DMRC QUARTERLY

Diabetes and Metabolism Research Center Newsletter

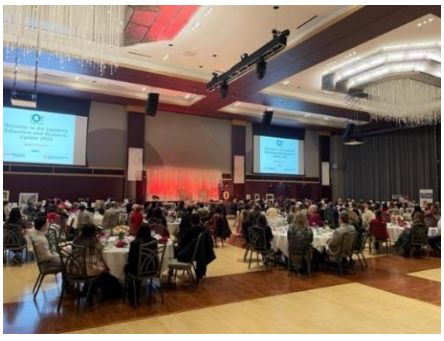
THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Winter, 2022

Greetings from the Director:

Best wishes for the holiday season! As we celebrate and make resolutions, it is an opportunity for all of us to pause and reflect on the people who give our lives meaning. I'd like to take this opportunity to express my heartfelt gratitude to our patients, community, partners, scientific colleagues, and friends for your unwavering support and dedication. You are the reason we strive to achieve our vision of "preventing and curing diabetes, obesity, and metabolic disease through innovative research and discovery."

I'm delighted to report that our annual Diabetes Research and Education Update "Dining for Diabetes" event was a huge success. This year, we were thrilled to have Mike Faist, a Grammy and Emmy winner with Tony and British Academy Film Award nominations, join us for a special presentation and the event was hosted by Jonathan Smith, also known as T-Bone, 97.1 The Fan radio host. We also send special thanks to Jay Anderson, Chief Operating Officer, Wexner Medical Center, for a great description of the plans for the new hospital. The primary goals of our dinner were to highlight the previous year of innovative research, share the future vision of the Diabetes and Metabolism Research Center (DMRC), and bring together community partners, medical professionals, and friends to develop possible strategies to make the world diabetes-free. The event was truly motivating!

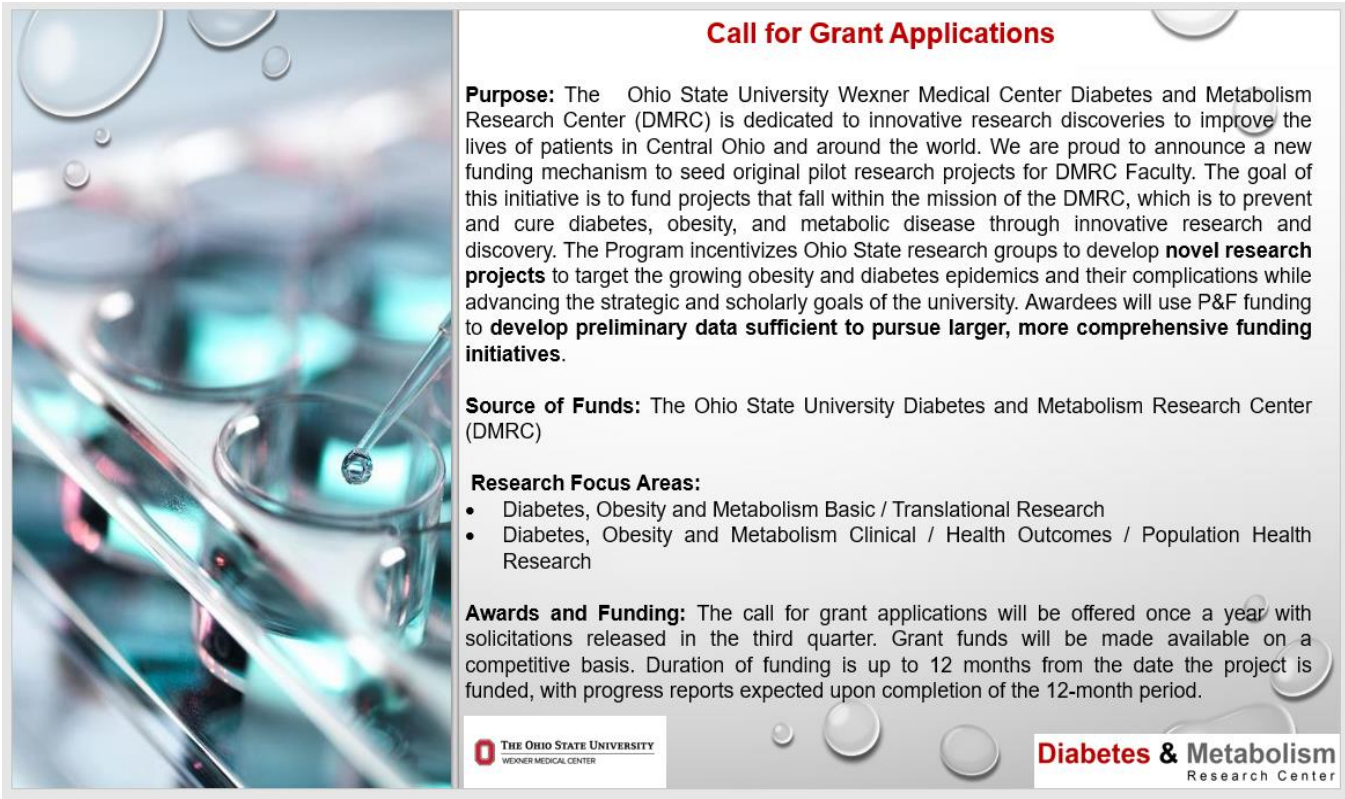


Warmest wishes for a bright, beautiful, holiday season!

Willa Hsueh, MD
Director, Diabetes and Metabolism Research Center

Announcements:

Application Deadline: **Applications are due January 3rd, 2023 by 5pm**



Award Period: Funds will start on February 1, 2023 and end on December 31, 2023
Please contact Nargis Dzhuraeva at Nargis.Dzhuraeva@osumc.edu for additional application details

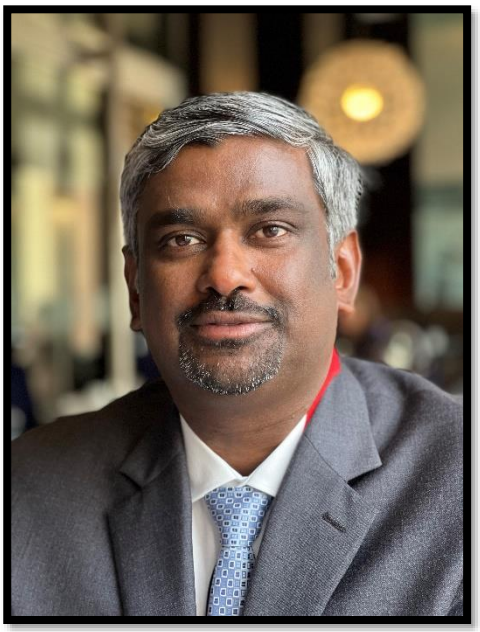
OSU News:

Congratulations to Dr. Doug Lewandowski!

Dr. Doug Lewandowski received the Bernard and Joan Marshall Distinguished Investigator Award and Lectureship from the British Society for Cardiovascular Research. The award recognizes **Dr. Lewandowski's** outstanding achievements and significant contributions to cardiovascular biology and medicine, and it includes the keynote lecture at the annual meeting of the British Society for Cardiovascular Research, which is being held on the campus of Oxford University to commemorate the society's 50th anniversary!

Researcher Spotlight:

Prabha Nagareddy, Pharm, PhD, FAHA



Dr. Nagareddy is an Associate Professor of Cardiac Surgery in the Department of Surgery, and an investigator at the Diabetes and Metabolism Research Center (DMRC). The research in his laboratory is broadly focused on elucidating the pathological basis of the so-called “cardiovascular risk factors” such as diabetes, obesity, high salt diet, RA and cigarette smoking to the cardiovascular/ cardiometabolic disease. For the last 10 years or so, they are specifically studying the role of neutrophil-derived alarmins such as S100A8 and S100A9 that are emerging as key signaling molecules in regulating inflammation both in acute and chronic conditions. They are interested in developing, validating, and repurposing various agents (e.g., monoclonal antibodies, pharmacological inhibitors) to reduce inflammation and improve outcomes in cardiovascular (e.g., atherosclerosis, heart failure) and metabolic diseases (e.g., diabetes, obesity, insulin resistance) by specifically targeting neutrophil secretome. His laboratory is experienced in various advanced research techniques such as single-cell and bulk RNA sequencing, proteomics, multi-color flow cytometry, echocardiography, bone marrow transplantation, parabiosis, mouse models of myocardial infarction, atherosclerosis, obesity, RA and diabetes.

Dr. Nagareddy says that pursuit of knowledge has always been his obsession and the propelling force behind all his achievements thus far. Coming from India, the “diabetes capital of the world”, he was intrigued by the devastating effect of diabetes on cardiovascular disease (CVD) not just because of the available epidemiological data but drawn from his own personal experience. Being born into a poor family that at times struggled for two nutritious meals, he has experienced the perils of sudden transition from a skinny teenager to an overweight adult. This transformation stirred his conscience in the early stages of his research career, instilled a sense of curiosity and responsibility and, most importantly empowered him to seek answers. Indeed, it is one of the most compelling reasons to pursue a career in diabetes and CVD research, he says. As soon as he acquired the requisite research skills (after my graduate studies), he was drawn to an R&D center of a pharma company that was involved in developing novel therapeutics for diabetic vascular complications (DVCs). His initial enthusiasm in the industry gradually declined due to the lack of advanced research facilities, hypothesis-driven studies and most importantly the restrictions that curtailed my desire to pursue independent ideas. So, to pursue higher education and advanced training, he enrolled in the MSc/PhD program at the University of British Columbia (UBC), Canada under the guidance of Dr. John McNeill. Dr. McNeill is one of the world’s leading scientists in DVCs. He had a distinguished research career spanning nearly 5 decades and having published almost a thousand papers, reviews and abstracts in top journals.

Dr.Nagareddy's PhD research in McNeill lab was primarily focused on investigating the molecular mechanisms of vascular dysfunction in diabetes and insulin resistance. He had a very successful and productive research career as a graduate student with multiple scholarships, a dozen manuscripts, including 8 first-authored publications in leading journals. Throughout his graduate studies at UBC (2002-2009), he was supported by more than one scholarship at a time and won numerous awards. It is therefore not surprising when Dr. McNeill says that "***Dr. Nagareddy is one of the top 3 students I have trained in 50 years of my long and illustrated career.***" Dr. McNeill is in his late 80s but still manages to send his annual holiday and Christmas cards. "I am truly indebted to his unwavering support and rigorous training that has still remained as the corner stone of my research career," Dr. Nagareddy says.

For postdoctoral training, Dr. Nagareddy joined Dr. Ira Goldberg's lab at Columbia University (CU), with a prestigious fellowship from CIHR (Canadian Institutes of Health Research). His research work explored a fundamental issue that was plaguing diabetic patients. i.e., why diabetic patients have higher incidence of CVDs? His findings uncovered a mechanistic link between blood glucose and proliferation of myeloid progenitor cells in the bone marrow, which contribute to increased burden of CVD in diabetic patients. These findings were published in Cell Metabolism (2013) with an editorial and highlighted on cover page. After a very productive postdoctoral training, he followed his wife to the University of Kentucky (UK) and ended up joining Dr. Susan Smyth's lab. Here, he embarked on another challenging and independent project seeking answers regarding the source of adipose tissue (AT) macrophages (ATM) in obesity. He discovered that adipocyte-derived S100A8/A9 (a danger signal) promotes adipose tissue (AT) inflammation by stimulating the NLRP3 inflammasome (a sensor of cellular stress) in AT macrophages. These findings were published in Cell Metabolism (2014) with an editorial and recently selected as one of the "Top 10 Breakthroughs of the Decade" by the journal. The data generated from these studies formed the basis of his first major grant (K99/R00) from the NIH. During his postdoctoral trainings, he received numerous young investigator awards (or finalists) from the American Heart Association (AHA) such as the Irvine Page (ATVB, 2015) and Outstanding Early Career Investigator Award from Basic Cardiovascular Sciences Council (2015). Upon completion of his post-doctoral training, he was recruited to the University of Alabama, Birmingham (2016). In less than 1 year, he published a major paper in the Journal of Clinical Investigation (2017) and received his first R01. Furthermore, he also received or was a finalist for many more early career awards such as The Brinkhous Young Investigator Award in 2017 (AHA) and The Young Investigator Award from International Society for Heart Research (ISHR, 2018).

Dr. Nagareddy was recruited to the Department of Surgery at OSU in 2019. He brought two NIH (R00 and R01) grants to the OSU and since then, has obtained one additional R21, R01 and a TPA grant from AHA. He is also a mentor on a T32 grant awarded to the DMRC (Dr. Hsueh, PI) and many other pending applications. Since moving to OSU, he as published more than 25 manuscripts with an average impact factor of 15. Many of these articles are published in high-impact journals such as Circulation, Circulation Research, Arteriosclerosis Thrombosis and Vascular Biology and The European Heart Journal. Furthermore, he was elected as a Fellow of the American Heart Association (FAHA, 2020) by the American Heart Association's BCVS council. He has also completed the faculty career acceleration program conducted by the Centre for Faculty Advancement, Mentoring and Engagement (FAME) by the OSU College of Medicine. Since his appointment as an Associate Professor at OSU, he has developed a rigorous and productive research program focused on defining the pathological basis of cardiovascular disease risk and developing novel neutrophil-based therapeutics. He has trained numerous postdoctoral fellows and considers mentoring and graduating trainees to independent faculties as the most

satisfying aspect of his career. He serves on the editorial boards of many respected journals such as Diabetes, Atherosclerosis, American Journal of Physiology, Pharmacological Research, Scientific Reports and others. He was awarded a “Distinguished Reviewer” award for 2020 from Diabetes. He is a regular reviewer for various career development and research grants for AHA, NIH and other international organizations. He also serves as MSTP subcommittee interviewer, faculty judge for campus events and review grants for OSU’s President’s Research Excellence (PRE) program.

In the News:

Journal of the Academy of Nutrition and Dietetics

Elon Musk, Bernie Sanders and Others Miss the Mark over Pricey Insulin

Big Pharma has taken much of the heat for sky-high insulin prices, but scrutiny could soon shift to other companies grabbing a growing slice of spending

Drug makers have taken much of the heat for sky-high prices, but scrutiny could soon shift to pharmacy-benefit managers A tweet from a fake Eli Lilly account earlier this month claiming insulin would be free was quickly corrected by the real company, but it was enough to spark the usual finger-wagging. Sen. Bernie Sanders, who has raised his hand to take over as chair of the Senate committee overseeing healthcare, argued that prices have increased so dramatically because three drug companies control the market. Elon Musk, the billionaire Tesla CEO who has his hands full trying to turn around Twitter, defended Eli Lilly, blaming higher prices on product advances. Left out of the debate are some poorly understood middlemen: Pharmacy-benefit managers, or PBMs, have captured a growing slice of America’s world-leading drug spending during the past decade. The spotlight could soon shift to them. More than 30 million Americans, or about 10% of the country, have diabetes, and more than million of them require daily insulin. The high cost, studies show, has forced more than one million Americans to ration their insulin—a dangerous action that could backfire not only on a diabetic’s health but on those who pay for their future care. While the three largest manufacturers of insulin—Eli Lilly, Novo Nordisk and Sanofi — charge more for their products in the U.S. than they do elsewhere, their take of overall spending has been decreasing in recent years as the relative power of middlemen has grown. PBMs have steadily gained negotiating clout by consolidating and merging with large insurance companies. The three largest PBMs are owned by CVS Health Corp. (which owns insurer Aetna), UnitedHealth Group Inc. and Cigna Corp.

Please visit The Wall Street Journal to read the full article.

Press Release:

Cooking Matters for Diabetes: A 6-week Randomized, Controlled Cooking and Diabetes Self-Management Education Intervention

Amaris Williams, Jennifer C Shrodes, Jessica N Radabaugh, Ashlea Braun, David Kline, Songzhu Zhao, Guy Brock, Timiya S Nolan, Jennifer A Garner, Colleen K Spees, Joshua J Joseph.

Diet-related self-care and health-related quality of life improved following the intervention conducted by researchers at The Ohio State University Wexner Medical Center and College of Medicine in collaboration with Local Matters. Consumption of vegetables increased while consumption of carbohydrates decreased. Participants who were food insecure had the greatest numerical improvements in hemoglobin A1c as well as statistically significant improvements in diabetes self-management activities. Diabetes mellitus remains one of the most common chronic illnesses in the United States. Type 1 diabetes mellitus represents approximately 3% to 6% of all diabetes cases in the United States. The other 94% to 97% of diabetes mellitus cases are type 2 diabetes mellitus (T2DM), which affects 34.1 million adults, totaling 13% of the adult population. Essential to the management of diabetes and prevention of complications is the adoption of evidence-based lifestyle behaviors, including healthy diet and physical activity. Diabetes self-management education and support (DSMES) teaches these concepts. DSMES improves hemoglobin A1c (HbA1c) by 0.5% to 1% on average in people with T2DM over 0.5 to 2 years and lowers rates of diabetes complications, improves quality of life, and leads to changes in lifestyle behaviors.

Medical nutrition therapy (MNT) is evidence-based nutrition care provided by a registered dietitian nutritionist that incorporates assessment, nutrition diagnosis, and interventions such as education, counseling, and monitoring with ongoing follow-up. MNT lowers HbA1c up to 2% in T2DM and 1.9% in type 1 diabetes mellitus over 3 to 6 months. The goal of both DSMES and MNT is to improve management of diabetes, leading to attainment of targets for HbA1c, blood pressure, and lipid control, which is critical for preventing micro- and macrovascular complications in diabetes.

Please visit the Journal of the Academy of Nutrition and Dietetics to read the full study findings.

Research Updates:

nature communications

Interferon Gamma Mediates the Reduction of Adipose Tissue Regulatory T cells in Human Obesity

David Bradley, Alan J. Smith, Alecia Blaszczak, Dharti Shantaram, Stephen M. Bergin, Anahita Jalilvand, Valerie Wright, Kathleen L. Wyne, Revati S. Dewal, Lisa A. Baer, Katherine R. Wright, Kristin I. Stanford, Bradley Needleman, Stacy Brethauer, Sabrena Noria, David Renton, Joshua J. Joseph, Amy Lovett-Racke, Joey Liu, Willa A. Hsueh.

Decreased adipose tissue regulatory T cells contribute to insulin resistance in obese mice, however, little is known about the mechanisms regulating adipose tissue regulatory T cells numbers in humans. Obesity is a world-wide pandemic associated with low-grade chronic

inflammation. As the major storage depot for excess calories and comprised of a variety of active immune cells, adipose tissue (AT) is uniquely poised at the crossroads of inflammation and metabolism. Therefore, defining the immune cell architecture of AT and mechanisms that lead to enhanced AT inflammation in obesity is critical in combating its metabolic complications. In mice, AT macrophages (ATMs) are the best understood immunomodulators, but elegant studies have identified adipose resident T lymphocytes (ARTs), including pro-inflammatory T helper (Th) type 1 cells, Th2 cells and anti-inflammatory regulatory T cells (Tregs), as important determinants of systemic metabolism. In lean mice Tregs protect against inflammation, and adoptive transfer of Tregs into obese mice or prevention of the drop in Tregs (13, 15) improves insulin sensitivity. Despite insights regarding the impact of immune cells in mouse AT, comparatively little is known about human AT, particularly Tregs. Therefore, the goal of this translational investigation was to define AT Treg changes in human obesity and identify potential mechanisms that could explain these changes. Here we show that Tregs are reduced in obese human AT and acutely decline after overfeeding. This AT Treg loss derives from two distinct mechanisms: adipocyte MHCII-mediated adaptive immune activation of Th1 cells (with increased IFNγ production that suppresses Treg differentiation), not previously shown in humans, and excess Treg loss through exhaustion, not previously reported, also robustly impacted by IFNγ. Our comprehensive investigation highlights a central role for IFNγ in mediating obesity associated inflammation in humans.

Please visit Nature Communications to read the full paper "***Interferon Gamma Mediates the Reduction of Adipose Tissue Regulatory T cells in Human Obesity***"

Science Updates:

Two Studies Link Serum Vitamin D Levels to Higher Risk of Diabetes in African Americans

Joshua J. Joseph, Susan Langan, Joseph Lunyera, Bjorn Kluwe, Amaris Williams, Haiying Chen, Michael C. Sachs, Kristin G. Hairston, Alain G. Bertoni, Willa A. Hsueh, Sherita H. Golden.

Vitamin D is a fat-soluble paracrine and endocrine signaler important for bone, glycemic and general health. Vitamin D3 is produced from ultraviolet light acting on 7-dehydrocholesterol in the skin to produce previtamin D3, which is converted to the less active precursor 25-hydroxyvitamin D (25[OH]D), and then enzymatically converted to the active form of the vitamin, 1,25-dihydroxyvitamin D (1,25[OH]D) by 1-alpha hydroxylase in the kidney and other tissues. Smaller amounts may be obtained from the diet (25[OH]D2) or supplements (25[OH]D2 or 3), which may be of greater importance in persons with little sunlight exposure. Vitamin D2 originates from certain fungi and can only be obtained from food or supplements. Although 25(OH)D2 represents a smaller fraction of total 25(OH)D, it binds the human vitamin-D binding protein with less avidity than 25(OH)D3, and thus may be more biologically active. 25(OH)D2 may be more important among populations with darker skin pigmentation, as melanin absorbs the ultraviolet radiation and leads to less vitamin D3 synthesis, for a given exposure compared to less pigmented skin. Similar to vitamin D3, Vitamin D2 is metabolized into 25(OH)D in the liver. Although 1,25(OH)D is the biologically active form, the more stable 25(OH)D is measured in serum to assess vitamin-D sufficiency. The role of vitamin D in calcium and bone metabolism is well established, but there is

increasing interest in the anti-inflammatory and metabolic effects of vitamin D given the rising prominence of type 2 diabetes mellitus (diabetes) and obesity. Pre-clinical studies reveal a link between vitamin D and insulin secretion. Vitamin D may influence insulin activity and insulin sensitivity through a number of mechanisms: (1) intracellular calcium levels determine the ability of insulin-sensitive cells to conduct insulin dependent activities, and vitamin D may regulate calcium flux between the extra- and intracellular milieu of pancreatic ß-cells; (2) vitamin D may stimulate the expression of insulin receptors in insulin-sensitive tissue; (3) vitamin D may activate PPAR-δ, which in turn regulates fatty acid metabolism in muscle and adipose tissue. Evidence for an inverse association of vitamin D with incident diabetes comes from observational cohort studies, interventional trials, and meta-analyzes with the majority non-Hispanic white (NHW) participants.

Please visit Nutrition & Diabetes to read the full paper *"Two Studies Link Serum Vitamin D Levels to Higher Risk of Diabetes in African Americans".*

Upcoming Events:

Weekly Tuesdays	**Diabetes-Friendly Recipes: FREE Live-Streaming Demos** **go.osu.edu/diabetesfriendlyrecipes** Join us every Tuesday at noon as chefs Katie McCurdy, BHS, and Stephanie Urrutia, RD, LD, and Certified Diabetes Care and Education Specialist Jenny Shrodes, RD, LD, bring you flavorful diabetes-friendly recipes, offer some tips and tricks, and answer your questions about cooking with diabetes all in under 20 minutes. Register once to receive weekly reminders.
Monthly 2nd Tuesday	**ADA Ask the Experts Q&A Podcasts** **diabetes.org/ask-the-experts** The American Diabetes Association (ADA) is a national nonprofit that seeks to educate the public about diabetes and to help those affected by it by funding research to manage, cure and prevent diabetes.
July 24th 2023	**5th Annual Islet Cell Invitational– Golfing for Diabetes** The Islet Cell Invitational is a golf and dinner event chaired by a patient with type 1 diabetes who wanted to do more for diabetes research. Proceeds from the event benefit the Diabetes and Metabolism Research Center (DMRC) at The Ohio State University Wexner Medical Center.
TBD 2023	**"Dining for Diabetes" Education and Research Update** The "Dining for Diabetes" Education and Research Update is a dinner program focused on the past year of innovative research and what's in store for the future at the Diabetes and Metabolism Research Center (DMRC). The evening includes fabulous food, special guests and a silent auction.