OU Health Harold Hamm Diabetes Center Quarterly Newsletter

Jed Friedman, Ph.D.,
Director,
OU Health Harold Hamm Diabetes Center
Chickasaw Nation Endowed Chair

CONTENTS

Director's Corner

Here, in 2022, we look back at a year that began with restrictions, cancellations, online meetings and a vaccine program. Despite the COVID-19 challenges in 2021, Harold Hamm Diabetes Center (HHDC) managed to continue its efforts in diabetes research and training, clinical care, philanthropy and program building. We continued to set records in fundraising, NIH research dollars, and recruitment of new post-docs, students, and faculty collaborators. We recently completed an updated analysis of our membership, funding and key areas of support. We are in the process of updating our membership guidelines, and producing our next version of "Research at the Root", a 25-page report that will document the goals, strategies and successes reached over the last 3 years.

We congratulate the poster-prize winners from the 18th annual HHDC research symposium, including a special shout-out to Dr. Ann Louise Olson, Ph.D., Professor of Biochemistry, for a fabulous job organizing the symposium. We also highlight 3 scientists who, in partnership with HHDC, bring new technologies to campus: Dr. John Clegg, Ph.D., who just joined the University of Oklahoma College of Engineering from Harvard, with expertise in immunoengineering, Dr. Chongle Pan, Ph.D. Associate Professor of Microbiology and Computer Sciences at the University of Oklahoma, with expertise and new RO1 funding in the microbiome, and Dr. Matthew Hart, Ph.D. recruited to the OUHSC Department of Biochemistry and Molecular Biology from UT-San Antonio, and the new Director of the Center for Drug Discovery and Therapeutics.

We will offer our 2022 Pilot grants, Team Science and equipment call for proposals later this month. HHDC has obtained donor matching funds, allowing us to offer our own call for proposals separate from the Presbyterian Health Foundation this year. A letter of intent will be due by January 31, with full proposals due March 11 to the office of Grants and Contracts.

Lastly, I wish to express my warmest thanks to you – our dedicated faculty and staff, members, donors and closest collaborators – for your strong commitment and efforts to help us through a both challenging and strong 2021. Harold Hamm Diabetes Center would not be the same without you.

I wish you all the best in 2022.

Jed Friedman, Ph.D.
Director, HHDC

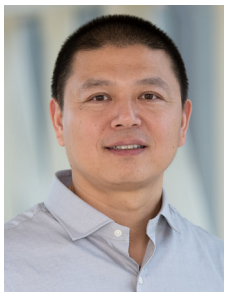
Reminder fo HHDC Members!

Please help us update your profile on the HHDC website.
Click on the icon to enter your information

OU Health | Harold Hamm Diabetes Center

The HHDC Newsletter is a quarterly newsletter that offers articles on HHDC events, funding opportunities, publications, research news, and training opportunities. Sign up below to receive our quarterly newsletter as well as periodic updates on the HHDC.

To submit an item for the newsletter, please send your announcement to ***katie-hoefling@ouhsc.edu***



Tiangang Li, Ph.D.
Associate Professor of Physiology
Harold Hamm Chair in Adult Diabetes Research

Research Spotlight: HHDC Researcher Awarded NIH RO1 Grant

OU Health Harold Hamm Diabetes Center research member Tiangang Li, Ph.D., has been awarded a $1.5 million RO1 grant from the National Institutes of Health (NIH) for his research around non-alcoholic fatty liver disease (NAFLD). NAFLD is now the most common liver disease worldwide and affects nearly 40% of obese youth and up to 50% of the general adult population with obesity. NAFLD is associated with diabetes and other co-morbidities.

The more severe form of the disease, Non-alcoholic steatohepatitis (NASH) is a prevalent liver disease with complex and heterogenous underlying causes. Now, new evidence suggests that dysregulated hepatic sulfur amino acid metabolism is associated with advanced human NASH and causes worsened fatty liver disease. However, significant knowledge gaps exist in our understanding of how sulfur amino acid metabolism modifies NASH severity, and what mechanisms control hepatic sulfur amino acid metabolism in normal physiology and liver diseases.

"The NAFLD is now the most common liver disease worldwide and affects nearly 40% of obese youth and up to 50% of the general adult population with obesity."

Dr. Li's study aims to understand how altered sulfur amino acid metabolism contributes to liver fat accumulation and inflammation in fatty liver disease. In addition, the study investigates the mechanisms regulating hepatic sulfur amino acid metabolism and if they serve as potential therapeutic targets for treating fatty liver disease.

HHDC Invests in new People and Technologies: *Thinking Outside the Box*

Harold Hamm Diabetes Center is investing in new technologies, including **John Clegg, Ph.D.**, who just joined the University of Oklahoma Gallogly College of Engineering from Harvard. HHDC supported Dr. Clegg's recruitment package because he works on Immunoengineering, part of the 3rd pillar of the 3 pathways to a cure. Modulating the immune system using engineering can target new cures in diabetes. Dr. Clegg and Dr. Friedman will collaborate on projects in 2022.

Chongle Pan, Ph.D., at the University of Oklahoma Gallogly College of Engineering, School of Computer Sciences, is another example of how HHDC is looking for technology outside the box for our Pathways to a Cure. By using computer modeling to predict disease, in the microbiome, for example, will help identify new targets for diabetes treatment.

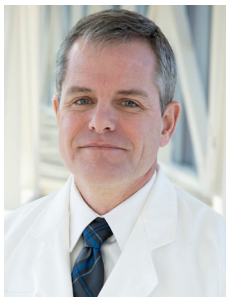
HHDC also supported **Mathew Hart Ph.D.**, recruitment package. Dr. Hart just joined the OUHSC Department of Biochemistry and Molecular Biology and is the new Director of the Center for Drug Discovery. Taking small molecules that are potentially interesting for diabetes and identifying their specific targets using high throughput screening can move compounds from mice potentially into Phase I trials.

2022 HHDC Pilot Program Funding – Three Thematic Areas of Focus

The call for proposals for Harold Hamm Diabetes Center Pilot Projects will be sent out in the coming weeks. Grants will be awarded in the following categories: Team Science, Equipment, Pilot Projects, Bridge funding, and new this year, Post-Doc Fellowship. Our focus this year will be on three thematic areas, Cancer and Diabetes, Diabetes/Obesity and diseases of aging across the lifespan, and collaboration with OUHSC human islet procurement.

Did you know? LifeShare, a local nonprofit, provides a ready source of human pancreas and other tissues for research.

LifeShare is the federally designated organ procurement organization in the state of Oklahoma and is responsible for organ and tissue donation statewide. LifeShare works closely with three transplant centers, OU Health Transplant Institute, INTEGRIS Baptist Medical Center, and St. John's Medical Center and 145 healthcare organizations in the state of Oklahoma to facilitate donation. The health history of the donors includes all possible conditions. LifeShare keeps extensive records and will work with investigators to create a detailed inclusion/exclusion list. For more information about this resource, please contact Clint Hostetler at **chostetler@lifeshareok.org**.



Kevin Short, Ph.D., FACSM
Associate Professor,
CHF Choctaw Nation Chair in
Pediatric Endocrinology/Diabetes

Research Summary: Kevin Short, Ph.D.

Kevin Short, Ph.D., is an Associate Professor and the CHF Choctaw Nation Endowed Chair in Pediatric Endocrinology. He earned graduate degrees in exercise physiology at Purdue University and Ball State University and completed post-doctoral training in endocrinology and metabolism at Mayo Clinic Rochester. Since joining the University of Oklahoma Health Sciences Center (OUHSC) in 2006, his research has focused on the impact of obesity, diabetes, nonalcoholic fatty liver disease (NAFLD) and exercise on cardiometabolic health in children and young adults. He and his collaborators and trainees have measured how vascular function, blood lipid profiles and biomarkers for insulin resistance are affected by obesity and type 1 and type 2 diabetes. Other recent projects focused on strategies to increase physical activity in adolescents, and the effect of exercise or high-fat meals on cardiovascular function and blood lipids.

"There are some histological differences in the liver between children and adults at the time of diagnosis that may be important for the trajectory of liver health, but this area has not been studied in detail."

In parallel with the childhood obesity epidemic, chronic metabolic diseases like type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD) are on the rise among youth worldwide. One of Dr. Short's current major interests is NAFLD in adolescents. For reasons that are not yet understood, the progression of NAFLD from moderate steatosis and fibrosis to more severe stages of the disease is often more rapid than what is observed in adults. NAFLD has become a leading cause of liver transplantation in young adults. There are some histological differences in the liver between children and adults at the time of diagnosis that may be important for the trajectory of liver health, but this area has not been studied in detail.

In collaboration with **Sirish Palle, M.D.**, Director of the pediatric NAFLD, they are working to understand the cardiometabolic causes and consequences of pediatric NAFLD. They recently completed a study showing that the plasma concentration of two microRNAs, miR-122 and miR-192, is increased in adolescents with NAFLD compared to healthy peers. This suggests that these might serve as non-invasive biomarkers for the presence and severity of NAFLD. This finding is important because the only routinely performed blood test for NAFLD, a measure of the enzyme alanine aminotransferase (ALT), provides inconsistent results. The current gold-standard approach for diagnosing NAFLD is liver biopsy. While biopsy is generally safe, there is a clear need for less invasive approaches for diagnosis and monitoring. Drs. Short and Palle, along with Dr. Friedman, are currently using stable isotope tracers and to examine carbohydrate/fat metabolism noninvasively, together with the molecular signatures of NAFLD in liver biopsies from pediatric patients. They plan to measure fat and carbohydrate metabolism in the liver using stable isotope tracers and to examine the molecular signatures of NAFLD in liver biopsies from pediatric patients.

Jennifer Chadwick, B.S. (Choctaw)
Native American Diabetes Research
Program Coordinator
Department of Pediatrics

Native American Land Acknowledgment

Recently, professionals have begun acknowledging Native Americans and their ancestral lands at meetings, during presentations, on websites, and within e-mail communications. A land acknowledgment is a formal recognition of the original land stewards and their relationship to the land. A land acknowledgment also expresses one's gratitude and appreciation of Native culture, wisdom, and expertise.

In drafting a land acknowledgment, there are a few key items to keep in mind. Before you begin, ask yourself why do I want to use a land acknowledgment? One would want to avoid sounding performative or because "everyone else is doing it". A land acknowledgment can be an impactful, supportive tool; just be mindful of your audience and your messaging. Secondly, in developing a land acknowledgment seek guidance and blessing from the Native Nations you are acknowledging. Native communities are rich in wisdom and their input would strengthen the impact of your message. Finally, avoid using land acknowledgment as a "moment of silence" but as a method to celebrate contributions and empower Native people.

Key elements to include in a land acknowledgment: Acknowledge the Native Nations that lived on the land pre-colonization, today and future generations. Many Tribal Nations are no longer living on their ancestral lands, it's important to include accurate and honest context as to why. Finally, A land acknowledgment should include current efforts you are making to correct the social inequalities that Indigenous communities are combating as the result of the loss of their land and culture. For example, an investigator might note, "To help address health inequalities, we are currently partnering with Native Nations on inclusive research that is empowering and solution-driven".

Though a land acknowledgment is a small gesture, it is important to couple the message with authentic actions. A respectful land acknowledgment that expresses openness, honesty, and transparency can be quite impactful and influential in bringing awareness and change.

For additional information, click on the icon below:

The University of Oklahoma American Indian Institute

Native Governance Center Guide to Indigenous Land Acknowledgment

Care About Climate's Five Steps to Writing a Land Acknowledgment

Are you planning to breastfeed? Help us learn more about what makes breastmilk so special!

To better understand maternal health and how it affects infant development, Dr. David Fields continues his NIH-funded project “Mother and Infants Linked for Health.” The MILk Study aims to provide insight into how physiologic changes during pregnancy affect breastmilk and how the components in the milk affect fetal growth, body composition, and metabolism. There are three study visits (1, 3 and 6 months) that will include anthropometric, body composition, and metabolism assessment in the infant along with a maternal blood draw. A primary objective of the MILk Study is to assess associations between maternal weight/metabolic health and her milk composition and the role it plays on her infant. A better understanding of milk composition and its determinants will allow us to develop more precise guidance for women on optimal lifestyle and dietary practices to support successful lactation and infant growth, thereby slowing the vicious cycle of obesity and diabetes that is currently seen in our society.

We are currently enrolling pregnant moms, both non-diabetic and those with gestational diabetes. For more information contact Katy Duncan at (405) 271-8001, ext. 42792 or **BabyPeas@ouhsc.edu** and click **here** for additional details.

David Sparling, M.D., Ph.D.,
Assistant Professor
Associate Section Chief of Pediatric Endocrinology
CHF Paul and Ann Milburn Chair in Pediatric Diabetes

Clinic Updates

Pediatric Diabetes & Endocrinology Clinic

It's an exciting and busy time in the Pediatric Diabetes and Endocrinology clinic! The end of the year is always full of new pump orders, new CGM starts, and all the usual holiday madness sprinkled in. Add on top of that the loss of several great staff members over the past few months, and you can imagine the stress. The great news is, though, that we've recently added multiple new team members to our group, and we're so excited to have them on board! Ameenah Johnson, RN, Ricky Hanks, RN, Lindsay Scott, RD/LD, Courtney Coulter, RN, Kaylee Brewer, RN, and Jennifer Holleman, RN, are all already here and learning the ropes, and Meghan Beaty, RN, will be joining at the end of December. Furthermore, Dr. Rebecca Schaub joined our faculty in mid-December as well! There are many new faces (that are all masked, so it may take some time for our patients to recognize them).

Mary Zoe Baker, M.D.,
David Ross Boyd Professor of Medicine
Department of Internal Medicine

Clinic Updates

Adult Diabetes & Endocrinology Clinic

As we enter the new year, we are experiencing a new surge of COVID. We are moving to virtual visits again to help keep necessary for the next month or so. One thing we have learned from COVID is how to ramp up telemedicine quickly.

We are actively recruiting new faculty, another podiatrist and a new CDE. We hope to have all of these positions filled

Congratulations to our 2021 Research Symposium Winners!

GROUP A:

First place: **Sabira Jazir**
Blocking Necroptosis Reduces Inflammation And Tumor Incidence In A Mouse Model Of Diet-Induced Hepatocellular Carcinoma

Second place: **Nikhil Patil**
Dissecting The Mechanism Of Cinnabarinic Acid Mediated Cytoprotection Against Non-Alcoholic Fatty Liver Disease

GROUP B:

First place: The Steven Chernausek Award: **Mary Ellen Jensen**
Mir-130b/301b Negatively Regulates Beige Adipogenesis In-Vitro And In-Vivo

Second place: **Kameron Sugino**
Higher Complex-Carbohydrate Diet During Pregnancy Increases The Natural Probiotic Bifidobacteriacea In Gut Microbiome In Women With Gestational Diabetes Mellitus

GROUP C:

First place, The Jian-Xing Ma Award: **Beibei Liu**
Mechanism Of Bdnf-Mediated Neuroprotection In Diabetic Retinopathy

Second place: **Ahmadreza Homayouni**
A Novel Feature Selection Method For Non-Image-Based Diabetic Retinopathy Prediction

New Grants to HHDC Members:

PI: Tiangang Li, Ph.D.
Co-Is: Jed Friedman, Ph.D, Michael Rudolph, Ph.D. and Wenyi Luo, PhD
Funding Organization: NIH
Grant Type: R01
Title of Grant: **Sulfur Amino Acid Metabolism and Regulation of Hepatic Metabolic Flexibility**
Dates: 01/01/2022 – 12/31/2026
Amount Awarded: $1,504,000

MPI: Michael C. Rudolph, Ph.D.
Funding Organization: OCASCR
Grant Type: Research
Title of Grant: ***Programming Adipose Stem Cells to Protect Against Diet-Induced Obesity (Yr2)***
Dates: 01/01/2022 – 12/31/2022
Amount Awarded: $145,074 Direct Costs
$17,409 Indirect Costs

PI: Cammi Valdez, Ph.D.
Funding Organization: Association for Research in Vision and Ophthalmology (ARVO)
Grant Type: Career Development Award
Title of Grant: ***Investigating Diabetic Retinopathy: New Tool Development***
Dates: 11/23/2021 – 12/30/24
Amount: $100,000

Media:

HHDC Member **Dr. Cammi Valdez** Awarded 2021 Tony Quinn Inclusive Excellence Award

Video Link | Award Link

HHDC Researcher **Dr. Michael Rudolph** interviewed about his paper, entitled: Resolving human lactation heterogeneity using single milk-derived cells, a resource at the ready. J Mammary Gland Biol Neoplasia. 2021;26:3-8. Click here:

HHDC Researcher **Dr. David Sparling** discusses the findings of a clinical trial where a new treatment using stem cells that produce insulin could be the closest step to a cure for Type 1 diabetes. Click here:

HHDC Members New Publications:

Mezuk, B., & Allen, J.O. (2021). Commentary: Rethinking the goals of diabetes prevention programs. *Diabetes Care*, 44(11), 2457-9. **doi:10.2337/dci21-0038**

Liu KH, Owens JA, Saeedi B, Cohen CE, Bellissimo MP, Naudin C, Darby T, Druzak S, Maner-Smith K, Orr M, Hu X, **Fernandes J**, Camacho MC, Hunter-Chang S, VanInsberghe D, Ma C, Ganesh T, Yeligar SM, Uppal K, Go Y-M, Alvarez JA, Vos MB, Ziegler TR, Woodworth MH, Kraft CS, Jones RM, Ortlund E, Neish AS, Jones DP. Microbial metabolite delta-valerobetaine is a diet-dependent obesogen. **Nature Metabolism**. 2021;3(12):1694-705. doi: 10.1038/s42255-021-00502-8. **https://www.nature.com/articles/s42255-021-00502-8**

Marshall NE, Abrams B, Barbour LA, Catalano P, Christian P, **Friedman JE**, Hay WW, Hernandez TL, Krebs NF, Oken E, Purnell JQ, Raghavan K, Roberts JM, Soltani H, Wallace JH, and Thornburg KL.
Nutrition in Pregnancy: Lifelong Consequences Conference Consensus Statement. American Journal of Obstetrics & Gynecology, (Accepted, In press), 2021

Nash MN, Dobrinskikh E, Newsom SA, Messaoudi I, Janssen RC, Aagaard KM, McCurdy CE, Gannon M, Kievit P, **Jacob E. Friedman JE***, and Stephanie R. Wesolowski SR. Maternal Western diet exposure increases periportal fibrosis beginning in utero in non-human primate offspring. Journal of Clinical Investigation Insights (Accepted, In Press). 2021. *Corresponding Author.

Matsuzaki, S., Eyster, C., Newhardt, M.F., Giorgione, J.R., Kinter, C., Young, Z.T., Kinter, M., **Humphries, K.M.** Insulin signaling alters antioxidant capacity in the diabetic heart. Redox Biol. (2021) Nov;47:102140. PMID: 34560411

Aminian, A., Vosburg, RW, Altieri, M., Hinojosa, M., **Khorgami, K.**, (2021). The American Society for Metabolic and Bariatric Surgery (ASMBS) updated position statement on perioperative venous thromboembolism prophylaxis in bariatric surgery: Surgery for Obesity and Related Diseases. DOI: **https://doi.org/10.1016/j.soard.2021.10.023** Online Link to the Paper **Here**

Kumari S, Bubak M, Schoenberg HM, Davidyan A, Elliehausen CJ, Kuhn KG, VanWagoner TM, Karaman R, Scofield RH, **Miller BF**, Konopka AR. **Antecedent Metabolic Health and Metformin (ANTHEM) Aging study: Rationale and study design for a randomized controlled trial**. J Gerontol A Biol Sci Med Sci. 2021 Dec 2:glab358. doi: 10.1093/gerona/glab358. Online ahead of print. PMID: 34865016

Summers JA and Martinez, E., (2021) Visually induced changes in cytokine production in the chick choroid: eLife 2021;10:e70608 DOI: **10.7554/eLife.70608**. There is an online link to the paper: **Visually induced changes in cytokine production in the chick choroid | eLife (elifesciences.org)**

Wu, D., Eeda, V., Undi, R. B., Mann, S., **Stout, M.**, **Lim, H.-Y.**, **Wang, W**. (2021). A Novel Peroxisome Proliferator-Activated Receptor Gamma Ligand Improves Insulin Sensitivity and Promotes Browning of White Adipose Tissue in Obese Mice. Molecular metabolism, 101363. PMID: 34710641. DOI: 10.1016/j.molmet.2021.101363

Herlea-Pana, O., Eeda, V., Undi, R. B., **Lim, H.-Y.**, **Wang, W.** (2021). Pharmacological Inhibition of Inositol-Requiring Enzyme 1α RNase Activity Protects Pancreatic Beta Cell and Improves Diabetic Condition in Insulin Mutation-Induced Diabetes. *Frontiers in endocrinology, 12,* 749879. PMID: 34675883. DOI: 10.3389/fendo.2021.749879

Spotlight Member Publications:

New target identified that lowers blood glucose discovered in the liver; cross-over with Cancer.

Cheng Chen, Lijie Gu, David J. Matye, Yung-Dai Clayton, Mohammad Nazmul Hasan, Yifeng Wang, Jacob E. Friedman, **Tiangang Li**, Cullin neddylation inhibitor attenuates hyperglycemia by enhancing hepatic insulin signaling through insulin receptor substrate stabilization. Proceedings of the *National Academy of Sciences (2022)* (In Press)

Hepatic insulin resistance promotes liver glucose over-production, which is a key cause of elevated fasting blood sugar in patients with type-2 diabetes and fatty liver disease. In this study, we found that insulin receptor substrate (IRS), a key protein component relaying the insulin signal transduction in liver cells, is degraded by Cullin RING E3 ligases (CRLs). We demonstrate that inhibition of CRLs by a pharmacological inhibitor, already in use in cancer patients, can delay IRS degradation, therefore enhancing liver cell response to insulin stimulation. Treating obese and insulin-resistant mice with a CRL inhibitor rapidly decreases blood glucose levels, suggesting that CRLs may be a therapeutic target for treating hyperglycemia in type-2 diabetes and fatty liver disease. This pharmacological inhibitor is in Phase II clinical trials in Cancer. Thus, modifications to this drug, or new molecules made specifically for this target in the liver may be directly applicable to treatment not only for cancer but for treatment of diabetes as well.

HHDC investigator collaborates to identify new microbiome metabolite that regulates body weight:

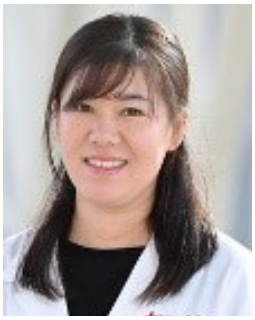
Liu KH, Owens JA, Saeedi B, Cohen CE, Bellissimo MP, Naudin C, Darby T, Druzak S, Maner-Smith K, Orr M, Hu X, **Fernandes J**, Camacho MC, Hunter-Chang S, VanInsberghe D, Ma C, Ganesh T, Yeligar SM, Uppal K, Go Y-M, Alvarez JA, Vos MB, Ziegler TR, Woodworth MH, Kraft CS, Jones RM, Ortlund E, Neish AS, Jones DP. Microbial metabolite delta-valerobetaine is a diet-dependent obesogen. ***Nature Metabolism***. 2021;3(12):1694-705. doi: 10.1038/s42255-021-00502-8.

Microbiome-derived metabolite δ-valerobetaine (VB) is a diet-dependent obesogen that is increased with obesity and is correlated with visceral adipose tissue mass in humans.

Dr. Jolyn Fernandes, together with Emory University collaborators, shows for the first time that a microbially-derived molecule causes diet-dependent obesity in mice and links to obesity-related phenotypes in humans. The metabolite, known as δ-valerobetaine (VB), was discovered in Germ-Free mice exposed to a normal microbiome. When VB was fed to mice on a Western diet it led to mitochondrial fatty acid oxidation inhibition, increased body weight and increased adipose tissue mass accompanied by downregulation of genes related to mitochondrial function, lipid metabolism and fatty acid oxidation. In humans, VB increased in participants of a clinical trial undergoing fecal microbiome transplantation (FMT) procedure. Further analysis showed that individuals with BMI > 30 have higher VB concentrations than individuals with BMI < 30. This data suggests impact of clinical procedures that reduce microbial colonization of this metabolite has the potential to impact human lipid metabolism. For more information, click here:

New HHDC Lab Staff:

Jianglei Chen, Ph.D.
Research Instructer
Li Lab



Yanhong Du
Sr. Staff Research Asst.
Li Lab