A NEWSLETTER FROM THE DALE AND DEBORAH SMITH CENTER FOR ALZHEIMER'S RESEARCH AND TREATMENT

Issue 1
Volume 2

MINDMATTERS

SIU MEDICINE
DALE & DEBORAH SMITH CENTER
FOR ALZHEIMER'S RESEARCH
& TREATMENT

the RESEARCH issue

From the Director

Erin Hascup, PhD

I'm in the lucky position of seeing how each area of our Center advances Alzheimer's care and treatment.

Whether it's how a community outreach program can provide a caregiver with a connection to a new friend or how a clinician offers that personal touch and comforting aura to an agitated patient, it's heartwarming to see how the Smith Alzheimer's Center provides encompassing care. But, there will always be a special place in my heart for our research.

The lab is where I started my career, and it's where I found my husband. It's rewarding working with a lab staff dedicated to finding new treatments for those with dementia, watch how curiosity and imagination take hold as new information comes to light and progress is made. I hope that comes through as you read through this issue that's dedicated to how our lab – right here in central Illinois – is finding ways to solve the puzzle that is Alzheimer's.

In this issue, read how the Hascup lab is working to get ahead of dementia and finding ways to stop problems before they start, meet some of the researchers behind the amazing work, and see where research might be headed next.

CONGRATULATIONS

to Caleigh Findley, PhD for her successful defense of her doctoral dissertation! We thank Dr. Findley for her energy, tireless efforr and many contributions to the Hascup lab research over the past four years.

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MEET A RESEARCHER

MACKENZIE PECK

Mackenzie Peck graduated from Millikin University in 2017 with a BS in Molecular and Cell Biology, and joined the Hascup lab as a researcher in 2020. Her work mainly focuses on cellular senescence in relation to aging and Alzheimer's disease. Mackenzie lives in Clinton, IL with her husband and several pets.

What interested you in molecular and cell biology at Millikin? How did that lead to the Hascup labs and studying aging and Alzheimer's?
I chose to attend Millikin because while it is a small school, one of its core values is "performance learning," which, in the sciences, translates to research opportunities built into the curriculum. I have always been interested in discovering the "hows" and "whys" behind biological concepts and processes, and having the ability to do that as an undergraduate was what sealed the deal for me.

After graduating, I explored several different career options, but continually felt like something was lacking — I missed the research aspect of things. Being part of the Hascup lab has allowed me to conduct research that is meaningful to me on a personal level, and is also meaningful to society as a whole. I am constantly learning, and I enjoy that!

What is a typical day in the lab like for you?
Most of my days are spent testing various tissues for gene expression and/or staining brain tissue for markers of Alzheimer's and cellular aging. It's pretty cool to be able to take those two different aspects of a study and put them together to get a better overall view of what is actually occurring in our study animals!

You have a great love for animals. What kind of pets do you have, and what would you like to add to your home if money/habitat weren't an issue?
I am definitely an animal lover! I have two dogs — a sleepy basset hound mix (Benji) and a very energetic lab/hound mix (Cricket). I also have a crested gecko (Abraxos), several hermit crabs (Spike, Mole, and Chirp), a salamander (very originally named Sally), a betta (Gyarados), and a lot of unnamed fish.

I think our current fish tank count is five (a 5-gallon, a 10-gallon, a 40-gallon, a 45-gallon, and a 75-gallon), but a sixth (another 5-gallon) is soon to be added!

I would love to have White's tree frogs at some point as well, and my husband desperately wants a tortoise!

Going on the offensive

Cell senescence may trigger the start of cognitive decline. Can we stop it before it starts?

When you catch a cold or cut your finger, the immune system begins the healing process by clearing damaged cells.

As we age, that process weakens. Health problems linger as immune systems aren't quite as robust as they once were, whether it's fighting bacteria, viruses, or cancer cells. But there's something beyond a cut healing more slowly that Alzheimer's researchers are taking a closer look at.

One of these changes in the aging process is senescent cell accumulation. Senescent cells are cells throughout the body that have essentially lived too long and need to be replaced. Normally, these cells would degrade, and leftover pieces would help build new healthy cells. But senescent cells are stubborn. They block the normal degradation process, and the body can't do anything to break them down.

"Somehow those cells send out certain signals to say 'Hey, I'm kind of tired. Not only am I not going to do any more work, but I'm actually going to harm you,'" said Kevin Hascup, PhD, assistant professor at the Smith Alzheimer's Center and the Department of Neurology at SIU School of Medicine.

Maybe you've heard of senescent cells before, possibly in relation to cancer. It has also been linked to other conditions of aging, including diabetes and stroke. Similar thoughts of the relationship between cell senescence and disease have been applied to Alzheimer's and dementia – if we're able to address the issue of cell senescence, perhaps we can figure out how to develop treatments that prevent the accumulation of dangerous senescent cells or how those senescent cells trigger healthy cells in the body. Right now, it's in the early stages of exploration.

"The buzzword — I don't like the buzzword, but I see it a lot — they're often referred to as zombie cells," Hascup said. "They're not living, but they're not really dead. They're in this in-between state.

"The problem is, they're releasing a lot of unhealthy factors that go throughout the body and damage healthy cells as well."

Reversing the damage?

While the research connecting cell senescence to Alzheimer's is in the early stages, the field of senescence is not new. The topic has been explored for more than 60 years, but the past decade has led to a better understanding of treatment.

This is where senolytic treatment comes in. Senolytics targets these senescent cells and kills them off, preventing any toxins they are releasing. So, the thought is by breaking up the accumulated senescent cells, we would be healthier and age-related issues would be less of a problem.

The Hascup labs hypothesized – what if senolytics were administered before cell senescence accumulated? Could it improve healthy aging? Could you delay the onset of dementia?

They administered two different senolytic treatments to male and female mice. The first was Fisetin, and the second was a combination Quercetin and Dasatinib, the latter of which is a senolytic cancer treatment. All of these are plant-derived, coming from fruits and vegetables like strawberries, asparagus, onions and others. The idea is that it takes time to build up senescent cells, so one theory is it might be harmful to take treatment more often than needed. Treatments were given monthly.

The results were mixed. Male mice models responded favorably to the Fisetin treatment, but it had no effect on females. The females taking the Dasatinib and Quercetin combination experienced a detrimental effect, compared to male models who had minimal effects.

"Overall, we were pretty surprised with a majority of the findings," Hascup said. "To see detrimental aspects in females for various aspects, including markers of inflammation, cognitive performance and metabolism — that was really the big one."

This study focused on those in young adulthood, through a preventive medicine lens. Providing senolytic treatment in older models could offer up different responses yet again.

"Trying to get a better understanding of what we're seeing in the Alzheimer's disease models is almost reverse to what we saw in the natural aging models," Hascup said. "Differences in genetics, different inflammatory states – all of that could play a big role."

As with the vast majority of research, the findings don't give one nice final answer. But it does point you in a better direction.

"One problem is that there's no single test for senescence," Hascup said. "Another problem is, that if you specifically state that you have senescent cells, it just indicates that

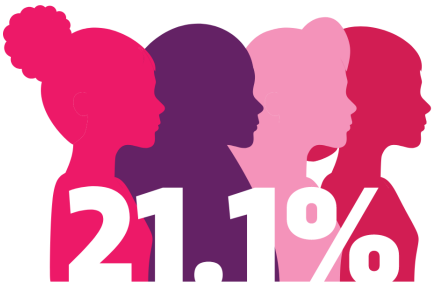
Want to read for yourself?

You can read the full article online. Scan the QR code to learn more.

Alzheimer's & women

Women have nearly twice the lifetime risk to develop Alzheimer's than men.

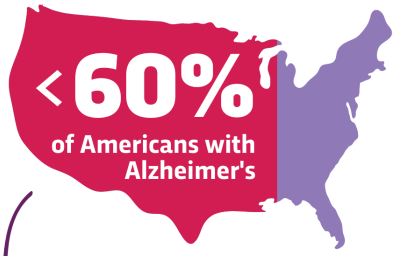
Why? That's a question researchers are still figuring out the answer to - and yes, it seems there's more to it than living longer. It's certainly one worth answering.



21.1%

of women 65 and older have a lifetime risk of developing Alzheimer's

(Compared to 11.6% of men)



<60%

of Americans with Alzheimer's

are women

That's

12%

of all women age 65 and older

OR 4.1 million total

(That's more than the population of 23 U.S. states)

you have inflammation. It could be from obesity, hypertension, MS, or a ton of other factors."

Different gender responses

That difference in response from male and female mouse models has already created some buzz in the research world.

First, let's back up. For a long time, the vast majority of research was only done with male models. It was 1) easier, and 2) cheaper considering you didn't need to accommodate for sex differences. In 2016, the National Institute of Health (NIH), began instituting a new policy requiring grant applicants for preclinical studies to report the balance between male and female cells and animals. Since NIH is the world's largest single funder of biomedical research, it made quite the ripple effect.

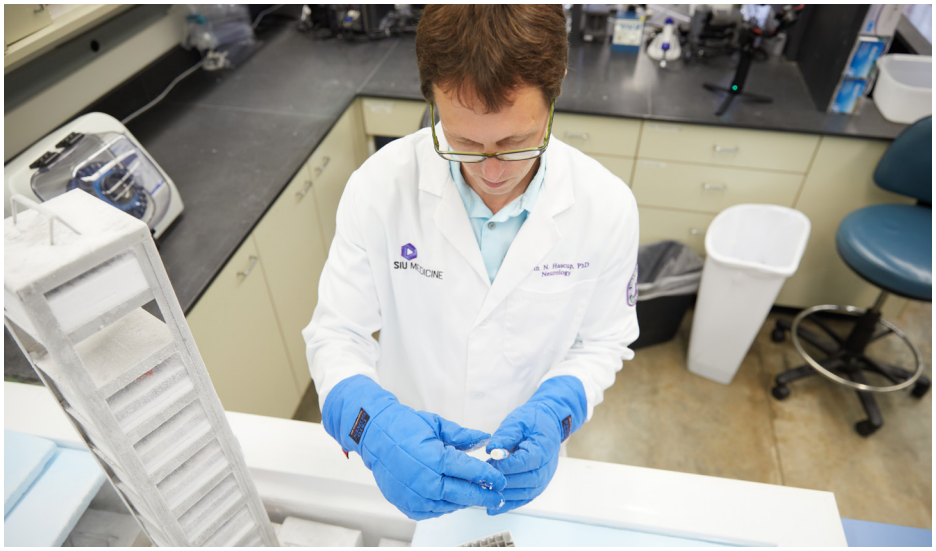
For Alzheimer's and dementia, it seems logical to study the differences between men and women. Nearly two-thirds of Americans with Alzheimer's are women, and while there are a number of theories why women are at a higher risk of developing Alzheimer's than men, the difference is not completely explained.

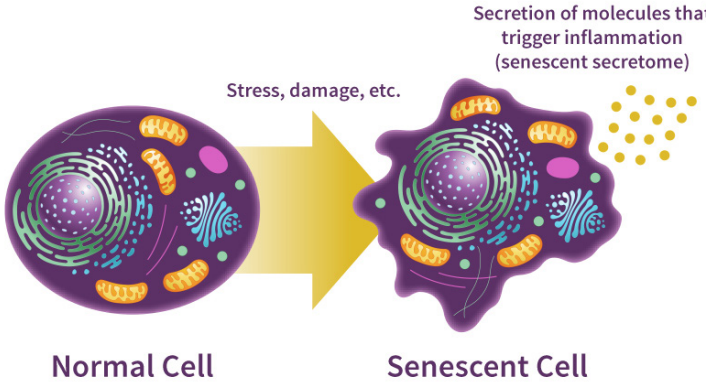
The findings from the publication out of the Hascup lab raise another important reason – treatments may elicit different reactions. And just because one treatment may affect one group positively doesn't mean that is the case for all.

"You separate the two sexes out, males may fare better with the drug, but females have no effect," Hascup said. "We all talk about personalized medicine, but at the end of the day it's a tricky thing to do."

■ ■ ■

Senolytics have risen in prominence thanks to its role in helping fight





cancer cells, as well as its promise in treating other age-related diseases. Research like that usually leads to drug and supplement companies releasing products and making claims about the health benefits based on preliminary data that may be simply aspirational.

"There are some marketed as anti-aging compounds, but there's very little literature showing how these compounds work in younger, healthier individuals," Hascup said. "Caution is recommended in this emerging field."

That's why the Hascup lab is pushing its research to better understand the potential of senolytics, and its affect on all people. These senolytic treatments are barely a decade old, so understanding how their properties could help or hinder different diseases is still coming to light.

"In the field, there's been a big effort put into understanding senescent cell accumulation. Understanding how that might impact aging, and how that might affect disease progression," Hascup said. "These compounds have been routinely shown in older mice near the end of their life span and in various models that they provide very good benefits.

"If you're a younger person taking this because you've seen an ad on TV, and think this will help me as I age, that might not actually be the case."

There is hope, and there is certainly a better understanding of how different treatments may affect those with Alzheimer's and dementia.

"If we can delay or slow the onset of biological aging, we have the opportunity to delay, prevent, or ameliorate chronic diseases."

Marking the turning point

Where should research start in solving Alzheimer's? That's a tricky question to answer

What exactly are researchers looking for when trying to solve the Alzheimer's puzzle?

"It depends on the researcher," says Kevin Hascup. "Really, the tried and true biomarkers are three — amyloid, tau and neurofilament light chain, or what is known as A/T/N."

Each progress in its own way in aging and with dementia. But no matter which biomarker scientists focus on, they are driving the field to explore the first signs of cognitive decline. The thought is, the faster we can identify that change, more effective treatments can be created.

Agreeing when it starts? That's a different and costly question, not only for researchers, but also patients.

"That's the problem. A PET scan could be $6,000 to $10,000 here in Springfield, so most people can't afford that, and insurance isn't going to pay for it unless you're in a study," Hascup said. "So, what the field considers early is identifying the first sign of cognitive decline.

"That's the tried and true method, but where scientists really want to drive the field toward is the biomarker that indicates changes before the cognitive decline is observed. That way we can intervene faster."

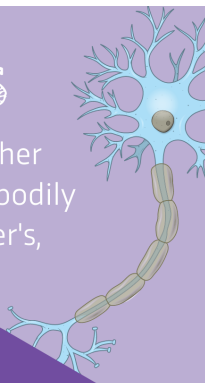
There's also the question of which A/T/N biomarker provides that first and best clue to cognitive decline. Amyloid is generally considered to appear first. Tau correlates with disease severity or disease progression. The amount present in the brain is determined primarily through imaging. Then you have what's referred to as neurofilament lightchain, which is determined through cerebrospinal fluid (CSF). It's also the least expensive of the tests, and the field is quickly looking at specific CSF markers of tau as well.

All of this was designed in the last decade to give clinicians a better understanding of where they are in disease progression, Hascup said.

In addition, a significant amount of research has been moving into markers of inflammation. This includes risk factors such as toxins you inhale, obesity, hypertension, etc. and results in some kind of chronic inflammatory state. Over time, these small molecules, even if it's just fat in your stomach, can move into your blood stream and cross into your blood. So, the more inflammation you have, the greater chance it's affecting the body as a whole.

On the hunt for biomarkers

So, how are researchers exploring Alzheimer's and its progression? As in the case with other diseases and health conditions, researchers use biomarkers — indicators in blood, other bodily fluids, organs, and tissues — to monitor health and response to medication. For Alzheimer's, there are three biomarkers that researchers gravitate toward:



Amyloid

- Group of protein
- Plaques form in the brain
- This biomarker is generally considered to appear first

Tau

- Protein predominately found in brain cells
- Correlates better with disease severity and progression

Neurofilament lightchain

- Found in cerebrospinal fluid
- Higher levels are indicative of neurons dying.

GETTING THE GREEN LIGHT

To continue pushing innovative research, the trait of curiosity is essential. Having the right equipment can make those lofty dreams possible.

The Hascup labs recently acquired a ZEISS PALM CombiSystem, a trailblazing combination of a laser microdissection tool and optical tweezers. Meaning, a researcher can identify particular cells or tissue they want, separate it, then catapult it to a contact-free collection area, all with one device. It drastically cuts down on the time needed to remove cells – or one cell or even part of a cell – that researchers are interested in studying. Sitting on an anti-gravity table, it increases the precision needed to capture them.

This state-of-the-art equipment is unique to central Illinois, enhancing the Hascup labs' abilities to do highly skilled technical work and answer more complicated questions.

Far above: Sam McFadden and Mackenzie Peck get a tutorial of the microdissection laser. Above: The microdissection laser in action. /**BEN ROMANG**

Advancements in technology are possible through funding at the state level, but also through private donations that are invested in finding breakthroughs for new ways to slow, prevent and reverse Alzheimer's and dementia. If you're interested in making advances like this possible, visit the link to the right.

SUPPORT RESEARCH

To help the Smith Alzheimer's Center's research lab continue to push the conversation around Alzheimer's research, visit:

forwardfunder.siumed.edu/care

A BRIEF LOOK AT OTHER RESEARCH

Chronic colder temperatures may worsen cognition in Alzheimer's

As people age, the body's ability to generate heat and maintain a steady internal body temperature worsens. New findings suggest that decline, combined with a chronic colder environment, may increase Alzheimer's disease progression — particularly in women. Constant cold exposure degraded cognitive performance in spatial learning and memory.

Lead author: Samuel McFadden

Friend or Foe? The role of glutamate in Alzheimer's

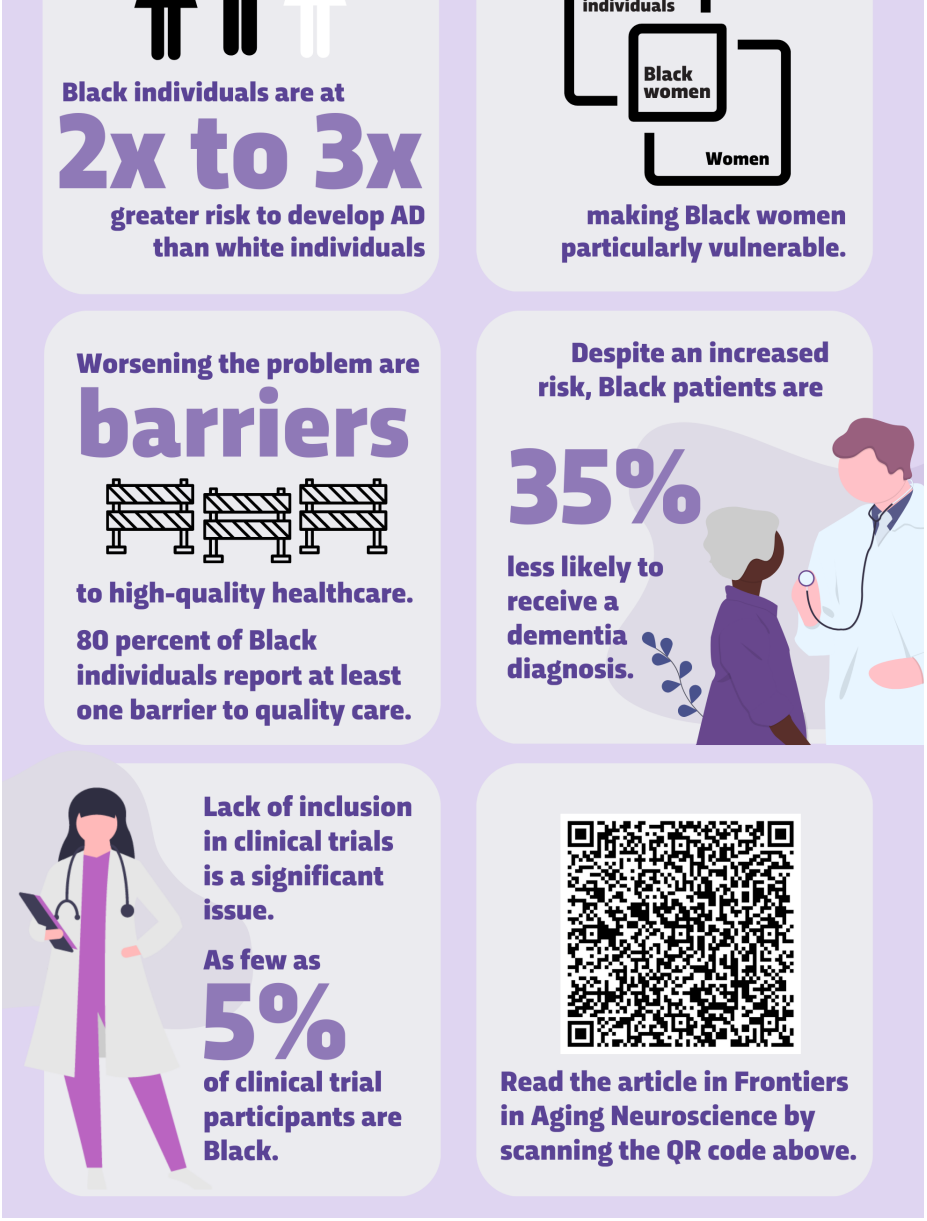
Glutamate, a chemical that nerve cells use to communicate to others cells in the brain, is a promising lead to developing treatments for Alzheimer's and dementia as technology continues to advance. This study suggests focusing on the central nervous system's glutamate levels as a biomarker.

Lead author: Makayla Cox

Psychological resilience in veterans may affect cognitive performance

Studying military veterans age 50 and older, this study reports that veterans who have increasing psychological resilience scores also have significantly higher cognitive performance scores — for every five-point increase in resilience, there was a corresponding 1.1 increase in cognitive performance scores.

Lead author: Dr. Justin McDaniel



Bolstering the research team

Aida Adlimoghaddam, PhD, joins the Hascup lab team at the Smith Alzheimer's Center in 2023 as a Research Assistant Professor. Most recently, she was the Senior Research Associate and Clinical Scientist at St. Boniface Hospital Research Centre in Winnipeg, Canada.

What sparked your interest in research?

As an undergraduate student, I developed a deep passion for biological sciences and discovered the vast array of research opportunities within the field.

However, what truly fueled my interest in Alzheimer's research was a personal connection. My grandmother was diagnosed with Alzheimer's disease and endured several years of struggle before succumbing to the illness. Witnessing the toll this disease took on my grandmother, as well as her friends and family, left a lasting impact on me.

What are your major focus areas in the realm of Alzheimer's research?

Given the absence of a cure for Alzheimer's disease, there remains a pressing need for new medicines and therapeutic strategies. As a result, my primary goals revolve around the development of innovative therapeutic approaches that can effectively prevent, slow down, and potentially cure Alzheimer's and other neurodegenerative disorders.

To achieve this, I am exploring the potential use of mitochondria as a novel therapeutic "medicine." Additionally, I aim to investigate the possibility of repurposing existing FDA approved drugs to target amyloid plaques, tau tangles, and inflammatory pathways associated with Alzheimer's and related neurodegenerative conditions.

What interests you outside of the lab?

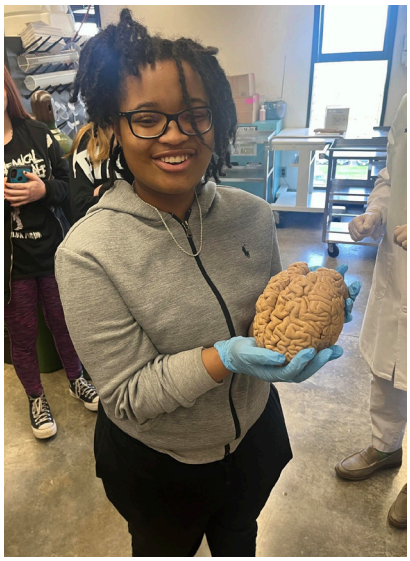
First and foremost, I enjoy spending time with my husband, Kyle, experiencing different cultures, through the exploration of new places both locally and abroad. I also really enjoy a good yoga session, watching a new movie, biking, hiking, skating, having a game night, camping/enjoying food and company outside around a fire.

What will you miss about Canada, and looking forward to with Illinois?

I will truly miss the convenience of gathering with friends and family. The thought of no longer being able to wake up and enjoy a skate along the longest natural river trail in the world, located in Winnipeg, will be a loss. However, I cannot deny that I will not miss enduring the extreme cold that encompasses nearly five months of the year in that region.

The prospect of experiencing four distinct seasons, forging connections, and immersing myself in unfamiliar traditions in Illinois is something I eagerly anticipate.

FUTURE RESEARCHERS



Southeast High School freshmen toured several research labs at SIU School of Medicine, including the Hascup lab at the Smith Alzheimer's Center, to learn more about the path to becoming a researcher and see firsthand what that might entail. /**AREN DOW**

Are you caring for someone with dementia?

This no-cost program can provide help

A new session of Dementia Caregiving 101 will run from August through September at the Lincoln Library in downtown Springfield.

Dementia Caregiving 101 is a program designed to equip those caring for someone with dementia or memory loss, and covers a wide range of topics. During the eight weeks, participants can register for one session or all eight – this helps caregivers find more information on the topics they are most interested in. Each session is two hours long – 2 p.m. to 4 p.m. at the Library (326 S. 7th Street).

Participants will learn how to develop strategies for managing the day-to-day care, recognize behaviors and develop more effective communication, create ways to better care for yourself, and much more. A full list of topics will be available on the registration page, as well as our website: siumed.org/alz101

Registration for the program can be done online through the website listed above, or by calling 217.545.7204. To learn more about the program, please email care@siumed.edu or call 217.545.7204.

MINDS IN MOTION

Use all five senses to improve or maintain mental, physical and emotional well-being.

NAACP | 801 S 11th St

ILLINOIS PRESBYTERIAN HOME COMMUNITIES | 2005 W Lawrence Ave

To register or learn more, email care@siumed.edu or call 217.545.5698.

Program coordinator Lindsey Teefey leads an exercise demonstration on Community Day. / BEN ROMANG

Education & connection

Thank you to all who made the 2023 Brain Aging Conference a success! Held at the Memorial Learning Center on March 9 & 10, more than 200 community members and professional healthcare workers came together to learn about dementia, caregiving, research and more.

Community day topics spanned from an introduction to Alzheimer's and dementia, the importance of exercise, how sleep and dementia are intertwined, addressing palliative and hospice care and more. Topics for Professionals day dove into the different subtypes of dementia — including Alzheimer's, Lewy body, vascular dementia — diagnostic testing and biomarkers, the latest on clinical research and how different lifestyle factors can play a major role in the progress of the dementia.

To see slides from presentations on both days, visit our website at siumed.org/alzconference.

We look forward to seeing you in Spring 2024 for next year's conference!

Special thanks

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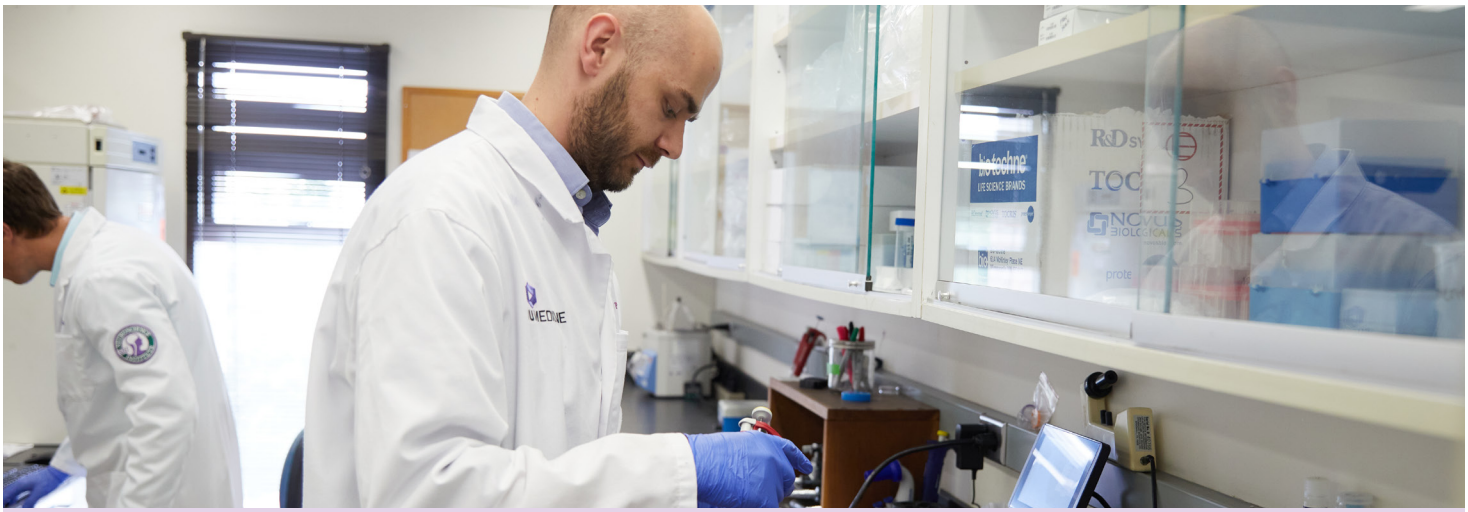

Championing innovative research.

From evidence-based programs supporting patients and their families to ongoing research dedicated to finding ways to slow progression of the disease to training the next generation of dementia care specialists, the Dale and Deborah Smith Center for Alzheimer's Research and Treatment has big ideas, big hearts and big goals.

Your gift impacts our communities and supports our vision of better health for all. Scan the QR code to the right, or visit forwardfunder.siumed.edu/care.

Thank you.

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