



Center researchers investigate expanded use of diabetes drug

Matt Robinson (left) and Sean Newsom (right) are leading a clinical trial in collaboration with Samaritan Athletic Medicine at their campus facility. (Photo courtesy of OSU College of Health)

ALSO IN THIS ISSUE:

A class of drugs taken by millions to treat type 2 diabetes unexpectedly improves skeletal muscle metabolism – and possibly promotes healthy aging in general.

This discovery is the work of a team of investigators at OSU, including Sean Newsom, PhD, Matt Robinson, PhD, and Alysia Vrailas-Mortimer, PhD, who have been investigating the unexpected benefits of the drugs.

Dr. Newsom is a kinesiology professor with the College of Health and a member of the Center for Healthy Aging Research (CHAR). He co-directs the Translational Metabolism Research

Laboratory with Dr. Robinson. Robinson, a kinesiology professor, also is a CHAR member along with Dr. Vrailas-Mortimer, a genetic and molecular biologist in the College of Science.

The drugs, known as “SGLT2 inhibitors,” target the process by which the kidneys filter blood and reabsorb glucose (sugar).

By inhibiting sodium-glucose cotransporter 2 proteins, which facilitate most of the kidneys’ glucose reabsorption, the drugs cause glucose to instead be excreted through urine. This leads to lower blood sugar levels.

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FROM THE DIRECTOR

Center milestone and new opportunities

Next year, the Center for Healthy Aging Research (CHAR) will celebrate its 20th anniversary.

Led by Karen Hooker (2005-2014), Carolyn Aldwin (2014-2021), and then by Emily Ho along with Karen as co-Directors (2021-2023), the center has engaged and connected researchers, trained undergraduate and graduate students in aging science, and brought researchers and community members together through the LIFE Registry.

Now, after spending a year as co-Director to show me the ropes, Emily Ho is stepping down from that position, although she will still have an active role as a CHAR faculty member and advisor.

I am most grateful to Emily for her time and support, and I look forward to working with her and the rest of the CHAR faculty as the center moves into the future.

Research and Community Resources

Part of that future involves our redesigned [website](#). Launched just a few weeks ago, the new website makes it more convenient for researchers, students, and community members to find the content most relevant to them.

In particular, we are starting to gather resources that can be accessed by anyone seeking information about healthy aging, with an eye toward being a central hub for informative resources and recommendations that are supported by research.

Member Interest Groups

We also have a new structure for CHAR members. Rather than disciplinary cores, we are starting to organize around cross-disciplinary interest groups.

The first interest group is focused on neurodegeneration, including diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Lou Gehrig's disease).

Our neurodegeneration journal club started up in April with an article about COVID-19 infection and risk for dementia. This month we had a lively discussion about whether and how cocoa and multivitamins might affect cognitive decline as we discussed a clinical trial that showed that multivitamins were associated with better cognitive function.

I was personally disappointed that cocoa didn't show more promising results, but I continue with my regular doses of dark chocolate just in case!



Suzanne Segerstrom, PhD, MPH

Director, Center for Healthy Aging Research; Jo Anne Leonard Petersen Endowed Chair for Gerontology and Family Studies

The group will stay in touch over the summer with a Zoom journal club meeting (topic TBA) and resume regular meetings in the fall.

Gerontology Conference

Several CHAR faculty members will be presenting at the 47th Annual OSU Gerontology Conference on May 31 at the Alumni Center:

- Carolyn Aldwin on resilience in military veterans
- Kathy Gunter and others on OSU extension programs for older adults
- Emily Ho on nutrition and aging well
- Deborah John on physical activity for older adults
- Alysia Vrailas-Mortimer on a new model of Parkinson's disease
- And I will talk about my research on how psychological stress affects aging of the immune system

The conference is open to everyone, so I hope to see you there. (See page 3 for more information.)

It is an exciting time for the center, and I am grateful to have a role in celebrating its accomplishments for the first 20 years and beyond.

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Alysia Vrailas-Mortimer (left) and Jackson Brim-Edwards (right) at work in the fly lab. Vrailas-Mortimer's research explores how and why humans age and the link between aging and age-dependent diseases such as Parkinson's disease, Charcot-Marie-Tooth disease, and muscular dystrophies.

More than a kidney drug

Not long after the first SGLT2 inhibitor was approved in 2013 to help treat type 2 diabetes, emerging data showed that the drugs appeared to provide other benefits, including improved heart health.

Eventually, the FDA began allowing different SGLT2 inhibitor brands to be used to reduce risk for adverse cardiovascular events in people with type 2 diabetes and/or heart failure.

"While they have risks like all medications, these drugs keep being associated with benefits beyond what they were designed for – heart health seems to be remarkably impacted when individuals take these medications," Newsom said.

But why are there cardiovascular and other health benefits from a drug that targets a protein solely located in the kidney, and could the mechanisms benefit people who are at risk for developing diabetes?

The prevailing theory had been that the unexpected benefits stem from weight loss or changes in blood pressure associated with lowered blood sugar. Newsom had a different idea based on his work with Robinson in their laboratory.

"We know that skeletal muscle is incredibly important, as it plays a critical role in regulating our blood

sugar in response to meals and insulin stimulus," Newsom said. "We thought it was possible these drugs may be improving blood sugar regulation as a result of 'off-target' actions in skeletal muscle."

From mice to people

The lab's first study on SGLT2 inhibitors tested whether the drug would improve skeletal muscle insulin sensitivity in mice. The treatment groups differed in their diets, with one being fed a high sugar/high fat diet that induced insulin resistance.

Led by their doctoral student at the time, Erin McGowan, the study showed improved glucose tolerance in all mice who were given an SGLT2 inhibitor.

That result was expected. However, neither group lost weight, which supported Newsom's skepticism about the prevailing theory for the drug's unexpected health benefits. To better understand the mechanism for improved glucose tolerance, researchers injected the mice with insulin and a radioactive glucose molecule to reveal whether the SGLT2 inhibitor improved insulin sensitivity in their skeletal muscles.

It did. When on the drugs, the mice with dietary-induced insulin resistance showed notable increases in their muscles' glucose uptake.

Newsom also worked with Robinson to research how the drug impacts cultured skeletal muscle cells. By focusing on muscle cells, the kidney and its SGLT2 proteins are eliminated as factors.

Their analysis elucidated emerging evidence that the inhibitors induce energetic stress in cells. Increased applications of the drug on cells caused decreased mitochondrial respiration, impairing the mitochondria's ability to provide energy.

Although impaired cellular respiration sounds like a negative, the state naturally activates a beneficial stress response because cells respond to impairment by making more energy.

"We're talking about a very small impact on the cells that is just enough to cause this cellular response," Newsom said. The cellular stress response is a component of being healthy and causes downstream benefits, such as increased fat oxidation, metabolism, and glucose uptake.

Based on these preliminary studies, Newsom and Robinson are now conducting a 13-week clinical study to test whether SGLT2 treatment improves skeletal muscle metabolism and therefore glucose regulation in people.

The study also explores the potential of using an SGLT2 inhibitor as a treatment for prediabetes. The randomized, double-blind, placebo-controlled intervention involves people who aren't diagnosed with type 2 diabetes but have risk factors related to weight or activity levels.

Backed by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases, the study is using skeletal muscle tissue samples to assess the intervention's metabolic impact.

Fruit flies and longevity

To further explore how SGLT2 inhibitors might provide benefits beyond their original purpose, Newsom is also researching the drug's impact on the lifespan of *Drosophila melanogaster*, a species commonly known as the fruit fly.

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The study is a collaboration with Dr. Vrailas-Mortimer, an expert in fruit fly research, with research assistance led by Newsom and Robinson's graduate student, Jackson Brim-Edwards.

Fruit flies are a model organism for studying aging and disease. They possess equivalent genes to approximately 60 percent of human genes, and they also have counterparts to an estimated 70 percent of the genes involved in human disease.

And because fruit flies have an average lifespan of approximately 70 days, researchers can quickly assess how interventions affect disease progression and longevity.

For Newsom's research, fruit flies offer an additional advantage because they don't have the SGLT2 protein, which means an SGLT2 inhibitor's impact can be tested independent of its intended effect on the human kidney and benefits related to that process.

"If we're showing that these drugs are having an impact on muscles and causing an energetic stress, then there may be adaptations or big

picture impacts that relate to healthy aging and longevity," Newsom said.

Their collaboration began in fall 2023 after Newsom received funding from the Wayne and Gladys Valley Foundation. The preliminary results are promising, with a variety of doses increasing lifespan by approximately 15 percent.

The team is currently investigating the lowest possible dose that elicits this response, and Newsom anticipates other notable data about the drug's impact.

As research deepens understanding of the SGLT2 inhibitors, Newsom notes that the drugs are likely impacting other tissues, not just skeletal muscle, with different drug brands causing different degrees of mitochondrial suppression.

Ultimately, Newsom hopes the research helps expand the currently limited therapeutic options for the millions of people who are prediabetic.

"We're finding an increasing number of benefits for an existing FDA approved drug, and that's exciting," he said.

Small choices, big results

While talking about the metabolic benefits of SGLT2 inhibitors, Newsom said it's important to remember that physical activity alone can improve blood sugar regulation.

In the December 2022 College of Health webinar "Modifying Metabolism: Small Choices, Big Results," Newsom and Robinson described the physiology of skeletal muscle metabolism and type 2 diabetes development and how simple increases in activity improve metabolic health.

A video recording of "**Modifying Metabolism: Small Choices, Big Results**" can be found on the Translational Metabolism Research Lab's website at health.oregonstate.edu/labs/tmrl

Nearly 100 million Americans – about one-third of the population – are prediabetic, which is characterized by elevated blood sugar levels that increase risk for various health issues.

The risk for diabetes increases with age. Meanwhile, many people struggle to find healthy, affordable food and time for physical activity.

However, Newsom and Robinson emphasize that any activity is good activity. Metabolic health is improved by casual exercise as well as short bursts of light activity during sedentary periods of time.

The activity may be as simple as walking to the copy machine and engaging in a few other mobile tasks during sedentary periods of desk work.

Their main message is that it's essential to limit sedentary time every day. Even if the results aren't visible in terms of weight loss or athletic performance, it doesn't take much to improve glucose metabolism and overall health.

Small, daily choices can yield big results.

Gerontology Conference set for May 31

"**Healthy Aging-Friendly Communities: Connecting people and places through research and practice**" is the theme for OSU's 47th Annual Gerontology Conference.

Held at the Alumni Center, the May 31 conference features 27 speakers and four moderated discussions with panelists. Topics include the impact of transportation, housing, and behavioral interventions on healthy aging, as well as the status of efforts to make Oregon an "age-friendly" state.

Anyone is welcome to register to attend, and continuing education certificates are available. The conference is a collaborative effort by OSU's College of Health, Extension Family and Community Health Program, Center for Healthy Aging Research, and Center for Health Innovation.

Visit osugero.org
to learn more and register.

2023 program scholars present at OSU symposium

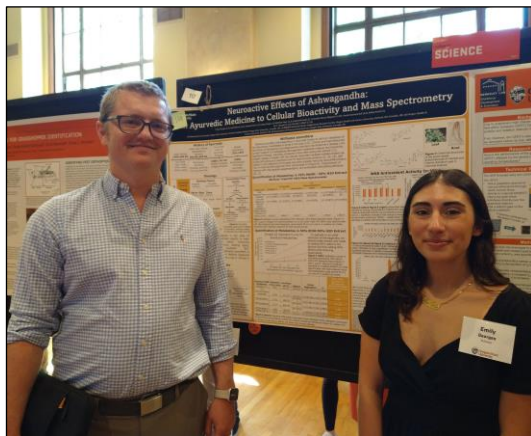
Four of the Center's 2023 LIFE Scholar Program participants presented at OSU's Spring Poster Symposium on May 16 (see photos below).

Sponsored by the Office of Undergraduate Research, the symposium gives undergraduates an opportunity to present their research, scholarship, and creative projects to the campus community and beyond.

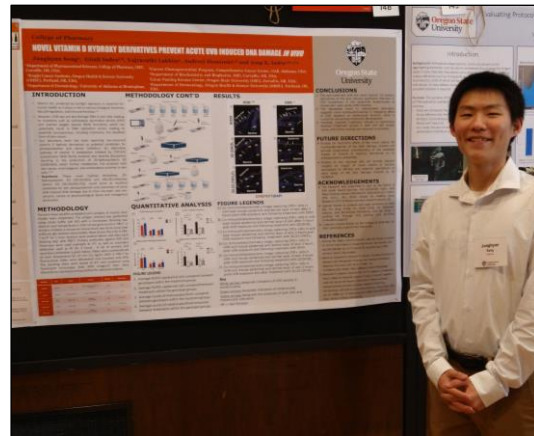
Other LIFE Scholars from the 2023 program have shared their research at national research conferences.

- April Knox, Najeeb Marun, and Philenroza Thavrin: 2023 Linus Pauling Institute Diet & Optimum Health Conference (Corvallis, Oregon).
- Marun also presented at the 2024 Allied Genetics Conference in Washington D.C., and Thavrin is planning to present at the 2024 American Society for Mass Spectrometry Conference (Anaheim, California).
- Chaz Kayser: 2024 American Society for Biochemistry and Molecular Biology's Discover BMB Conference (San Antonio, Texas).

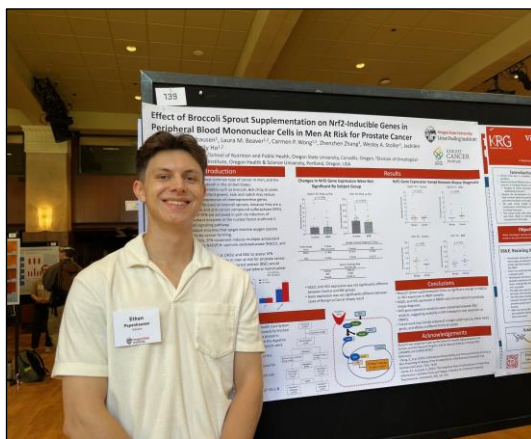
Top left: Mentor Luke Marney with Emily Georges (Neuroactive effects of Ashwagandha)



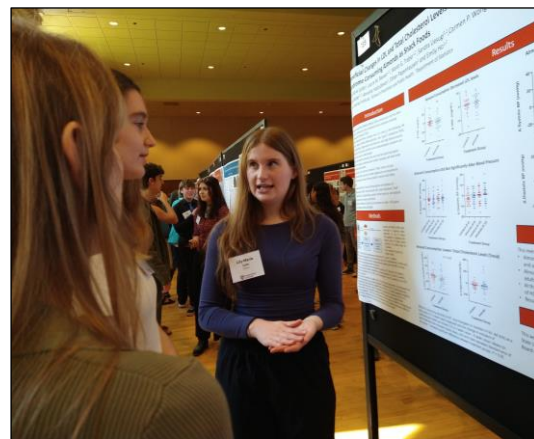
Top right: Junghyun Song (Preventing UVB-induced DNA damage with novel vitamin D3 derivatives)



Bottom left: Ethan Papenhausen (Broccoli sprout supplementation to reduce prostate cancer risk)



Bottom right: Lily-Marie Lytle (Almond consumption and beneficial changes to cholesterol levels)



LIFE Scholars selected for 2024 summer research program

The Center for Healthy Aging Research has named four OSU students as this year's participants in the LIFE Scholar Summer Research Program.

The undergraduate students will work with faculty mentors over the summer term to expand their science skills in the interdisciplinary realm of healthy aging research.

To help support their work, the center and faculty advisors together provide a maximum award of \$2,000 per student.

Donor support helps make the center program possible. This year's awardees and their proposed projects are:

- **Prongbamee Colling** (mentor: Claudia Maier) – Protein dynamics in Alzheimer's pathogenesis: Exploring Aβ₁₋₄₂ aggregation and cellular consequences
- **Hailey Harris** (mentor: Alysia Vrailas-Mortimer) – Empagliflozin influence on lifespan and locomotive function in *Drosophila melanogaster*
- **Phoebe Lee** (mentor: Claudia Maier) – Lipidomic analysis of Alzheimer's disease in young 5xFAD mouse brains by MALDI-MS
- **Dhilan Thanik** (mentor: Alysia Vrailas-Mortimer) – The role of protein homeostasis in neuromuscular disorders

Multivitamin use improves biomarkers for older men

Multivitamins are commonly recommended to support good health as people age. However, that advice may be ignored or viewed with skepticism amid conflicting reports about their actual impact on health.

To help address the uncertainty, Oregon State University researchers Tory Hagen, PhD, and Kathy Magnusson, PhD, led a study to measure the effects of daily multivitamin supplementation on older men.

Dr. Hagen and Dr. Magnusson are members of the Center for Healthy Aging Research (CHAR) and primary investigators at OSU's Linus Pauling Institute.

Older adults are at greater risk for micronutrient deficiencies. As people age, they tend to eat less food, leading to lower micronutrient intake. Also, changes in dietary habits, decreased micronutrient absorption, chronic inflammation, and the influence of certain medications may contribute to deficiencies.

Yet only a few studies have examined how multivitamin use affects vitamin and mineral status in older adults, and that information is limited, notes Alexander Michels, PhD, an LPI faculty member who was the study's research coordinator.

The LPI research team's findings suggest that multivitamins may be a key tool for healthy aging.

Study Design

The LPI research team used CHAR's LIFE Registry to recruit most of the study's 35 participants. Participants were all age 68 or older and in generally good health. The study focused on men because multivitamins are often tailored for either men or women, and previous studies indicate that men are at a greater risk for nutritional deficiencies.

The study was double-blind and placebo-controlled – for at least six months, half of the participants took a daily supplement, and the other half took a placebo, and neither group knew which version they were taking. Participants were not allowed to take other supplements during the study, except for vitamin D if it was prescribed by their doctor.

To assess effects, blood concentrations of vitamins and minerals were measured. Tests to establish baseline status showed that almost all participants started with “suboptimal” vitamin concentrations, but only a few were deficient.

The LIFE Registry is a participant registry of Oregonians age 50 and older who agree to be contacted about research opportunities. To learn more, call 541-737-5080 or visit health.oregonstate.edu/healthy-aging/life-registry

Publication:

Michels, A.J.; Butler, J.A.; Uesugi, S.L.; Lee, K.; Frei, B.B.; Bobe, G.; Magnusson, K.R.; Hagen, T.M. Multivitamin/Multimineral Supplementation Prevents or Reverses Decline in Vitamin Biomarkers and Cellular Energy Metabolism in Healthy Older Men: A Randomized, Double-Blind, Placebo-Controlled Study. *Nutrients* **2023**, *15*, 2691. doi.org/10.3390/nu15122691



Definitions of optimal and suboptimal were based on literature reports that relate the blood concentrations of particular vitamins to an increased risk for disease or death.

A Call for Supplementation

By the end of the study, the impact was clear. Participants in the multivitamin group had statistically significant increases in blood concentrations of several vitamins compared to the placebo group. This was notable for vitamin B6, vitamin D, and vitamin E, as well as β -carotene, a carotenoid compound that contributes to vitamin A status.

Meanwhile, several participants taking the placebo had blood nutrition biomarkers fall during the study. Hagen said, “This suggests that food alone was not enough to keep their micronutrient levels up.”

To connect findings to a measurable impact on bodily function, researchers analyzed oxygen consumption in participants' white blood cells, which is a convenient biomarker of general metabolism.

“We were amazed to find that the men who took the placebo showed a reduction in cellular oxygen consumption,” Hagen said. This suggested an overall decline in metabolism.

“This was not observed in men who took the multivitamin, suggesting a connection between vitamin status and white blood cell function that we are eager to explore further.”

“All of this creates a strong case for multivitamins on top of a balanced diet,” Hagen said.

Center For Healthy Aging Research Newsletter

Joan Rutkowski, Newsletter Editor

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