OU Health Harold Hamm Diabetes Center Quarterly Newsletter

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

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Director's Corner

Welcome to the spring 2022 issue of the OU Health Harold Hamm Diabetes Center (HHDC) newsletter. This year we are positioned to make impressive progress through our partnerships with OU Health Sciences Center (OUHSC) basic sciences and OU Health. With a strong commitment and expectation in mind, I want to share a bit about how we are poised for our greatest year yet. In this issue, we highlight our comprehensive publication: Research at the Root, The Pursuit that Drives Us. Last published in 2018, the staff at HHDC has worked diligently to update our investigators research base, current funding and a look back at where we've been, and where we are going in 2022. Click here to read it online:

In addition to clinic updates, media presentations and new grants and publications, in this issue, we highlight Dr. Ben Miller, from the Oklahoma Medical Research Foundation (OMRF), who is researching the metabolic effects of Metformin in aging and exercise, and Dr. Yun Le, Professor of Endocrinology and Ophthalmology, who is researching therapeutic strategies to treat diabetic retinopathy. We welcome a new pediatric endocrinologist, Dr. Rebecca Schaub, M.D., and new RD, CDE Kaely Jackson.

2021 Hamm Prize Laureate, Dr. Andrew Hattersley, will deliver the Hamm Lecture in Diabetes Research on May 4 on Zoom. However, HHDC will host a live, in-person reception at this year's American Diabetes Association meeting in New Orleans for the first time since 2019!

HHDC and the OUHSC campus are poised for major changes this year. A new strategic plan for the OUHSC campus will be released in May that will set the stage for diabetes clinical care and research over the next five years. I want to recognize our dedicated, disciplined and devoted faculty and staff for their continued support.

All the Best,

Jacob E. Jed Friedman, Ph.D.
Director, OU Health Harold Hamm Diabetes Center

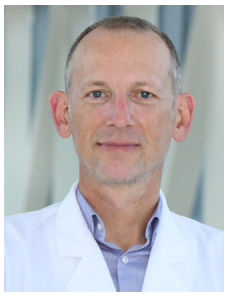
Reminder for HHDC Members!

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***



Benjamin Miller, Ph.D.
Member
Aging & Metabolism Research Program
Oklahoma Medical Research Foundation

National Institute on Aging Awards Multi-Million Dollar Grant to HHDC Member

Benjamin Miller, Ph.D., a member of OU Health Harold Hamm Diabetes Center, is the principal investigator in an OMRF study that recently received a $3.1 million grant, awarded by the National Institute on Aging (NIA). The grant term extends through December 31, 2026.

The grant will fund a study, "Determining the Context Specificity of Metformin Treatment on Muscle Mitochondria and Healthspan," which will explore the effects of metformin, the most widely prescribed medication for the treatment of Type 2 diabetes.

Miller, a principal scientist at OMRF, said metformin is increasingly recognized for effects that resemble the benefits of exercise. "Like aerobic exercise, these beneficial effects appear to be mediated through an energetic and/or redox stress mechanism. This raises the prospect that the two approaches could have additive or even synergistic effects."

The hypothesis is that metformin's effects on healthspan and lifespan are context-specific: beneficial in the context of low energy demand/mitochondrial capacity, but detrimental in the context of high energy demand/mitochondrial capacity. To test this hypothesis, the study will leverage a rat model with divergent selection for intrinsic aerobic capacity, referred to as high capacity

"Like aerobic exercise, these beneficial effects appear to be mediated through an energetic and/or redox stress mechanism. This raises the prospect that the two approaches could have additive or even synergistic effects."

and low capacity runners (HCR/LCR). By selecting for maximal treadmill running capacity, LCR and HCR rats diverged in intrinsic mitochondrial function, lifespan and metabolic traits that increase or decrease risk for chronic disease.

Changes in mitochondrial function will be assessed using ex vivo respirometry measuring the interplay among three thermodynamic forces. The proposal uses targeted kinetic and quantitative mitochondrial proteomics to understand appropriate or aberrant cellular remodeling, and novel in vivo imaging approaches to understand changes in mitochondrial morphology and dynamics.

The specific aims of this study are to determine if these outcomes are context-specific:

- Mitochondrial changes linked to metformin treatment
- The effects of metformin on adaptations to aerobic exercise training
- The beneficial effects of metformin on healthspan and lifespan

It is expected that with metformin treatment, remodeling of mitochondria will be consistent with improved outcomes in LCR rats, with possible detrimental impact in HCR rats, or without effect, with or without exercise training. Additionally, it is expected that metformin will extend healthspan and lifespan in LCR rats, but not in HCR rats. Successful completion of these aims will reveal the importance

of context specificity on metformin action and the mechanisms underlying its positive, and potentially negative impacts, on healthspan and lifespan. This information is critical, given the increasing off-label use of metformin in healthy individuals without chronic disease and/or overt metabolic dysfunction. Results from this project will help inform who can benefit from metformin treatment, and more importantly, who should avoid it.

Miller earned a master's degree in kinesiology at the University of Wisconsin, Madison. Following the completion of his doctoral degree in integrative biology at the University of California, Berkeley, he pursued post-doctoral studies in muscle physiology at the Institute of Sports Medicine in Copenhagen, Denmark. In August 2018, he joined the Aging and Metabolism Research Program at OMRF.

Generally focused on the translation of basic biology of aging into treatments to increase human healthspan, Miller's particular focus is proteostatic mechanisms in mitochondria to increase stress resistance to slow aging. With an exhaustive list of research projects and reports, Miller has extensive experience in translating potential treatments to clinical human trials. His publications have established new and rigorous standards, pioneering novel approaches to data analytics.

Rebecca Schaub, M.D.
Assistant Professor
Department of Pediatrics

HHDC Welcomes New Pediatric Endocrinology Provider, Rebecca L. Schaub, M.D.

Board Certified in general pediatrics and pediatric endocrinology, Rebecca L. Schaub, M.D., joins the team at OU Health Harold Hamm Diabetes Center, adding depth to our pediatric-specific clinical and research initiatives.

With a Master of Science degree in genetics, Dr. Schaub is also fellowship-trained in pediatric endocrinology, having completed a program at Baylor College of Medicine and Texas Children's Hospital in Houston. She completed a pediatrics residency at the University of Texas Health Science Center, San Antonio, where she also earned her medical degree.

As a faculty member at Baylor, she practiced at the Children's Hospital of San Antonio. Dr. Schaub was also active as a board member of Camp Independence of San Antonio, a summer camp program for children with Type 1 diabetes.

Her research experience has yielded more than a dozen peer-reviewed publications exploring a wide range of topics, including the endocrine problems associated with genetic syndromes.

In her role at HHDC, Dr. Schaub's clinical and research interests are focused on Type 1 diabetes. She is enthusiastic about new technologies that are improving the quality of life for children with this disease and their families. She is also looking forward to her first Camp Blue Hawk, the section's summer camp for children with Type 1 diabetes.

Dr. Schaub, a member of the Cherokee Nation, said being part of the incredible work at HHDC is also a homecoming of sorts. "Edmond was the hometown of my late father, and strong family ties also drew me to this area. I'm looking forward to becoming part of this community, personally and professionally."

Dr. Schaub and her husband of 27 years have two adult sons. Their preferred recreational activities include travel and exploring the great outdoors.

Yuen Le, Ph.D.
Professor, Department of Medicine
Harold Hamm Chair in Adult Diabetes Research

Research Spotlight: HHDC Researcher, Yun Le, Ph.D.

Yun Le, Ph.D., is a Professor of Medicine, Adjunct Professor of Cell Biology and Ophthalmology, Harold Hamm Chair in Diabetes Research, and Director of NIH Diabetes Center of Biomedical Research Excellence. For the past two decades, his lab has been working on the pathogenic mechanisms and therapeutic strategies of diabetic retinopathy, a major complication of diabetes and the number one cause of blindness in Americans.

His lab is one of the few in the world to study multiple aspects of diabetic retinopathy, including the breakdown of both blood-retina barriers, neuroprotection, and neurobiology in the disease. His work is supported by the National Institutes of Health, American Diabetes Association and Juvenile Diabetes Research Foundation.

Blood-Retina Barriers

The existence of two blood-retina barriers presents a challenge in maintaining blood circulation in the retina under physiological and pathological conditions. The retina is very sensitive to various issues that can lead to the loss of structural integrity of retinal barriers and cause blood leakage that affects vision. Dr. Le's lab is a pioneer in using conditional gene expression technology to address factors that cause this barrier breakdown – a 30-year technical question that was left a mystery until now. These studies, along with other team science projects Dr. Le participated in have revealed several major knowledge gaps in this breakdown and treatment in diabetic retinopathy.

"His lab is one of the few in the world to study multiple aspects of diabetic retinopathy, including the breakdown of both blood-retina barriers, neuroprotection, and neurobiology in the disease."

Neuroprotection and Neurobiology in Diabetic Retinopathy

Vascular endothelial growth factor (VEGF) is a major pathogenic factor for blood-retina barrier breakdown in diabetic retinopathy, neovascular age-related macular degeneration (AMD), and other retinal vascular disorders and anti-VEGF drugs have emerged as a major therapeutic strategy for these diseases.

The goals of Dr. Le's lab are to 1) study the physiological function of VEGF, 2) investigate the potential side-effect of anti-VEGF drugs during the treatment of diabetic retinopathy and AMD, and 3) determine the mechanism of retinal neurodegeneration in diabetic retinopathy.

To determine the potential mechanism of retinal function changes in diabetic retinopathy, Dr. Le's lab developed a procedure to determine the immediate impact of VEGF on retinal function with electroretinogram and demonstrated that VEGF is a direct regulator of photoreceptors and a contributing factor for diabetes-induced photoreceptor function changes, which was regarded as a novel discovery in retinal physiology and metabolism.

Dr. Le's work in this area is critical to the development of neuroprotective strategies in diabetic retinopathy, the understanding and interpretation of clinical trial results and patient care for anti-VEGF therapies in diabetic retinopathy.

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

Native American Research Partners

To better understand the emerging problem of type 2 diabetes in youth, Dr. Kenneth Copeland and OUHSC partnered with tribal Nations and communities within Oklahoma on the TODAY/TODAY2 studies, Treatment Options of Diabetes in Adolescence and Youth. Now with Dr. Jeanie Tryggestad as study PI, the TODAY Study Phase 2 recently concluded and published the long-term complications of type 2 diabetes in the New England Journal of Medicine.

The study found that people with youth onset type 2 diabetes – some as young as 10 years old at diagnosis -- have a high risk of developing complications, have a greater chance of multiple complications within 15 years after diagnosis, and are much more aggressive than type 2 diabetes in adults. We believe this data illustrates the importance of immediate and aggressive care in the prevention and treatment of type 2 diabetes in youth.

Part of our research agreement with the partnering sovereign tribal Nations is to return the study's results to their communities and health care systems. We have begun sharing study results with these communities through a press release and presentations. Dr. Tryggestad recently presented these results at the Choctaw Nation Health Systems' General Medical Session, the Association of Diabetes Care and Education Specialists (ADCES) State Conference, the Harold Hamm Diabetes Symposium, and soon Grand Rounds for the Chickasaw Nation Department of Health and the National ADCES Conference. This spring we are traveling to tribal communities to share the study's results with tribal health care physicians and staff, tribal leaders, and community members. We welcome any invitation to speak on the risk of type 2 diabetes in youth and are open to recommendations on ways to share this information with families, communities, and tribal Nations.

We are very grateful for the continuous support of our TODAY Study partnering with tribal Nations.

Photo, Left to Right: *Jeanie Tryggestad, MD TODAY2 Study PI and Associate Professor of Pediatrics in the Section of Diabetes and Endocrinology at the University of Oklahoma Children's Hospital, Rev. Bobby Saunkeah, RD, MSHCE, CIP the Chickasaw Nation Director of the Division of Research and Public Health and the IRB Chair, and Michael Peercy, MPH the Chickasaw Nation Epidemiologist/Biostatistician and IRB Administrator.*

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

Things continue to go very well in the pediatric clinic! We've been growing with new staff members and a new provider, getting everyone on board with all the policies and procedures for OU Health and our section, and keeping up with the ongoing increase in new patients. Our fellowship was just re-accredited by the ACGME, which is great; we're proud to continue to educate the future of pediatric endocrinology, from our MAs to our MDs! We've heard there are a lot of exciting treatments on the horizon and are looking forward to getting these to our patients as soon as they're approved (and we've received training!). In the meantime, as insurers continue to cover more and more new technologies and treatments for our kids with Type 1 and Type 2 diabetes (it seems like more are approved every day), we're continuing to ramp up any and every treatment option we can for our kids. And we continue to screen for the possibility of development of Type 1 diabetes through TrialNet, and continue to have research studies on the slowing of development of T1D through that as well!

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 spring, we are thankfully seeing the COVID surge in the rear-view mirror. We have gone back to in-person visits for most patients.

Kaely Jackson
R.D., L.D., CDCES

We are very delighted to welcome Kaely Jackson, R.D., L.D., CDCES, our new Diabetes Educator. Kaely has many years of experience as a diabetes educator and our patients and physicians are already glad that she is on our team.

We expect to have a new endocrinologist and a podiatrist on board by the fall.

New Grants to HHDC Members:

PI: Benjamin Miller, Ph.D.
Funding Organization: NIA
Grant Type: R01
Title of Grant: **Determining the Context Specificity of Metformin Treatment on Muscle Mitochondria and Healthspan**
Dates: 04/01/2022 – 12/31/2026
Amount Awarded: $3,100,000

Media:

Dr. Jeanie Tryggestad participated in Top American Indian Health Concerns panel. | Video Link:

Dr. Friedman and his graduate student Michael Nash presented a paper at a Keystone Symposia on Myeloid Cells: From Birth to Immunity and Disease titled: *"Maternal Western Diet Programs Inflammatory Trained Immunity in Fetal and Juvenile Non-human Primates through Hematopoietic Stem Cells and Macrophages"* in person at the Keystone Conference, Banff, CN, Mar 07, 2022.

Dr. David Fields named Associate Editor for Obesity, the official journal of The Obesity Society.

HHDC Members New Publications:

Davis J, Fischl AH, **Beck JK** et al. 2022 National Standards for Diabetes Self-Management Education and Support. Diabetes Care. 2022 Feb 1;45(2):484-494.

Laura E Fischer, Bruce M Wolfe, Nora Fino, Miriam R Elman, David R Flum, James E Mitchell, Alfons Pomp, Walter J Pories, Jonathan Q Purnell, Mary-Elizabeth Patti, LABS Investigators. Postbariatric hypoglycemia: symptom patterns and associated risk factors in the Longitudinal Assessment of Bariatric Surgery study. Surgery for Obesity and Related Diseases. PMID: 34294589 DOI: 10.1016/j.soard.2021.04.021

Perng W, **Friedman JE**, **Janssen RJ**, Glueck D, and Dabelea D. Endotoxin biomarkers are associated with adiposity and cardiometabolic risk across six years of follow-up in general-risk youth: A prospective study in the EPOCH cohort. Journal of Clinical Endocrinology, Mar 11:dgac149, 2022 PMID: 35276001.

Patil NY, Tang H, Rus I, Zhang K, **Joshi AD**. ***Decoding Cinnabarinic Acid-Specific Stanniocalcin 2 Induction by Aryl Hydrocarbon Receptor***. Mol Pharmacol. 2022 Jan;101(1):45-55. doi: 10.1124/molpharm.121.000376. Epub 2021 Nov 11. PubMed PMID: 34764210.

Shah KB, **Fields DA**, Pezant NP, Kharoud HK, Gulati S, Jacobs K, Gale CA, Kharbanda EO, Nagel EM, Demerath EW, **Tryggestad JB**. ***Association of Gestational Diabetes Mellitus With Altered Abundance of Exosomal MicroRNAs in Human Milk***. Clin Ther. 2022 Jan 25;. doi: 10.1016/j.clinthera.2022.01.005. [Epub ahead of print] PubMed PMID: 35090750.

HHDC Members New Publications:

Shah AS, Gidding SS, El Ghormli L, **Tryggestad JB**, Nadeau KJ, Bacha F, Levitt Katz LE, Willi SM, Lima J, Urbina EM. ***Relationship between Arterial Stiffness and Subsequent Cardiac Structure and Function in Young Adults with Youth-Onset Type 2 Diabetes: Results from the TODAY Study***. J Am Soc Echocardiogr. 2022 Feb 8;. doi: 10.1016/j.echo.2022.02.001. [Epub ahead of print] PubMed PMID: 35149207.

Shah RD, Braffett BH, **Tryggestad JB**, Hughan KS, Dhaliwal R, Nadeau KJ, Levitt Katz LE, Gidding SS. ***Cardiovascular risk factor progression in adolescents and young adults with youth-onset type 2 diabetes***. J Diabetes Complications. 2022 Mar;36(3):108123. doi: 10.1016/j.jdiacomp.2021.108123. Epub 2022 Jan 3. PubMed PMID: 35123868; NIHMSID:NIHMS1777150.

Pincu Y, **Tryggestad JB**, **Teague AM**, **Short KR**. ***The effect of a high fat meal on heart rate variability and arterial stiffness in adolescents with or without type 1 diabetes***. J Diabetes Complications. 2022 Mar;36(3):108130. doi: 10.1016/j.jdiacomp.2022.108130. Epub 2022 Jan 14. PubMed PMID: 35067450

Landreth S., **Teague A.**, Jensen M., Gulati S., **Tryggestad, J**. ***Impact of Maternal Diabetes Exposure on Soluble Adhesion Molecules in the Offspring***. Nutrition, metabolism, and cardiovascular diseases: NMCD. Forthcoming. doi: 10.1016/j.numecd.2022.01.034. PMID: 35256229

H. Xu, R. Ranjit, **A. Richardson**, and H. Van Remmen. ***"Muscle mitochondrial catalase expression prevents NMJ sisruption, atrophy and weakness in a mouse model of accelerated sarcopenia."*** J. Cachexia Sarcopenia Muscle, 12: 1582-1596, 2021.

K. Kurup, S.N. Mann, J. Jackson, S. Matyi, M. Ranjo-Biship, **W.M. Freeman**, **M.B. Stout, A. Richardson**, and **A. Unnikrishnan**. ***"Litter expansion alters metabolic homeostasis in a sex specific manner."*** PLoS one, 16: e0237199, 2021.

N. Thadathil, E.H. Nicklas, T. Lewis, **A. Richardson**, and S.S. Deepa. ***"Necroptosis increases with age in the brain and contributes to age-related neuroinflammation."*** Geroscience, 43: 2345-2361, 2021.

Y. Su, D.R. Claflin, M. Huang, C.S. Davis, P.C.D. Macpherson, **A. Richardson**, H. Van Remmen, S.V. Brooks. ***"Deletion of neuronal CuZnSOD accelerates age-associated muscle mitochondria and calcium handling dysfunction that is independent of denervation and precedes sarcopenia."*** Int. J. Mol Sci., 22: 10735, 2021.

S. Mohammed, N. Thadathil, R. Selvarani, E.H. Nicklas, D. Wang, **B.F. Miller**, **A, Richardson**, and S.S. Deepa. ***"Necroptosis contributes to chronic inflammation and fibrosis in aging liver."*** Aging Cell, 20: e13512, 2021.

Hao Wu, Vikram Norton, Kui Cui, Bo Zhu, Sudarshan Bhattacharjee, Yao Wei Lu, Beibei Wang, Dan Shan, Scott Wong, Yunzhou Dong, Siu-Lung Chan, Douglas Cowan, **Jian Xu**, Diane R Bielenberg, Changcheng Zhou, Hong Chen. ***Diabetes and Its Cardiovascular Complications: Comprehensive Network and Systematic Analyses***. Front Cardiovasc Med. 2022 Feb 17;9:841928. PMID: 35252405 PMCID: PMC8891533. DOI: 10.3389/fcvm.2022.841928.

New HHDC Lab Staff:

Snehasis Das, Ph.D.
Post-Doctoral Research Fellow
Rudolph Lab

HAMM LECTURE in DIABETES RESEARCH

Andrew T. Hattersley, CBE, FMedSci, FRS
Professor of Molecular Medicine
University of Exeter Medical School, U.K.

Join us for a special opportunity to hear the 2021 Harold Hamm Prize Laureate

HAROLD HAMM INTERNATIONAL PRIZE for BIOMEDICAL RESEARCH in DIABETES

Precision Diabetes: The Next Advance in Patient Care

WEDNESDAY, MAY 4 | NOON
VIRTUAL CONFERENCE

REGISTER AT: https://zoom.us/meeting/register/tJcqce-hrDwuG9bas4T_m7rylzFVVLdtK_us

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