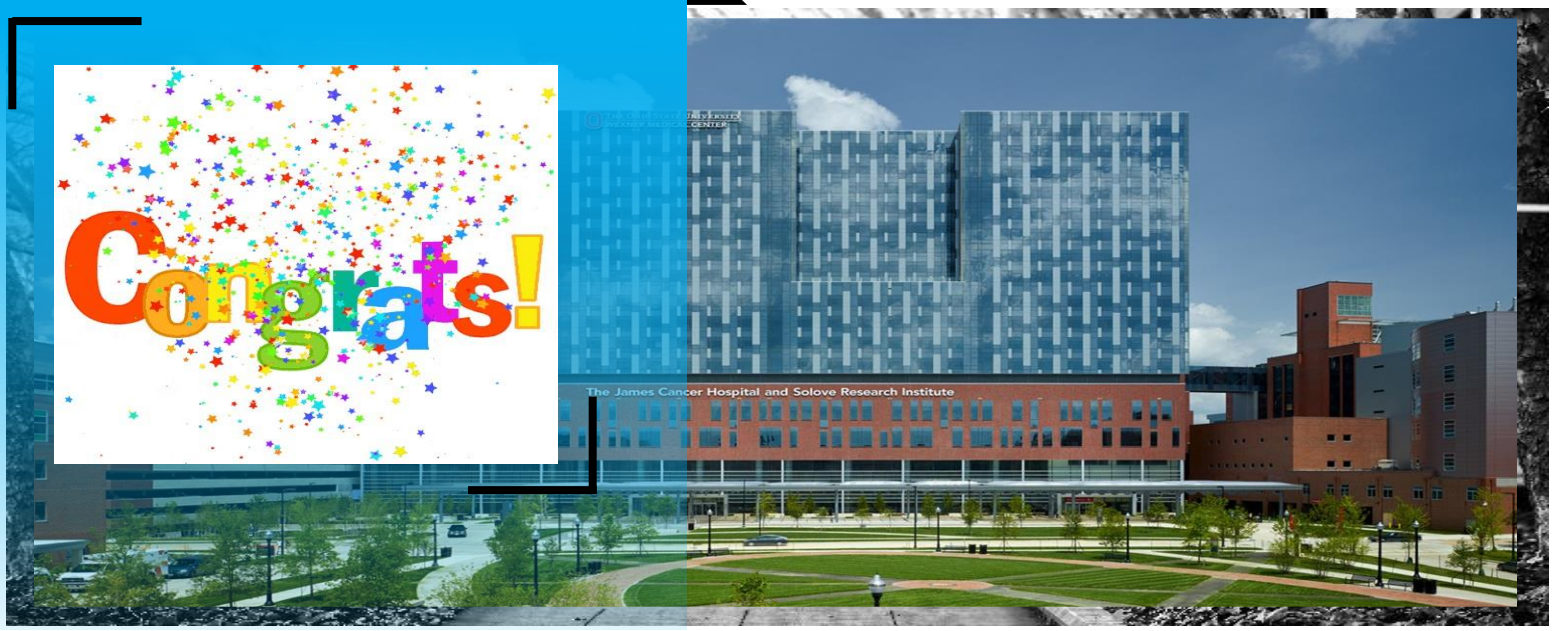
Diabetes and Metabolism Research Center is dedicated to advancing diabetes research, education and patient care. We're working toward prevention, and ultimately the cure, of type 1 and type 2 diabetes. Our vision is to create a world in which diabetes doesn't exist.

Everyone has a challenge in life. There's always something you're overcoming…We get knocked down, but we can get back up. Chase your dreams. Rely on your support team. Find out what resources you have and use them. Don't let diabetes stop you. – Will Cross

Researcher Spotlight

Kedryn Baskin, Ph.D

Dr. Kedryn Baskin is an Assistant Professor in the Department of Physiology and Cell Biology, is a member of the Diabetes and Metabolism Research Center (DMRC), the Davis Heart and Lung Research Institute (DHLRI), and the Center for Muscle Health & Neuromuscular Disorders. Kedryn has extensive scientific training in multiple disciplines, including cardiovascular physiology, metabolism, and molecular biology. During her training she was supported by 2 predoctoral fellowships, 2 postdoctoral fellowships, and started her independent career funded by a K01 Mentored Research Scientist Development Award (NIDDK) and a Career Development Award (American Heart Association). Dr. Baskin's research focuses on understanding the basic molecular mechanisms controlling cardiac and muscle physiology, specifically how metabolic signals regulate transcription and how transcriptional changes regulate metabolism. Her lab has uncovered novel pathways of transcriptional regulation of cardiovascular disease and skeletal muscle development, which hinge upon how transcriptional machinery works. One transcriptional regulator, a protein called MED12, is extremely important in maintaining healthy heart function. Too much, too little, or genetic mutations in MED12 wreak havoc on the heart and cause dilated cardiomyopathy, a form of heart failure. Dr. Baskin's recently funded R01 focuses on how disruption of MED12 causes dilated cardiomyopathy, and how MED12 can be therapeutically targeted to treat cardiomyopathies. Her lab has also recently established that MED12 is required for skeletal muscle development, and genetic mutations in MED12 cause severe myopathies. Interestingly, mechanisms of MED12 function are very different in heart and skeletal muscle and Dr. Baskin's lab is currently investigating how the tissue specificity of this protein is regulated. During the course of her transcriptional studies, Dr. Baskin recently discovered a group of novel proteins secreted from the heart, called cardiomyokines (discovery of cardiokines). Many of these newly discovered proteins are metabolically active and regulate systemic metabolism. Current studies in her lab have identified a subgroup of cardiomyokines secreted from the heart after exercise, demonstrating a role for the heart beyond its pumping function. These findings are paradigm shifting as they accentuate the endocrine function of the heart and its role in inter-organ crosstalk and regulation of systemic metabolism, which could lead to novel therapies for treatment of obesity and metabolic syndrome. Dr. Baskin's lab is also investigating how nutrients control gene expression and transcription. In previous work she discovered that inorganic phosphate (Pi), used in excess as a flavor enhancer and food preservative in processed foods, negatively impacts skeletal muscle function, metabolism, and transcriptional regulation. Her lab is currently working to uncover mechanisms by which Pi does so, including Pi sensing and Pi signaling mechanisms, and to understand why dietary Pi almost exclusively impacts skeletal muscle. They recently discovered that many of the negative side effects of Pi are reversible by dietary intervention, but cannot be prevented by exercise. Negative side effects of Pi are a growing concern given that the average American consumes over three times the suggested daily allowance of Pi. Dr. Baskin has published in high-impact journals including Cell Metabolism, Circulation, Circulation Research, Journal of Clinical Investigation Insights, among others. She is internationally recognized for her contributions to the cardiovascular and metabolism fields and has presented her work in forums including the American Heart Association Scientific Sessions, Experimental Biology Meeting, the American Physiological Society, to name a few.



Congratulations to our DMRC researchers for their outstanding work and getting awards to continue to bring change and improve many people's lives!

- **Dr. Kristin Stanford Ph.D.** and **Dr. Doug Lewandowski, Ph.D.** were awarded **$3.1 million** by the NIH National Heart Lung and Blood Institute for their research project titled "Adipose tissue mediates cardiac metabolic remodeling in the pathologically stressed heart in the absence of primary metabolic stress."

- **Dr. Kristin Stanford Ph.D.** and **Dr. Daniel Gallego Perez, Ph.D.** received **$1.9 million** grant funding from the NIH National Institute of Diabetes and Digestive and Kidney Diseases for their project titled "Engineering the release of oxylipins through the skin."

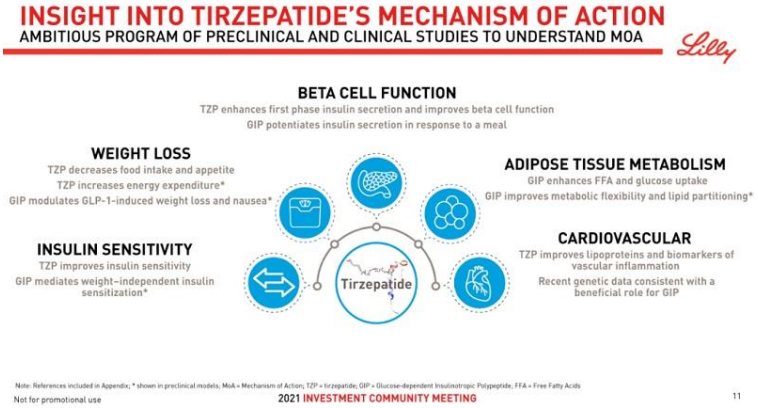
Dr. Kristin Stanford Ph.D the assosiate director of the DMRC has received two multi-principal investigator awards!

- **Dr. Seth Weinberg, Ph.D.**, **Dr. Sai Veeraraghavan, Ph.D.**, and **Dr. Tom Hund, Ph.D.** received **$3,685,919** grant funding from the NIH National Heart Lung and Blood Institute for their project titled "Distinct Ion Channel Pools and Intercalated Disk Nanoscale Structure Regulate Cardiac Conduction."

- **Dr. Kristy Townsend** was awarded a P&F grant from the MDRC at the University of Michigan and the DMRC at Ohio State, for a project titled "Determining the functional impacts and mechanistic actions of the sensory neuropeptide calcitonin gene-related peptide (CGRP) in adipose tissue." The goal of this project is to better understand how sensory nerve activity in adipose tissue impacts lipolysis, vascular function, and other metabolic processes. White adipose tissue of mice is densely innervated by both sympathetic and sensory nerve types, but the majority of prior research has solely focused on the actions of sympathetic nerves. Sensory neuropeptide actions have been overlooked. An R01 for this work will be submitted later this year. Aspects of this work were recently shared at the University of Michigan's CDI-MOD meeting on May 17, 2023, where Townsend's talk was titled "An evolving understanding of the functions of sensory nerves in adipose tissues."

Mounjaro and Type 2 diabetes

Mounjaro (Tirzepatide) an Eli Lilly and Co. drug approved to treat type 2 diabetes under the brand name Mounjaro, helped people with the disease who were overweight or had obesity lose up to 16% of their body weight, or more than 34 pounds, over nearly 17 months. The U.S. Food and Drug Administration (FDA) approved Mounjaro a year ago for patients with diabetes. The late-stage study of the drug for weight loss adds to earlier evidence that similar participants without diabetes lost up to 22% of their body weight over that period with weekly injections of the drug. For a typical patient on the highest dose, that meant shedding more than 50 pounds. Having diabetes makes it notoriously difficult to lose weight, said Dr. Nadia Ahmad, Lilly's medical director of obesity clinical development, which means the recent results are especially significant. "We have not seen this degree of weight reduction," she said. The late-stage study of the drug for weight loss adds to earlier evidence that similar participants without diabetes lost up to 22% of their body weight over that period with weekly injections of the drug. For a typical patient on the highest dose, that meant shedding more than 50 pounds. Having diabetes makes it notoriously difficult to lose weight, said Dr. Nadia Ahmad, Lilly's medical director of obesity clinical development, which means the recent results are especially significant. "We have not seen this degree of weight reduction," she said. If approved for weight loss, tirzepatide could become the most effective drug to date in an arsenal of



medications that are transforming the treatment of obesity, which affects more than 4 in 10 American adults and is linked to dozens of diseases that can lead to disability or death. "If everybody who had obesity in this country lost 20% of their body weight, we would be taking patients off all of these medications for reflux, for diabetes, for hypertension," said Dr. Caroline Apovian, a director of the Center for Weight Management and Wellness at Brigham and Women's Hospital. "We would not be sending patients for stent replacement." Tirzepatide is the first drug that uses the action of two hormones, GLP-1 and GIP, for greater effects. It also targets the chemical signals sent from the gut to the brain, curbing cravings and thoughts of food. Though the drugs appear safe, they can cause side effects, some serious. The most common reactions include diarrhea, nausea, vomiting, constipation, and stomach pain. Some users have developed pancreatitis or inflammation of the pancreas, and others have had gallbladder problems. Mounjaro's product description warns that it could cause thyroid tumors, including cancer. Mounjaro is now on the OSU Medical Formulary.

AP News:Powerful new obesity drug poised to upend weight loss care

FDA approves first treatment to delay onset of type 1 diabetes

The monoclonal antibody teplizumab, which is marketed under the brand name Tzield, from ProventionBio and Sanofi is given through intravenous infusion. It is thought to work by turning down the body's misdirected attack on its own insulin-producing cells. The idea is that protecting these cells buys people more time before they become dependent on insulin to manage their condition. In clinical trials, Tzield delayed progression to full-blown diabetes by a little over two years. But the benefits have lasted much longer in some of the study participants. Tzield is approved for use in people 8 and older who are in stage 2 of their type 1 diabetes. In that stage, doctors can measure antibodies that attack insulin-producing beta cells in the person's blood, and they have abnormal blood sugar levels, but their body can still some insulin. The treatment comes in a single 14-day course of infusions that each last 30 to 60 minutes. The most common side effects reported in the trial participants were low white blood cells and lymph cells, rash and headache. "The way in which not just industry but our medical system go about managing autoimmune diseases, and especial type 1 diabetes, is really suboptimal in today's day and age," ProventionBio co-founder and CEO Ashleigh Palmer said. "What we do is, we wait until the symptoms of the disease present to doctors, and then doctors treat the patient's symptoms chronically for a lifetime. The trouble is that in type 1 diabetes, when the symptoms first present, it's too late." Tzield holds off the disease before symptoms appear by stopping the autoimmune disease process and the underlying destruction of beta cells. The treatment essentially reboots the immune system, preserving beta cell function. "We really have no preventative measure for type 1 diabetes to date, and that is despite [the National Institutes of Health] funding hundreds of millions of dollars over the last 20-plus years of a program called TrialNet that has tested many, many different things, including this, and some of this came out of that work," said Dr. Robert Gabbay, chief scientific and medical officer for the American Diabetes Association. "The incidence of the type 1 is mainly in kids and teenagers, and when you are in the turmoil of adolescence, when you just want to forget that you have it," said Olivier Bogillot, Sanofi's head of US general medicines. "So when you have the ability with a treatment to just delay the onset of the disease, you can change the way the quality of life is impacted for families and for those kids." ***A delayed diagnosis of type 1 diabetes could have a significant impact.*** Tzield is now on the OSU Medical formulary.

CNN: FDA approves first treatment to delay onset of type 1 diabetes

Diabetes Friendly Cooking Demonstration

Diabetes & Metabolism Research Center

THE JAMES Mobile Education Kitchen

- Live Streams Every 2nd and 4th Tuesday at 12:00 pm
- Delicious and Healthy Recipes in 20 Minutes
- Taught by CDCES Jenny C. Shrodes and Chef Michael Carnahan
- Smartphrase .COOKINGDEMO
- Register Here: https://go.osu.edu/diabetesfriendlyrecipes