DMRC QUARTERLY

Diabetes and Metabolism Research Center Newsletter

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

July, 2022

Greetings from the Director:

I hope that this summer will fill your home with great memories and may all the happiness in the world embrace you. Let your fun be unlimited with friends and family. I'm excited to announce that our next DMRC event will be the annual "**Islet Cell Invitational,**" which will take place on September 26, 2022, at Columbus Country Club. This year, we are proud to announce Cameron Mitchell Restaurants as our presenting sponsor. Our goal is to raise funds for the Diabetes & Metabolism Research Center and to ultimately fund the resources needed to bring human trials here to OSU for efforts already underway to test a functional cure for type-1 diabetes. The Ohio State University Wexner Medical Center treats thousands of patients with diabetes and has one of the largest patient populations of individuals with type-1 diabetes. OSU has a number of exceptional programs specifically for type-1 diabetes, including an adolescent to adult transition program and a diabetes technology clinic. OSU is uniquely positioned to be at the forefront of cutting-edge technology to functionally cure type-1 diabetes and prevent the complications of this insidious disease. Please join us at the 4th annual Islet Cell Invitational to fight diabetes and make world free of diabetes. Please see the event details below.

I also want to mention a highlight of the recent American Diabetes Meeting in June, 2022. Tirzepatide, a recently approved glucagon-like peptide-1 agonist combined with a gastric inhibitory peptide agonist, induced as much weight loss in some individuals as does bariatric surgery (New England J of Medicine, June, 2022)! See story below.

4TH ANNUAL ISLET CELL INVITATIONAL

PRESENTED BY

CAMERON MITCHELL
RESTAURANTS

COLUMBUS COUNTRY CLUB
SEPTEMBER 26TH, 2022

BENEFITING THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER'S DIABETES AND METABOLISM RESEARCH CENTER

ISLET CELL INVITATIONAL

Benefiting

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER

COLUMBUS COUNTRY CLUB



FACT SHEET

Date:	Monday September 26, 2022
Location:	Columbus Country Club 4831 E Broad St Columbus, OH 43213
Format:	Foursomes +1/Shotgun Start/Scramble
Agenda:	10:00a.m. – 12:00p.m. Registration 12:00p.m. – 12:10p.m. Shotgun Start with Boxed Lunches from TBD 5:00p.m. - 6:00p.m. Cocktail Reception 6:00p.m. – 8:00p.m. Dinner provided by TBD

Please contact Event Chairman John Rechil john.rechil@marcusmillichap.com at 614.360.9037 or 614.390.8454 or Nargis Dzhuraeva nargis.dzhuraeva@osumc.edu of the Diabetes & Metabolism Research Center with any questions.

Wishing you a bright, beautiful, and happy summer!

Willa Hsueh, MD

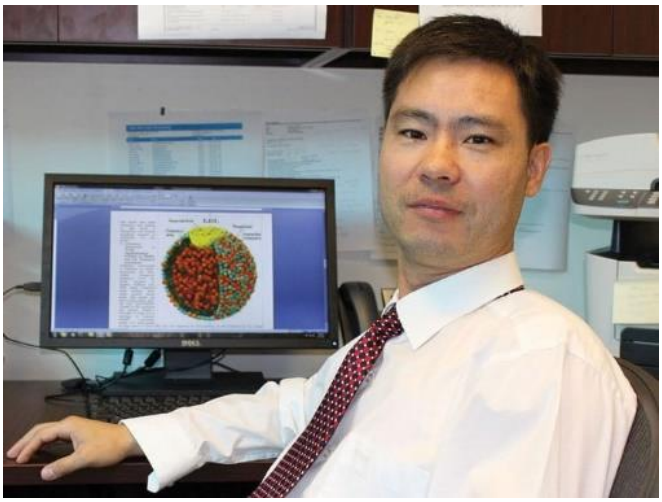
Director, Diabetes and Metabolism Research Center

Division of Endocrinology, Diabetes and Metabolism

Researcher Spotlight:

Dr. Deliang Guo, PhD

Dr. Deliang Guo, PhD, is the founding director of the Center for Cancer Metabolism in the OSU James Comprehensive Cancer Center, and he is a member of the Translational Therapeutics program in the CCC. Dr. Guo holds the Urban and Shelly Meyer Professorship in Cancer and is a Professor in the Department of Radiation Oncology. His research focuses on the mechanistic understanding of dysregulated lipid, glucose and amino acid metabolism in cancers. He is an expert in glioblastoma (brain cancer) but his lab also uses hepatocarinoma (liver cancer), breast cancer, lung cancer, and other models to explore shared metabolic traits among fatal and incurable cancer types to understand how these diseases are able to resist treatment as well as grow and proliferate unchecked. Dr. Guo's research specifically examines metabolic pathways that intertwine with and influence lipogenesis, controlled by the crucial transcription factor SREBP-1. SREBP-1 (Sterol Regulated Element Binding Protein) is found in the endoplasmic reticulum, where it is bound to a regulatory protein called Insig by SCAP (SREBP Cleavage-Activating Protein). While Insig-SCAP-SREBP complex remains bound in the ER, cells cannot produce lipids. Dr. Guo's early research revealed that oncogenic EGFR/PI3K/Akt signaling drives lipid metabolism alterations in glioblastoma by activating SREBP-1 and showed that SREBP-1 is a promising molecular target for glioblastoma and other lethal cancers. Over his 11+ years at OSU, Dr. Guo and his lab made two groundbreaking and major discoveries that revealed the mechanisms that all cells (including cancer cells) use to release SREBP-1 from the ER and activate lipid production. First, in 2015, they discovered that glucose was required for SREBP-1 activation but not because glucose is a building block of lipids. SCAP must be stabilized by N-glycosylation, a chemical pathway that requires glucose, or else it degrades and is unable to transport SREBP-1 from the ER (Cheng et al. 2015 Cancer Cell). Cancer cells highly upregulate glucose uptake for energy and lipid production as well as for glycosylation pathways. (NOTE: this publication was featured as one of the "Ten Key Breakthroughs and Insights" for 2015 cancer research by the American Cancer Society). Dr. Guo's biggest discovery came just this year, when he and his lab found that the



actual “on switch” for lipogenesis was the small molecule ammonia. Previously dismissed as a waste product of amino acid metabolism, Dr. Guo and his lab found that both glucose and ammonia were required to activate lipid production in cells. They then found that this ammonia comes from glutaminolysis, or the metabolic conversion of the amino acid glutamine to glutamate, also highly-upregulated process in cancer cells as glutamate can be used in the TCA cycle for energy just like glucose. Ammonia binds to N-glycan-stabilized SCAP, causing it to change shape and release from Insig. SCAP then transports SREBP-1 to the Golgi Apparatus, where it is cleaved by enzymes. The N-terminus of SREBP-1 is then transported to the nucleus where it activates lipogenesis genes. (Cheng et al. 2020, *Nature Metabolism, chosen as the May cover story for the journal*). The beautiful thing about this story is that lipid production and cellular lipid metabolic processes ultimately rely on both glucose metabolism and amino acid (glutamine specifically) metabolism, linking the three most important basic metabolic elements of the cell together. Dr. Guo’s research focuses on understanding the various intertwined regulatory and cell-signaling pathways that govern lipogenesis, glutamine and glucose metabolism. All cancers rely heavily on lipids for proliferation (lipids are the major building block of new cells), and solid tumors such as glioblastoma require stores of lipids in organelles called lipid droplets to prevent toxic buildup of lipids during times when glucose is abundant as well as to provide energy for the cell when glucose is scarce. His ultimate research goal is to use this fundamental knowledge of the mechanisms of cellular metabolism to develop novel treatments for incurable cancers. His lab’s current research focuses on finding inhibitor combinations that can suppress lipogenesis in cancer cells. Preliminary results in both in vitro as well as xenografted animal models show that this can significantly reduce heretofore untreatable cancers like glioblastoma by starving cancer cells of the lipids they desperately need for maintenance and proliferation. Because lipogenesis is a fundamental process to all cells in the human body, his research has translational implications for treatment of other metabolic diseases such as diabetes or metabolic syndrome. Dr. Guo has a spectacular history of funding. He currently holds 4 R01 grants, 3 as the PI and one as the MPI.

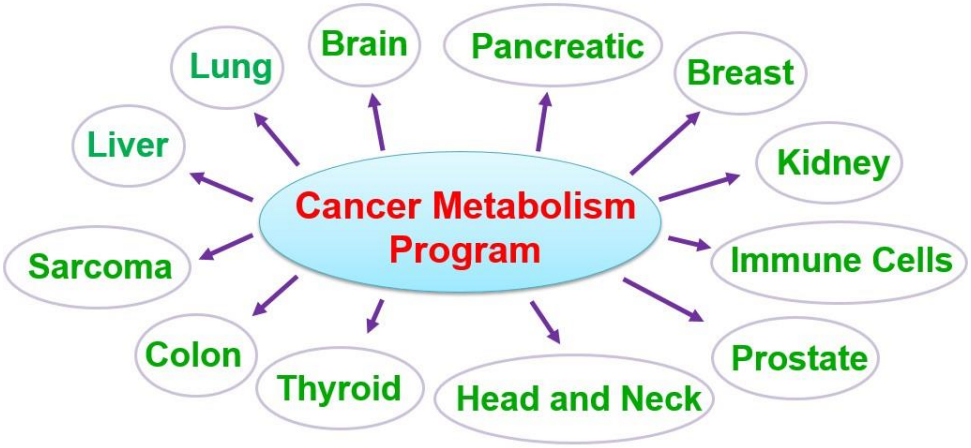
OSU News:
Introducing the Center for Cancer Metabolism

A new **Center for Cancer Metabolism (CCM) at Ohio State** aims to become a world-renowned research entity focused on basic and translational studies regarding cancer metabolism and the development of therapies targeting tumor metabolic pathways. Faculty and researchers in the

CCM—which is housed within Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James)—apply multidisciplinary technologies and techniques (from cell biology and biochemistry to molecular biology, chemical biology and pharmacology) to answer challenging questions in the field of cancer metabolism.

The center is led by Director **Deliang Guo, PhD**, professor and vice chair for clinical and basic research in the Department of Radiation Oncology, and basic science director of the Center for Neurological Malignancies and Cancer Neurology. A member of the Translational Therapeutics Program at the OSUCCC – James, Dr. Guo also recently was named to the Urban and Shelley Meyer Professorship in Cancer for his stellar research in cancer metabolism. He has published papers in such high-impact journals as *Cancer Cell*, *Cancer Discovery*, *Cell Metabolism* and *Proceedings of the National Academy of Sciences*. His work is supported by four NIH R01 grants, as well as funding from the American Cancer Society and the OSUCCC – James. The CCM is seeking faculty and researchers who specialize or are interested in cancer metabolism research to become members of the center. Membership includes such benefits as: preferential scheduling for shared CCM resources and equipment; eligibility for internal CCM pilot funding; opportunities to present at weekly research meetings, periodic seminars and an annual symposium; and the opportunity to meet with distinguished external CCM guest speakers. The primary benefit of membership is a chance to participate in a collaborative, interdisciplinary environment that generates novel research projects. Expected outputs include multi-PI, P01 and small individual grants for research, in addition to high-impact journal publications, translational studies and drug development.

The Center for Cancer Metabolism:
Boundary-Spanning Research Across Cancer Types



Developing Innovative Therapies for Cancer Treatment
Through Interdisciplinary Collaboration

More information about CCM members, membership guidelines and how to apply for membership is available on the CCM website. Membership is open to all scientists at Ohio State with an interest in cancer metabolism research. Positions are also open for faculty, post-docs, research staff and graduate students.

Press Release:

The NEW ENGLAND JOURNAL of MEDICINE

The New England Journal of Medicine "*Tirzepatide Once Weekly for the Treatment of Obesity*."

Obesity is the most prevalent chronic disease worldwide, affecting approximately 650 million adults. Excess adiposity and its numerous complications, including cardiovascular disease and type 2 diabetes, impose a considerable economic burden and constitute major contributors to global morbidity and mortality. Treatments that result in substantial weight reductions may improve outcomes for people living with obesity. Historically, the treatment of obesity focused almost exclusively on lifestyle-based approaches. However, evidence that diet and exercise prompt physiological counter regulatory mechanisms that limit weight reduction and impede weight maintenance has led to the realization that obesity is a complex, multicomponent metabolic disease of energy homeostasis involving central and peripheral mechanisms. Once obesity is present, those mechanisms render a return to lower weight difficult. Accordingly, several clinical guidelines now recommend treatment with anti-obesity medications for people with obesity or for those with overweight and weight-related complications. Recent studies with long-acting glucagonlike peptide-1 (GLP-1) receptor agonists demonstrated that greater efficacy with acceptable safety could be achieved by targeting the pathways of endogenous nutrient-stimulated hormones. Glucose-dependent insulinotropic polypeptide (GIP), another nutrient-stimulated hormone, regulates energy balance through cell surface receptor signaling in the brain and adipose tissue. A molecule that combines both GIP and GLP receptor agonism theoretically may lead to greater efficacy in weight reduction. Tirzepatide is a once-weekly subcutaneous injectable peptide (approved by the Food and Drug Administration [FDA] for type 2 diabetes) engineered from the native GIP sequence, with agonist activity at both the GIP and GLP-1 receptors. Preclinical data demonstrated that the affinity of tirzepatide for GIP receptors was equal to the affinity of native GIP for GIP receptors, whereas tirzepatide bound GLP-1 receptors with affinity

approximately five times weaker than native GLP-1 bound GLP-1 receptors. GIP activation appeared to act synergistically with GLP-1 receptor activation to allow greater weight reduction in mice than that achieved with GLP-1 receptor monoagonism. In phase 2 studies in people with type 2 diabetes, tirzepatide induced clinically relevant weight reduction, warranting further investigation for the treatment of obesity. The present trial, SURMOUNT-1, evaluated the efficacy and safety of tirzepatide in adults with obesity or overweight who did not have diabetes. The trial had several strengths. Its global nature, large sample size, and overall high completion rate make the findings relatively generalizable. Overall, 86% (approximately 90% across the tirzepatide groups) of the participants completed the trial, despite the Covid-19 pandemic. The weight reduction in the placebo group was similar to results observed with placebo in other recent obesity pharmacotherapy trials and is likely to reflect a similar level of adherence to the lifestyle intervention. Finally, the duration of the trial (72 weeks) enabled participants to reach a weight plateau in the 5-mg group and near-plateaus in the 10-mg and 15-mg groups; the additional 2-year treatment period for participants with prediabetes should provide further insight into the maximum and long-term weight-lowering effect of tirzepatide in people with prediabetes. This trial had certain limitations. The enrolled participants with obesity and overweight may represent a subpopulation with a greater commitment to weight-management efforts than the general population with obesity. Furthermore, the measured baseline cardiometabolic risk factors in the trial population, such as blood pressure and lipids, were relatively normal, possibly attenuating the potential to show improvement, though meaningful changes in these variables were observed. Overall, only 5.5% of trial participants with overweight (BMI of 27 to <30) were included; further studies would be needed in such patients. In the present trial, all three doses of once weekly tirzepatide demonstrated substantial and sustained weight reduction in adults with obesity.

Please visit: The New England Journal of Medicine to read the full paper "*Tirzepatide Once Weekly for the Treatment of Obesity*."

Research Updates:

Nature Metabolism: *"Ammonia stimulates SCAP/Insig dissociation and SREBP-1 activation to promote lipogenesis and tumour growth"*

Tumorigenesis is associated with elevated glucose and glutamine consumption, but how cancer cells can sense their levels to activate lipid synthesis is unknown. Here, we reveal that ammonia, released from glutamine, promotes lipogenesis via activation of sterol regulatory element-binding

proteins (SREBPs), endoplasmic reticulum-bound transcription factors that play a central role in lipid metabolism. Ammonia activates the dissociation of glucose-regulated, N-glycosylated SREBP-cleavage-activating protein (SCAP) from insulin-inducible gene protein (Insig), an endoplasmic reticulum-retention protein, leading to SREBP translocation and lipogenic gene expression. Notably, 25-hydroxycholesterol blocks ammonia to access its binding site on SCAP. Mutating aspartate D428 to alanine prevents ammonia binding to SCAP, abolishes SREBP-1 activation and suppresses tumour growth. Our study characterizes the unknown role, opposite to sterols, of ammonia as a key activator that stimulates SCAP–Insig dissociation and SREBP-1 activation to promote tumour growth and demonstrates that SCAP is a critical sensor of glutamine, glucose and sterol levels to precisely control lipid synthesis. Lipids form the basic structure of the plasma membrane and of all cellular organelle membranes, which makes gaining sufficient lipids a precondition for cell growth and proliferation. Under physiological conditions, lipid levels are mainly regulated by SREBPs, a family of transcription factors that include three isoforms, SREBP-1a, SREBP-1c and SREBP-2. SREBP-1c mainly regulates the expression of genes controlling fatty acid synthesis, whereas SREBP-2 regulates cholesterol synthesis and uptake and SREBP-1a, which has the highest transcriptional activity and regulates all processes. Recently, a series of studies from our group and others have demonstrated that SREBP-1 is highly activated in malignancies such as glioblastoma (GBM), liver, breast and colorectal cancers. Nevertheless, the regulation mechanisms of SREBP-1 activation and lipid metabolism in cancer cells remain elusive. SREBPs are synthesized as inactive precursors (~125 kD) that are retained in the endoplasmic reticulum (ER) membrane and are activated through a tightly controlled ER–Golgi–nucleus translocation process. SREBPs first bind to SCAP, which further binds to COPII-coated vesicles that transport the SCAP–SREBP complex from the ER to the Golgi. In the Golgi, SREBPs are sequentially cleaved by site-1 and site-2 proteases, which release their N-terminal forms (~65 kD) that then enter into the nucleus to activate lipogenic gene expression. However, the trafficking of the SCAP–SREBP complex is suppressed by the ER-retention protein, insulin-inducible gene protein (Insig), which includes two isoforms, Insig-1 and Insig-2. Insig binds to SCAP to retain the SCAP–SREBP complex in the ER. Previous studies have revealed that cholesterol or 25-hydroxycholesterol (25-HC) can bind to SCAP or Insig to enhance their association, which mediates a negative feedback loop to modulate SREBP activation; however, the key step activating the dissociation of SCAP from Insig for subsequent translocation remains unclear. Our recent study demonstrated that glucose stimulates SREBP activation and lipogenesis by promoting SCAP N-glycosylation and stability. In this study, we unexpectedly found that when glutamine is lacking, glucose alone is unable to activate SREBPs and lipogenesis despite low

cholesterol levels and stable SCAP N-glycosylation. We unveiled that N-glycosylated SCAP requires the stimulation of ammonia released from glutamine to undergo sequential conformational changes to dissociate from Insig and promote SREBP translocation and lipogenesis. We identified the binding site of ammonia in the central location of SCAP transmembrane domain, including D428 and serine S326/S330 residues and demonstrated that the function of ammonia is prevented by 25-HC, which blocks access to its binding site on SCAP, thereby suppressing SCAP–Insig dissociation and SREBP activation. Our study further suggests that targeting the key molecular link between glutamine, glucose and lipid metabolism is a promising strategy for treating malignancies and metabolic syndromes. Glutamine is necessary for SREBP activation and lipogenesis. In addition to glucose, cancer cells also consume large amounts of glutamine, the most abundant amino acid in human blood, and require dramatically elevated lipogenesis to promote tumour growth. Whether there is an intrinsic molecular connection between glutamine, glucose and lipid synthesis is unknown. To test this, we first conducted a transcriptome analysis using RNA sequencing in lung cancer H1299 cells to determine the response of lipogenic genes to absence versus presence of glutamine (Gln) or glucose (Gluc). Unexpectedly, neither glutamine nor glucose alone was able to activate the expression of genes regulating fatty acid and cholesterol synthesis and uptake, including SREBF1, SREBF2, ACLY, ACACA, FASN, SCD1, HMGCR and LDLR, as compared to absence of both. Notably, activation of lipogenic genes required the presence of both glutamine and glucose, but SCAP gene expression was not affected by either glutamine or glucose.

Please visit: Nature Metabolism to read the full paper *"Ammonia stimulates SCAP/Insig dissociation and SREBP-1 activation to promote lipogenesis and tumour growth".*

From the Clinic:

Gestational Diabetes

Gestational diabetes occurs when your body can't make enough insulin during your pregnancy. Insulin is a hormone made by your pancreas that acts like a key to let blood sugar into the cells in your body for use as energy. During pregnancy, your body makes more hormones and goes through other changes, such as weight gain. These changes cause your body's cells to use insulin less effectively, a condition called insulin resistance. Insulin resistance increases your body's need for insulin. All pregnant women have some insulin resistance during late pregnancy. However, some women have insulin resistance even before they get pregnant. They start

pregnancy with an increased need for insulin and are more likely to have gestational diabetes. Having gestational diabetes can increase your risk of high blood pressure during pregnancy. It can also increase your risk of having a large baby that needs to be delivered by cesarean section (C-section). If you have gestational diabetes, your baby is at higher risk of:

- Being very large (9 pounds or more), which can make delivery more difficult
- Being born early, which can cause breathing and other problems
- Having low blood sugar.
- Developing type 2 diabetes later in life Blood sugar levels will usually return to normal after your baby is born.

However, about 50% of women with gestational diabetes go on to develop type 2 diabetes. You can lower your risk by reaching a healthy body weight after delivery. Visit your doctor to have your blood sugar tested 6 to 12 weeks after your baby is born and then every 1 to 3 years to make sure your levels are on target. There can be done a lot to manage your gestational diabetes. Go to all your prenatal appointments and follow your treatment plan, including:

- Checking your blood sugar to make sure your levels stay in a healthy range.
- Eating healthy food in the right amounts at the right times.
- Follow a healthy eating plan created by your doctor or dietitian.
- Being active. Regular physical activity that's moderately intense (such as brisk walking) lowers your blood sugar and makes you more sensitive to insulin so your body won't need as much. Make sure to check with your doctor about what kind of physical activity you can do and if there are any kinds you should avoid.

Working with your Ohio State doctors, taking medications as advised, eating well, exercising, and getting enough sleep and rest will help minimize your risk of diabetes and assure better health for you and your newborn.

Science Updates:

Allyson Evans, Ph.D, Editor-in-Chief, Cell Metabolism Cell Press, held special seminar here at the OSU to share helpful tips on preparing and submitting paper.

Cell Press

Was founded in 1974 with the publication of Cell, “A journal of exciting biology”. More than 50 scientific journals across the life, chemical, physical, earth, material sciences and health sciences. Committed to editorial excellence, innovation, research integrity, and reproducibility. Our journals ensure visibility of your work. Webinars, podcasts, blog posts, Cell Symposia, social media, commercial products.

Cell Metabolism

It launched in 2005 as the Monthly Journal. They publish exciting, high-impact metabolic research (from basic biology to translational and clinical studies). Their mission is to lead and serve, aiming to be an integral and active part of the metabolism community. Additionally, they are known for their high level of author engagement and reputation for rigor and for providing high peer and lay audience visibility.

Pre-submission Inquiries can be submitted to the journal and editors will give prompt feedback based on the abstract. Editors also can advise about wither it fits scope and whether they would encourage a full submission: https://info.cell.com/cell-metabolism-presubmission-inquiry.