

DANCING TO REMEMBER:

The Science of Brain Healthy Activities

- Native Knowledge: Addressing Alzheimer's Disease in American Indian Communities
- The Tiny Worm Driving UW Alzheimer's Research
- The Ride for Alzheimer's Motorcycle Tour
- Hot off the Press: Highlights of AAIC 2017
- Essays & Poems: Garden Walkers



Hello readers!

The UW ADRC and its associated clinical and educational programming are busy, and we are pleased to bring you a second issue of *Dimensions* for 2017!

In these pages we hope you will gain, first, an appreciation for the range of our efforts, from super-specialized Alzheimer's research in a decidedly lower species, to ground-breaking efforts to organize Alzheimer's research for indigenous American peoples, to enthusiastic outreach statewide. More importantly, we hope you hear the undertone of a new and positive message about Alzheimer's disease: persons living with memory loss and dementia have much to offer, strengths to work from, and a perspective that can help us be a more effective Center.

We continue to be grateful for your interest and support of our work. The Ellison Foundation, the Richard M. and Maude Ferry Charitable Foundation, and the Sky Valley Whirlwinds and other generous groups, make it possible for us to move faster and reach out further than ever before. We're all in with you. With your help, we can prevail against this disease. Happy reading!

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DIMENSIONS The University of Washington Alzheimer's Disease Research Center (UW ADRC) is affiliated with the UW Medicine Memory and Brain Wellness Center (MBWC) and the Veterans Affairs Puget Sound Health Care System (VA). The UW ADRC has been funded by the National Institute on Aging since 1985 to facilitate cutting-edge research on Alzheimer's disease and other neurodegenerative conditions that cause dementia. The UW ADRC focuses on Alzheimer's disease biomarker research and advancing prevention methods and clinical treatment for dementia, particularly through precision medicine. The UW ADRC is also supported by the Friends of Alzheimer's Research, the Ellison Foundation, and members of the public.

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Bulletin - Featured Work of 2017

Our ADRC researchers are often busy doing research, writing publications, and launching new partnerships. We've highlighted some new work and awards that we think you'll find interesting.

Precision Medicine

Incidence of cognitively defined late-onset Alzheimer's dementia subgroups from a prospective cohort study // Paul Crane, Emily Trittschuh, Shubhabrata Mukherjee, Eric Larson, Thomas Grabowski, C. Dirk Keene, Thomas Bird, Laura Gibbons

This study explores the notion that typical late-onset Alzheimer's disease may be comprised of distinct groups of individuals. The researchers found that they could use cognitive tests to categorize people with Alzheimer's disease on the basis of patterns of cognitive functioning in four domains: memory, visuospatial, language, and executive functioning. These subgroups seem to be biologically distinct, with different neuropathological findings and genetics. These findings suggest that a non-invasive, widely available technology – cognitive testing – can differentiate people with Alzheimer's disease into biologically relevant and distinct subgroups – and each subgroup may respond differently to treatment.

Dementia Prevention

Dementia prevention, intervention, and care // Eric Larson, Linda Teri (part of a commission of 24 international experts)

This commission produced a novel life-span-based model of dementia risk. The team estimated that roughly 35 percent of all cases of dementia are attributable to nine potentially modifiable risk factors. The authors strongly recommend treating hypertension in middle aged and older people without dementia. Other interventions include more childhood education, regular exercise, social engagement, smoking cessation, and management of hearing loss, depression, diabetes, and obesity. **See page 13.**

Cognitive Resilience

Resistance to Alzheimer Disease Neuropathologic Changes and Apparent Cognitive Resilience in the Nun and Honolulu-Asia Aging Studies // Caitlin Latimer, Dirk Keene, Maggie Flanagan, Thomas Montine

Why do some people maintain cognitive function into old age? It's a mystery that has long stumped researchers. Super-agers fall into two categories. People who are 'resistant' to disease never develop neuropathological lesions; whereas people who are 'resilient' do develop abundant neuropathological lesions yet do not succumb to the expected cognitive impairment, even in late life.

In this study, researchers compared the brain autopsy findings of two famous cohorts. The Honolulu-Asia study includes Japanese men born in Oahu between 1900 and 1919, and the Nun Study comprises Caucasian Roman Catholic nuns born in the US between 1890 and 1916.

The team investigated the biological and clinical signs of resistance and resilience to four diseases: Alzheimer's, vascular injury, Lewy body, and hippocampal sclerosis. They found that sex, ethnicity, genetic, and lifestyle factors may influence the resistance to developing these types of brain insults in aging. However, the proportion of individuals who were resistant to all four diseases of the brain—or who displayed cognitive resilience —was identical between participants of the two studies. This result surprised the team. They had expected that some people would show resistance to one particular disease or another. This finding leads the researchers to speculate that some people simply show general resilience or resistance to all neurodegenerative diseases.

New Methods

Modulation of Hematopoietic Lineage Specification Impacts TREM2 Expression in Microglia-Like Cells Derived From Human Stem Cells // Suman Jayadev, Gwenn Garden

Microglia are tiny cells that run the immune system of the brain. The Jayadev Lab and collaborators hypothesize that genetic factors contribute to Alzheimer's disease by causing microglial dysfunction. They produced a reproducible method for generating microglia from human stem cells. This technique enables researchers to make microglia from living patients and test if these cells aren't working properly. They can search for genetic modifiers of the disease and, eventually, test for drugs that normalize their immune cell function.

New Initiatives

A Focus on Frontotemporal Degeneration (FTD) // Kimiko Domoto-Reilly

The UW ADRC is expanding its focus to include FTD, a spectrum of brain disease that affects language, behavior and motor function. The center has become a site for the Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) Consortium funded by the NIH's NCATS and the NINDS. Dr. Kimiko Domoto-Reilly is the Principal Investigator at the UW ADRC site. To learn more about this research opportunity, visit: www.rarediseasesnetwork.org/cms/artfl/About-Us.

The UW ADRC is also a site for the new Biogen clinical trial for behavioral variant FTD. This study at seeks to identify the most sensitive cognitive tests, detect FTD progression, and evaluate how better knowledge of disease progression influences function, caregiver burden, and quality of life. Dr. Domoto-Reilly is the Principal Investigator of this study at the UW ADRC, one of ten study sites.

Dementia with Lewy Body (DLB) Consortium Study // Debby Tsuang

A new NIH grant established a national consortium focused on improving the diagnosis and understanding the cause for Dementia with Lewy Bodies (DLB). Dr. Debby Tsuang, co-investigator in the UW ADRC Clinical Core, now runs the DLB Consortium Study site at the VA Puget Sound Health Care Center / University of Washington, one of nine participating clinical centers. The study, led by principal investigator James Leverenz, M.D., of Cleveland Clinic and former UW ADRC researcher, is aimed at finding DLB biomarkers, which can assist with diagnosis, detect disease progression, and ultimately measure response to treatment.

New Grants

Late-Life Consequences of TBI and Military Service: A Population-Based Study Department of Defense, \$2.5 million // Paul Crane

MSUT Modified Pathological Tau in AD and Model Organisms National Institute on Aging's RFA for Capturing Complexity in the Molecular and Cellular Mechanisms Involved in the Etiology of Alzheimer's Disease, \$3.1 million // Brian Kraemer See page 15.

Measurement of Early Symptoms of Alzheimer's Disease National Institute on Aging, \$2.8 million // Paul Crane

Collaborative Research: Relationship of Cortical Field Anatomy to Network Vulnerability and Behavior, National Science Foundation's Integrative Strategies for Understanding Neural and Cognitive Systems (NCS) program, \$1 million // Thomas Grabowski





"I tell you what," Marty Bahr said to his brother Joe. "If you promise to raise funds for Alzheimer's disease research after I pass on, I'll donate my brain to science."

It was an unusual promise. And, over the past ten years, it has had an extraordinary result.

Marty Bahr had always been an ambitious, assertive person. He climbed the ranks of a major Seattle insurance company to become an executive. "Marty liked planning big projects and tackling goals," said his wife Laurie Bahr. "He bordered on a Type A personality." And, as his friends and family attest, Marty's persistent nature never faded, even as he began to experience memory problems in 1995 at age 50.

At that time, the medical community generally did not recognize that people under the age of 65 could develop dementia. And so without knowing that 100,000 people in the US were experiencing the same thing, Marty ended his career and struggled over daily tasks such as using electronics, cooking, and driving. In 2000, Marty received a diagnosis of early onset Alzheimer's disease from clinical researchers at the UW ADRC, directed at the time by Dr. Murray Raskind of the UW Department of Psychiatry & Behavioral Sciences.

"Marty and I hadn't been close for years," said his brother Joe Bahr, who began to visit often. "But in a strange way, the experience brought us closer together." On walks and phone calls, Joe heard Marty's frustration building and eventually decided to help his brother channel this energy into action. Joe offered to ask his square dancing club, the Sky Valley Whirlwinds in Mill Creek, WA, if they would host fundraiser dances for Alzheimer's disease research.

Marty upped the ante, offering to gift his brain to science if Joe followed through on the plan. "I won't need it when I'm dead, so if it can help somebody, I'll do it," he had said.

Since 2008, Joe Bahr and the Sky Valley Whirlwinds have held a square dance fundraiser on the last Sunday

of February, from 1 to 4 pm. On February 26, 2017, the Sky Valley Whirlwinds hosted the 10th Annual Alzheimer's Benefit Dance in Woodinville's Leota Junior High School gymnasium. Women in chiffon petticoats, tiered prairie skirts, and ruffled blouses and men in belt buckles, bolo ties, and cowboy boots whirled around the room, arm in arm, following the cues called out over a microphone: "Bow to your partner, bow to your corner." "Heads forward and back." "Circle left." "Swing your partner." "Now.... promenade!"

"It was the highest level of square dancing I've ever seen," said Marigrace Becker, Memory and Brain Wellness Center's (MBWC) Program Manager of Community Education and Impact and a square dance enthusiast herself. Becker and Dr. Thomas Grabowski, Director of the ADRC and neurologist at the MBWC, attended the event to recognize Joe Bahr's effort. Next Page...

8 "What stands out to me is Joe's effervescent energy and commitment to the cause and the memory of his brother," said Becker. "He is an example of how all of us, in our own circles and wherever our passions lie, can take that motivation and help build support for Alzheimer's disease research and support programs."

Dancing and the Brain

For Bahr, this square dancing event does more than raise funds for research. This effort also promotes lifestyle choices shown to protect cognitive health and prevent decline during aging. "Square dancing goes along so well with the idea of brain health and dementia," he says. "In the dance, the announcer calls out the moves, and each group of eight dancers must follow the instructions together, all at the same time.

They must respond quickly, or the whole square breaks down. It's good exercise for the brain."

Dr. Kristoffer Rhoads, neuropsychologist at the MBWC and the ADRC, agrees. "First of all, the complex cross-body movements of dancing recruit the procedural memory system and give it a work out," says Rhoads.

Procedural memory, a form of long-term memory, underlies our habits and learned sequences of movement, making it so we don't need to think much about how to walk, row a boat, or perform our favorite dance. "It's also the form of memory that stays intact longer in people with Alzheimer's disease," he says, "and it may help people compensate for losses in short-term memory."

Indeed, epidemiological studies have found that ballroom dance has a protective effect against dementia onset in older adults and reduces symptoms in older adults with depression.

A recent study at the University of Illinois in Urbana and other schools looked deeper into the influence of dancing on the aging brain. The study enrolled physically inactive men and women aged 60 to 79. Taught by an instructor, they practiced choreographed country western dance combinations for an hour, three times a week. The routines grew progressively

more challenging.

Over six months, the researchers used brain imaging to monitor the effects on the participants' brains. The scans showed that, compared to study controls who took walking or stretching classes, only the adults in the dancing group showed denser white matter in the brain's fornix. This tiny triangle of tissue deep in the brain plays an important role in making and recalling memories, as well as motor performance and problem solving.

The six months of a winning combination of factors—cognitive challenge from learning dance steps, social stimulation from being with new friends, emotions triggered by music, and intense exercise—strengthened this part of the brain in older adults, who previously weren't big exercisers.

The Active Ingredients of Brain Healthy Habits

To swing Joe Bahr's intuition full circle, activities like square dancing are great for brain health because they simultaneously address many of the known mid-life health and lifestyle risk factors for dementia—including hypertension, obesity, depression, and social isolation. In fact, numerous

studies have found that people who are physically, socially, and mentally active in mid life are less likely to experience cognitive decline and dementia.

Some of the strongest evidence for exercise's benefit to cognition comes from the Finnish Geriatric Intervention to Study and Prevent Cognitive Impairment and Disability. People over 65 completed a lifestyle intervention of healthy diet training, vascular risk factor management, and aerobic exercise, and they showed slower cognitive decline and improved mental agility.

(Pictured: Dr. Thomas Grabowski, Joe Bahr, and the attendees of the Sky Valley Whirlwinds 2017 Alzheimer's Benefit Dance)

In a 2015 study of older adults at risk for dementia, researchers including UW MBWC's Dr. Angela Hanson and Wake Forest University's Drs. Laura Baker and Suzanne Craft found that six months of





high-intensity group exercise sessions (working up a sweat for 45 minutes, 4 times per week) lowered levels of Alzheimer's-related proteins in cerebrospinal fluid.

The intervention also increased blood flow to the brain and boosted executive functions, such as time management and attention.

Other types of cognition benefit from a workout, too. The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial recruited cognitively healthy older adults and provided 10 hour-long sessions that trained them in skills targeting one of three types of cognitive ability: memory, reasoning and problem solving, or speed of processing. Each group showed improvements on the specific task they were trained on and reported less difficulty in everyday activities, such as managing finances or planning meals, up to 10 years after the intervention.

"But, the interesting thing is if you look into the ACTIVE trial data," says Rhoads, "the benefit comes from the people who did the cognitive training in groups. The people who worked on the intervention alone did not yield as much of a benefit as those who did it in a group setting."

From his work in the clinic and the Healthy Action to Benefit Independence & Thinking (HABIT®) study, Rhoads has seen the power of interventions in social groups.

"To unpack the ingredients of that group benefit," he says, "I would guess that some of it is accountability—that shared feeling of 'We're all in this together.' Being in a group activates our competitive streaks, which ratchet up performance and motivation to continue. A lot of people do a lot better being accountable to someone else than themselves. Also, being part of a group is a wonderful buffer against isolation and depression." In short, the group aspect motivates people to stick with the behavior intervention long enough to see a difference, and it's often fun.

Square dancing is far from the only brain healthy pastime. On the following page, our center's researchers, clinicians, and staff offer their personal favorites. There's something for everyone. And that's welcome news for those of us who don't like to dance, or those who can no longer twirl a partner or remember all that fancy footwork.

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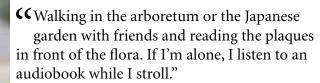
As Marty Bahr had wished, researchers received the gift of his brain upon his death on December 30th, 2008. His memory lives on beyond the square dance hall in a different kind of beneficial group endeavor. After Marty and Laurie moved to Chicago, they had tried several Alzheimer's disease support groups. But they found little in common with the participants, who were all much older. The couple pushed hard at Rush University Medical Center for more recognition of younger onset dementia and services designed specifically for people who fall ill before retirement and Medicare/Medicare eligibility, and often have children still living at home.

Marty's persistence paid off. In April of 2004, Rush University and the Alzheimer's Association formed the first-ever support group for people living with early-onset Alzheimer's. *Without Warning* (www.without-warning.net) began with two couples, including Marty and Laurie. Now, it offers a welcoming community resource to over 75 people in the Chicago area.

As for Joe, he has now donated close to \$50,000 of proceeds from the annual Remember to Dance benefit to the UW ADRC and Rush University Medical Center. He plans to retire from Seattle Metro in several years and devote time to inspiring other square dancing clubs across the country to hold fundraisers for Alzheimer's disease research and promote dementia prevention. "By the end, this effort will have enveloped the world," he says.•

Learn more: remembertodance.org

- Checking out low tide off Alki Beach when the beach naturalists are there. I print up a list of animals/plant life to look for and bring it with me. Doing this alone is fun, but almost more fun with a small group."
- Dr. Emily Trittschuh, Associate Professor, UW Department of Psychiatry and Behavioral Sciences
- **C** A nature photography hike with my best friend."
- Dr. Thomas Grabowski, Director, ADRC / Medical Director, UW Medicine Memory and Brain Wellness Center (MBWC)



- Krista Specketer, Research Coordinator, Pacific Udall Center

time favorite! We have native wild or naturalized edible berries from the end of May to the beginning of September. Especially abundant are the naturalized blackberries that ripen in mid-August; find them along roads and in most parks.

Get a bucket of juicy berries in about 15 minutes in a good spot! Many of the native edible berries grow in forested parks around Seattle, as well as in the mountains. However, if you're concerned about plant identification, think about going to one of the great u-picks in the area instead." (Side note: Berries, especially blueberries, are a brain healthy food.)

- Dr. Annika Noreen, Program Manager, UW ADRC



Year-round bike commuting – outdoor exercise, and a chance to think about the day ahead and past. Then, home for time with my wife, chickens, and piano playing.

- Dr. Eric Larson, ADRC Administrative Core, Associate Director/ Clinical Professor, UW School of Public Health, Health Service/ Adult Changes in Thought Study.

Rock climbing and bouldering are a perfect mix of physical, psychological, and technical challenges. Climbing with a partner or bouldering with a group of friends is also inherently social and supportive—especially important for the falls!"

- Dr. Kristoffer Rhoads, Neuropsychologist, ADRC / UW MBWC

Yes Keeping track of what grows in my yard through the year. I take my copy of Sunset Western Garden Book, and put a sticky note when I notice a specific plant species. I also carry a small notebook for my simple record of what tasks I do, so I remember next year —with this record, I can rely on my notes, instead of on my memory!"

- Genevieve Wanucha, Science Writer, UW ADRC / MBWC

Getting together with friends to play card games, board games, or book discussions. These activities are fun of course, but they also help create cognitive reserve to prevent future dementia."

- Dr. Angela Hanson, Geriatrician, UW MBWC

Coing the Sunday *New York Times* crossword puzzle with my partner. It may take us a few days to finish it, but it always feels good when we do."

- Louren Reed, Research Coordinator Lead, Pacific Udall Center

husband and I have taken tango lessons. Next up, maybe waltz! There's just so many things to keep track of: the music, where to step next, where my partner is, trying not to run into the other dancers. It's been a fun way to meet new people, get some exercise, and keep challenging my brain."

- Elisabeth Lindley, Registered Nurse Practitioner, UW MBWC

ct Tap dancing classes at my local dance studio, where I am constantly challenged to pick up new steps and remember old ones. It's great exercise and extra fun with a great group of ladies."

- Erin Bowles, Research Associate, Kaiser Permanente Washington Health Research Institute/ Adult Changes in Thought Study.

Contra dancing! I always come away with a huge smile on my face from meeting friendly people. It's a great workout and takes a lot of concentration to quickly learn the moves of each dance." - Marigrace Becker, Program Manager, Community Education and Impact, UW MBWC

Wy favorite activity is yoga - I love it for the combination of mental relaxation with physical challenge." - Dr. Ruth Kohen, Geriatric Psychiatrist, UW MBWC



Local Brain Healthy Opportunities for People Living with Memory Loss, Friends, and Partners

Exercise/Outdoors/Nature

Friendly Folk Dance - A 4-week series at Yesler Community Center, 917 E Yesler Way, Seattle, WA 98122. Wednesdays, October 11 – November 1, 10:30 a.m. – 12 p.m. Free. Register with Cayce Cheairs, Seattle Parks & Recreation: 206.615.0100, cayce.cheairs@seattle.gov. Seated and standing options.

Garden Discovery Walks - The MBWC partners with Seattle Parks and Recreation and Seattle P-Patch to provide free monthly nature experiences for people living with memory loss, and their family and friends. Explore nature and savor the season with monthly walks through Seattle public gardens, followed by a creative, nature-inspired activity. Light refreshments provided. Every first Friday, 10 a.m. February-November. Free. Pre-Register with Cayce Cheairs, Seattle Parks & Recreation: 206.615.0100, cayce.cheairs@seattle.gov. **See Page 26**.

Out and About Walks -Invigorate body, brain and spirit with these free 2-3 mile moderately paced walks in parks and neighborhoods throughout Seattle for people with memory loss and their loved ones. Walks include information about the architecture, history, sculptures and gardens along the route. The event ends with a social gathering in a nearby cafe. Friday, 10 a.m. Contact Seattle Parks and Recreation at 206.684.4664 to register or visit www.momentiaseattle.org/out-about-walk.

Yoga Classes, Online - Free yoga classes sponsored by the Northwest Parkinson's Foundation: **www.nwpf. yourbrandlive.com/yoga**.

Food

Community kitchen - Thursday, Oct 19. 4-6pm. \$5 for food supplies. Greenwood Senior Center. Let's cook and eat together! Come prepare and enjoy a delicious communal meal full of brain healthy and seasonal ingredients. Space is limited—reserve your spot as soon as possible by calling 206.297.0875.

Learning

Healthy Brain Aging Seminars - The MBWC offers public talks on brain health at ERA Living communities throughout the year. RSVP's required, please see below.

Tuesday, September 19, 10:30 a.m.: How Aging Affects Brain Function with Dr. Bruce Ransom. University House Wallingford, 4400 Stone Way N. RSVP 206.452.3209.

Tuesday, October 10, 2 p.m.: Art, Creativity & Memory with Dr. Lee Burnside. Ida Culver Ravenna, 2315 NE 65th St. RSVP 206.452.3188.

Social/Community

Our Time Has Come - Our Time Has Come is an 8-week series in which persons living with memory loss come together to design a dementia-friendly communities project of their choice. Participants learn what other local activists have accomplished, consider their own strengths and interests, and take one powerful step to make their community a better place in which to live with memory loss. Previous projects include building awareness at a summer day camp and within a local retirement community. A free program; next session Winter 2018. Contact Marigrace Becker: mbecker1@uw.edu

Artist Within: A New View of Dementia- See the exhibition at the Washington State Convention Center through October 1st, Second Floor.

* Find more dementia-friendly activities on the Momentia website at www.momentiaseattle.org

Hot off the Press

Highlights from the recent Alzheimer's Association International Conference 2017 in London by Angela Hanson, MD. Geriatrician, UW Memory and Brain Wellness Center



I study how diet affects the brain, so I was particularly interested in talks and posters involving that topic. Here are my highlights:

- More evidence that the **Mediterranean diet**, and the similar MIND diet, protects against dementia!
- The **Women's Healthy Aging Project** (WHAP) from Australia shows that people who ingested foods that were higher on the 'diet inflammatory index' were more likely to develop dementia. Foods that are inflammatory include added sugar, fried foods, and saturated fats.
- The ketone diet: There's a lot research going on right now to characterize the metabolic abnormalities of the Alzheimer's brain and whether these differ by APOE genotype or by sex, and how we can use that information to help tailor treatments and diets for patients. Several different laboratories are studying the ketone diet, or supplements that mimic ketosis, as a treatment for Alzheimer's. Ketone bodies are the brain's way of dealing with a lack of glucose (such as during starvation), but they might be a treatment for Alzheimer's as people with this disease show defects in brain glucose metabolism. However, the science is in early stages, and, given the side effects that can occur with a ketone diet, I advise doing this only within the context of research for now.
- **Dementia prevention**: The *Lancet* launched a Commission to review the available evidence and produce recommendations about how to best manage or even prevent dementia. Their recommendations were to "be ambitious about prevention" including:

Early Life: Improving childhood education.

Mid Life: Stopping smoking and managing high blood pressure, obesity, and hearing loss.

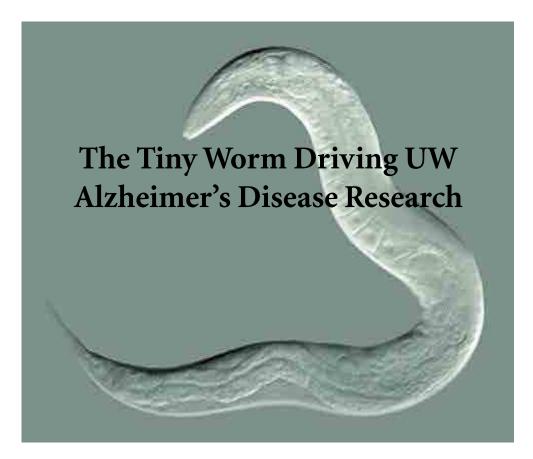
Late Life: Treating depression and diabetes. Maintaining social engagement.

However, the researchers didn't look at sleep, alcohol use, air pollution, or diet. Interestingly, the commission identified **hearing loss** as a modifiable risk factor for dementia. They speculate that the reasons for the association could be that hearing loss "might add to the cognitive load of a vulnerable brain or lead to social disengagement or depression," or even could accelerate atrophy of the brain itself.

More can be found here: http://www.thelancet.com/commissions/dementia2017



Dr. Angela Hanson



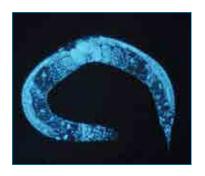
Powerful." "Fantastic." "Cute." "Rad." "Far out." This is how UW ADRC researchers have been overheard talking about the *Caenorhabditis elegans* roundworm. Why do they love this 1-mm creature?

First, scientists find these little worms to be a valuable model to study aspects of human diseases, such as Alzheimer's. *C. elegans* has intestines, muscles, a pharynx, and a simple nervous system of 302 neurons, compared to our 100 billion. Because the body is transparent, researchers can use a light microscope to look at any tissue they want at a 200-nm resolution, which is enough to observe physiology in living detail.

To make a worm model of neurodegenerative disease, researchers insert a gene that triggers the worm's genome to express one of the toxic proteins related to Alzheimer's disease in humans—including tau, amyloid beta, TDP-43, or alpha synuclein. The toxicity of these proteins probably plays out similarly in *C. elegans* because much of the cellular machinery for processing proteins is similar across all animal species. The worms develop paralysis, delayed swallowing, and other 'phenotypes' of disease.

Researchers can use these worm models to quickly screen for any genes or compounds that modify the toxic effects of these pathologies or progression of diseases in the worm—a step towards finding therapeutic targets in humans.

Here is a tour through the different ways that worms play starring roles in ADRC-related projects in UW Medicine's Department of Pathology and the Department of Geriatrics & Gerontology.



Exosomes are nano-sized packages, called vesicles, floating around many cell types, including neurons. They are like text messaging for cells, carrying genetic signals and proteins to distant areas of the body. They also scoop up waste in neurons, such as amyloid beta peptides, and clear it out. However, some scientists strongly suspect that some exosomes may spill some of their toxic cargo, contributing to the spreading of Alzheimer's disease pathology in human patients.

The Kaeberlein Lab and collaborators are developing the simple round-worm, *C. elegans*, as a model to study how toxic Alzheimer's disease-related proteins affect exosome function.

Through a collaborative effort with the groups led by Dr. Michael MacCoss in the UW Dept. of Genome Sciences, Dr. Dirk Keene in the UW Dept. of Pathology, and Dr. Alexander Mendenhall in the UW Dept. of Pathology, they uncovered that these worm vesicles act much like human exosomes. Their studies to date indicate that exosomes in Alzheimer's disease-model worms also package up toxic proteins and send them out of neurons. This project was selected for a talk at the 21st International *C. elegans* meeting in June.

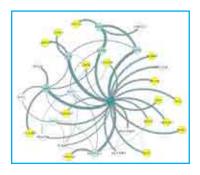
The Kaeberlein Lab's Dr. Josh Russell and his collaborators in the ADRC Neuropathology Core use biotechnology to detect Alzheimer's pathology in exosomes from worms and samples of cerebrospinal fluid from human patients. One laser-based tool, flow cytometry, suspends cells in a stream of fluid and passes them through an apparatus for counting or analysis. Ultimately, they want to find out if exosomes could be used in early diagnosis and treatment.



In healthy *C. elegans*, exosomes do something interesting. During the molting process, the worm's skin cells bubble out exosomes, which then assemble into three stripes on each side of the worm's body. Dr. Alex Mendenhall in the UW Dept. of Pathology says they look like "racing stripes" on a sports car.

In research stemming from an ADRC-funded project, the Mendenhall Lab team found that worms producing toxic proteins don't form the racing stripes correctly. Other labs have observed this as well. Sometimes the stripes are absent, and sometimes they look strange—"like someone spilled the ink for the racing stripes," says Mendenhall. This suggests that the Alzheimer's-related proteins mess up exosomes' ability to lay down the stripes.

This finding is exciting because they now have a phenotype of disrupted exosome function. They can screen for genes that have an effect on this phenotype. They will then knock out promising candidate genes in their worm models of Alzheimer's disease, to see if symptoms get better or worse. This critical knowledge could point to ways to intervene in exosome biology to delay the progression of Alzheimer's disease.



Think "multidisciplinary" is just an academic buzzword? ADRC researchers made a big discovery using bioinformatics, *C. elegans* worms, and postmortem human brains.

Dr. Shubhabrata Mukherjee, a statistical geneticist and Research Assistant Professor, UW Department of Medicine, used a systems biology computational approach to identify a network of genes involved in Alzheimer's risk. The hub gene—or the gene with the highest degree of connections to other genes within the network—was UBC, a key gene in the ubiquitin pathway known to repair DNA.

Drs. Matt Kaeberlein and Josh Russell validated that UBC is linked to Alzheimer's disease in their *C. elegans* worm models. And collaborators in the Ertekin-Taner lab at Mayo Clinic Jacksonville found reduced levels of UBC expression in those from people with Alzheimer's disease. They conclude that UBC is an organizing member of this gene network, which may show decreased activity in people who eventually develop Alzheimer's disease. The hope is that a therapeutic could target the ubiquitin pathway.



What initiates the early phases of neurodegeneration and its progression through brain cells? Research led by Dr. Brian Kraemer, Research Associate Professor in the UW Medicine Division of Gerontology, found new evidence that enzymes called kinases are integral to FTLD-TDP-43 disease progression in *C. elegans* worms.

Dr. Kraemer, along with Dr. Nicole Liachko, Acting Assistant Professor, and Laura Taylor, Graduate Research Associate, are working to understand why phosphorylation of TDP-43 goes wrong. "If we could ever prevent that modification, we would prevent these diseases from happening in the first place," says Taylor.

Kraemer's group has received new funding from the National Institute on Aging (NIA) for a project to study the role of the tau protein in Alzheimer's disease, using a variety of model organisms of tau toxicity, including *C. elegans* worm, mouse, and human cells. Specifically, the grant allows the team to continue studying how the sut-2/MSUT2 gene controls tau aggregation and toxicity, and therefore determines a cell's vulnerability to tau pathology. This knowledge may provide a novel candidate therapeutic target for pharmacological intervention.



Contact Information

- UW Alzheimer's Disease Research Center: 206.744.0588
- For a list of all UW ADRC Clinical Trials & Studies, please visit: depts.washington.edu/mbwc/research/clinical-trials
- Visit the NEW UW ADRC website: uwadrc.org
- Visit the ADRC's partner website: depts.washington.edu/ mbwc (UW Memory and Brain Wellness Center)

Support the Alzheimer's Disease Research Fund

Donations help support patient- and family-centered care, research breakthroughs in Alzheimer's-type dementia and related disorders, and the training of tomorrow's physicians. And by giving — perhaps in gratitude for care, or in memory of a loved one — you can help improve the lives of your friends, your family, and others in your region.

If you would like to be our partner in enhancing health and changing lives, please contact the UW Medicine Advancement Office at 206.543.5686. To donate online, please visit www.supportuwmedicine.org/adrc.



Native Knowledge

Addressing Brain Aging and Alzheimer's Disease in American Indian and Alaska Native Communities

The National Alzheimer's Coordinating Center stores all clinical data and brain tissue that 30 Alzheimer's Disease Centers (ADCs) around the country collect from study participants. Scientists rely on this rich research resource; however, it includes very little information about American Indians and Alaska Natives. As a result, researchers lack rigorous knowledge about the burden, risk factors, and social, economic, and health consequences of Alzheimer's and related conditions in Native populations.

"The reasons for this massive underrepresentation have to do with disparities in health, education, and socioeconomic conditions that limit access to a diagnosis of memory loss and participation in research," says Dr. Astrid Suchy-Dicey, an epidemiologist at Washington State University and project lead of the UW ADRC Satellite Core.

Now, a group of health disparities researchers from the ADRC are working to solve that problem. The effort, led by Dr. Suchy-Dicey and ADRC Satellite Core Principal Investigator Dr. Dedra Buchwald, both investigators with Washington State University's Partnership for Native Health group, builds on a decades-long investment in designing health research infrastructure in Native communities.

It all started in 1988, when the National Heart, Lung, and Blood Institute funded the Strong Heart Study, the most extensive examination of cardiovascular disease in more than 4,500 American Indians from 13 tribes across three geographic regions of the U.S. Surviving members of the study cohort have participated in many subsequent examinations, including the Cerebrovascular Disease and its Consequences in American Indians study. In this study, participants undergo cognitive testing, questionnaires, MRI brain scans, and genetic testing at two time points. For the study's second time point, some of those participants are returning for further tests related to vascular brain disease, Alzheimer's disease and cognitive decline.

"They are heroes," says Dr. Suchy-Dicey of the American Indian elders who still participate in the study. By now, they are all over 70 years of age and must overcome physical challenges, long distances, and frequent bad weather traveling to local brain imaging centers. But for many participants, the extensive research sessions don't get in the way of two decades of participation in research.

The data that Drs. Suchy-Dicey and Buchwald are collecting will comprise the first-ever longitudinal study of cardiovascular disease and Alzheimer's disease in American Indians, which will allow researchers to better evaluate the prevalence and major modifiable risk factors for cognitive impairment and dementia, and ultimately, to suggest ways to address disparities and promote healthy aging.

CThey are heroes."

"This is a landmark study that represents the cooperation of many widely separated communities and researchers that is a wonderful example of community-based research," says Dr. Buchwald. "Using the information collected to date, we are already developing interventions to prevent cerebrovascular disease among our tribal community members."

Dave Baldridge (Cherokee) is the Executive Director of IA2 International Association for Indigenous Aging, a non-profit in New Mexico working with tribal councils and stakeholders to devise progressive solutions for issues facing aging Native communities. "I've long considered Dedra Buchwald the leading voice for Native American health," he says, "and I'm delighted that her team is interested in these issues, given the underfunding and lack of emphasis on elders and mental health in the services provided by the Indian Health Service."

The ADRC Satellite Core team has already made some key observations. The current cognitive measures used to detect memory loss, standardized across ADRCs, were originally derived and validated based on primarily white middle-class populations. Because American Indian elders have unique language, cultural, and educational backgrounds, researchers must adjust some of the traditional measures of cognitive performance to accurately identify impairment due to a neurodegenerative disease.

Fortunately, the team thinks the longitudinal cognitive and health data they are collecting will be able to detect rapid loss of cognitive function over time in the the Strong Heart Study cohort. They aim to establish a 'proxy' gold standard of detecting memory loss and





Dr. Dedra Buchwald

Dr. Astrid Suchy-Dicey

dementia for their study population. They hope their work will improve the National Institute of Health's testing toolkit for underserved minorities.

Under the guidance of Dr. Buchwald, Dr. Suchy-Dicey spends most of her time on this project. This enormous effort entails coordinating between the many different partner institutions, the Indian Health Service, tribal councils, site recruiters, and local hospitals and radiology centers. She and a research coordinator deal with complicated budgets and data ownership concerns that arise from working with sovereign tribal entities.

"If you imagine doing a research project involving several independent European nations, you might get some idea of what complexity is involved," she says. Fortunately, they benefit from pre-existing research structures and good relationships with the Native community leaders.

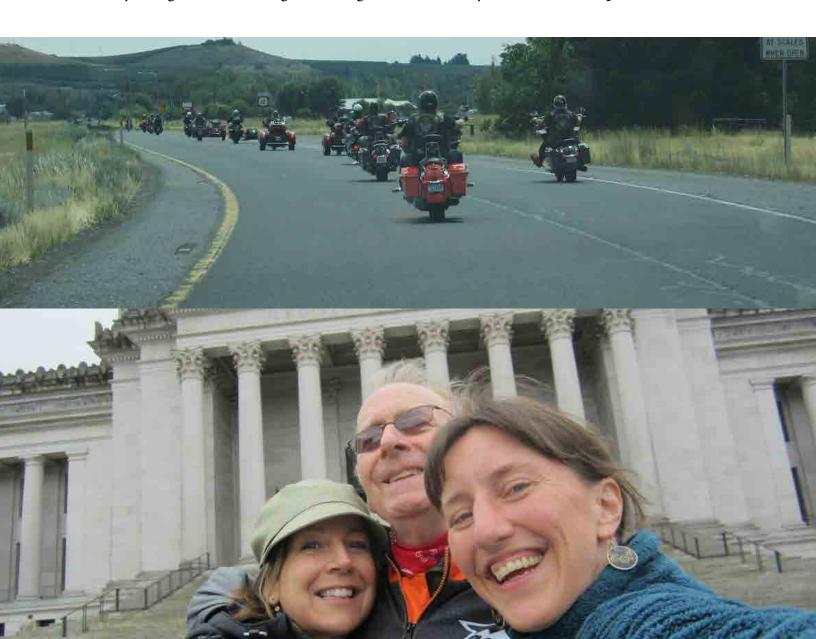
"I think one of the major strengths of the Strong Heart Study is that the team has been very serious about incorporating community perspectives, consulting with community advisory boards, and including investigators who are Native themselves," says Suchy-Dicey. "The Strong Heart Study's strong research ethics and mutually-respectful community partnerships have driven the success of this work in the ADRC Satellite Core." •

- >Jump to Page 23 to learn about the ADRC's outreach to local native communities and their clinics!
- > Photo Credit: Partnerships for Native Health/ Strong Heart Stroke Study



Adventure, Advocacy and Building Awareness: This summer's Ride4Alzheimer's motorcycle tour

By Marigrace Becker, Program Manager for Community Education and Impact, MBWC



"I want to help a lot of people." - Don Reddington

It was the morning of the 4th of July, in Twisp, WA, and my first time meeting Don Reddington. Diagnosed with Alzheimer's several years before, he had written a series of articles about his experience for the Methow Valley News. Now, he and his daughter Donni were taking this advocacy to the next level: riding side-by-side in motorcycle and sidecar, stopping for rallies in six cities across the state to encourage others with dementia and their loved ones. As Program Manager for Community Education and Impact for the UW MBWC, I would accompany them for the next 10 days, driving a support vehicle and sparking interest in dementia-friendly communities along the way.

"For Don, it's all about encouraging other people who have dementia," Donni told me. "He wants people to know that there is life beyond diagnosis. You can find ways to cope and make the most of each day."

Starting with the 4th of July parade in Twisp, we made a full circle around the state, touching down in Bellingham, Seattle, Olympia/Lacey, Yakima, Spokane and Wenatchee. At these stops, local partner organizations hosted rallies – including food, music, and presentations - for people with dementia, their loved ones, and all who support a dementia-friendly community. While Donni shared stories from the road, I discussed the state's Dementia Action Collaborative and our efforts to build dementia-friendly communities, and the host reviewed local resources for people with dementia. Meanwhile, Don mingled and connected with people one-on-one, sharing his experience and insights.

"It was really exciting to see it all come together!" said Donni. "The hosts were amazing. At each rally, I felt overwhelmed with joy!"

Each event had its own flair – in Bellingham, the Alzheimer's Society of Washington hosted us at Boundary Bay Brewery, with live music on the patio overlooking the Puget Sound. At Lacey Senior Center, the rally kicked off with Zumba dancing in the parking lot. Over in Yakima, hosts Doug Ellison and Doug Scott organized the Eagle Riders and other local motorcycle groups to escort Don and Donni into town.

While the tour was not without its challenges – the motorcycle broke down after summiting the first mountain pass! – it was ultimately very uplifting. A few moments stand out.

One such moment took place at Walkabout Creek Tavern in Naches, as the first of the Eagle Riders escorts pulled into the parking lot. For all their rough exteriors – black leather, skulls and cross-bones, tattoos and grizzled beards – these riders had some of the biggest hearts of anyone we met along the way. Immediately embracing Don as "brother," they clapped him on the shoulder and presented him with an honorary shirt from their group. Bonding over shared experiences in Vietnam, Don quickly became part of the crew. He remarked later, "I really got a kick out of those guys!"

Another highlight came midway through the rally at Seattle's Greenwood Senior Center. Although he hadn't planned on speaking, Don felt compelled to spontaneously step up to the microphone. He began by asking social worker Carin Mack to read a quote from his articles: "Although some days are better than others, my goal is to enjoy life and remember that 'Life is good." **Next Page...**



For the next 30 minutes, he shared his perspectives on living with dementia – from the challenge of people leaving him out of conversations, to the value of family support, and the practical ways he'd been there for another friend with Alzheimer's – going on walks with him, bringing over his dog for his friend to enjoy, or simply spending time together. As he finished his powerful message, applause rang out.

In the days to come, Don often reflected back on that rally and the impact he was able to have. "I'll never forget that time," he said. "With my Alzheimer's, it's hard to talk like that! I cannot believe how well it went."

As the tour came to a close, we pulled into Wenatchee's Pybus Market for the final rally. Surrounded by friends and family eager to swap stories and snap photos, we had successfully reached the finish line. "The trip was a gamble," said Donni. "I wasn't sure how each day would play out, or if we'd be able to finish it. But we did it!"

With over 200 people attending rallies, TV news pieces in both Seattle and Yakima, and various individual conversations along the road, the Ride4Alzheimer's certainly accomplished its goal of encouraging people with dementia and their loved ones across the state.

"It had a big impact up here in Bellingham," said Jan Higman, executive director of the Alzheimer's Society of Washington. "Everyone loved listening to Don's story. And his articles he left behind – they have been flying off the shelves!

Lynne Korte with the state's Aging and Long Term Support Administration agreed: "It was great having the Ride4Alzheimers come through Olympia. The Washington State Plan to Address Alzheimer's Disease and Other Dementias calls on all of us to play a role in creating more dementia-friendly communities. Don and Donni are doing just that, showing us all it's possible to live well with dementia."

Back in Twisp for the celebration dinner after the 10 days, 1500 miles and 6 rallies I asked Don about his favorite part. "All of it!" he said with a smile. "And I think it's going to become a bigger thing!"

With all the people who were impacted along the way, and the growing commitment to building dementia-friendly communities in Washington State, I couldn't agree more. •



Marigrace Becker, MSW, is the Program Manager of Community Education and Impact at the UW Memory and Brain Wellness Center. You can find MBWC's community events, educational programs, news, memory loss handbook, and more resources at the following link: www.depts.washington.edu/mbwc/

Native Knowledge: ADRC Reaches Out to Local Puget Sound American Indian Communities and Clinics

In an ambitious collaboration between the ADRC's Outreach & Education Core (ORE) and WSU's Partnerships for Native Health (P4NH), researchers are focusing on American Indian and Alaska Native communities in the local Seattle area and tribally operated land in Washington State. The project aims to address the lack of information about brain aging and dementia, culturally responsive clinical care, and avenues to research participation.

Project leader Meghan Jernigan (Choctaw Nation of Oklahoma), a staff scientist at P4NH, wants to open a dialogue, in hopes of building an understanding of the knowledge, attitudes, and cultural beliefs about dementia within Native communities. At local pow wows, she has administered over 400 surveys to assess basic knowledge about Alzheimer's disease and dementia, such as risk factors, caregiving, treatment management, and feelings

about research and brain donation.

"We noticed that folks are not entirely familiar with the medical terms of dementia," says Jernigan. "But,

that's not very surprising. When we performed resource inventories of clinics serving Native populations, we found that none of them offered pamphlets or informational material about dementia."

Already, the ORE Core team has created brochures and a series of wall posters for local clinics, in collaboration with the Alzheimer's Association and the Seattle Indian Health Board. Jernigan regularly visits local clinics to ask about the need for these resources, and finds many opportunities to distribute them.

"We want get people talking about dementia and why is it an important health issue for families and the public. Ultimately, we would like to make basic

public health improvements, such as increasing peoples' access to appropriate screening at the right time and linking them with resources. We want folks to feel as though they know what questions to ask their primary care providers."

In tandem, Dr. Kimiko Domoto-Reilly, Principal Investigator of the ADRC's ORE Core and neurologist

> at the UW Memory and Brain Wellness Center, is working to develop dementia care training programs for the staff at clinics serving Native communities.

"We want to educate care providers, so that they are able to make diagnoses, but also offer answers for families who ask What's next?," says Dr. Domoto-Reilly. To do so, the ORE Core will design an educational and training module for clinicians, with help from UW Medicine's

Drs. Kristoffer Rhoads and Barak Gastner.

The ORE Core also wants to understand why people from Native communities don't participate in Alzheimer's disease research studies or brain donation. ADRC researchers have long tried to increase the

diversity of their clinical cohort in order to learn about the factors of risk, and also resilience, unique to these communities.

In collaboration with the ADRC's neuropathologist Dr. Dirk Keene, the team is developing a scientific presentation tailored for patients at community clinics serving native communities. The presentation offers basic facts about

Alzheimer's disease research, as well as a sense of what it means to participate in longitudinal clinical studies and brain donation.

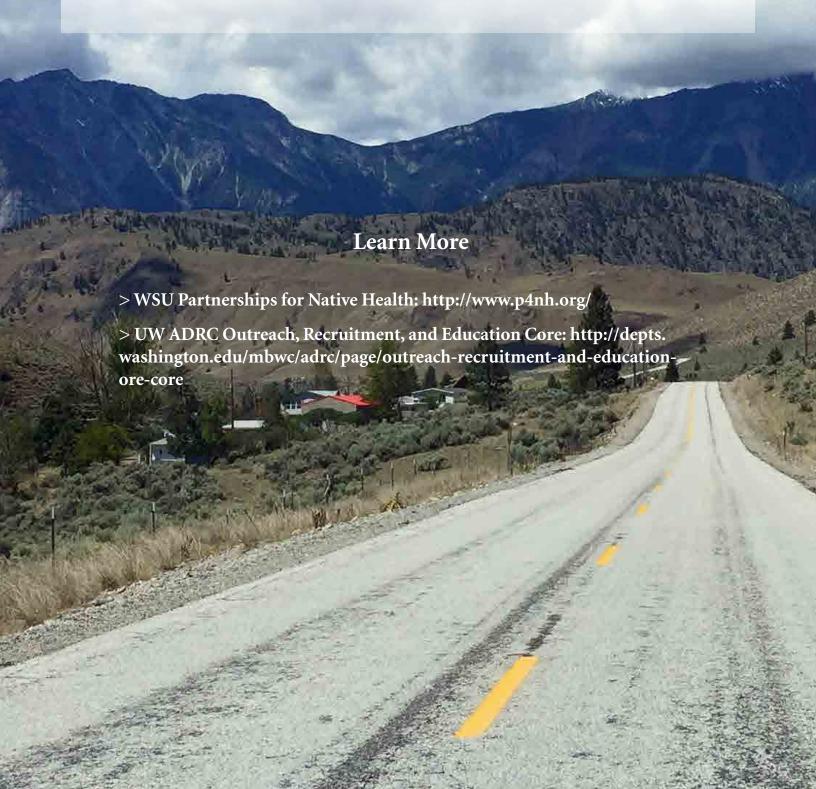
Dr. Kimiko Domoto-Reilly

Meghan Jernigan

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Afterwards, they will conduct focus groups to unpack what the attendees think about the science. They hope to explore the unique concerns that may influence decisions around brain donation, such as conflict with cultural norms and expectations about what to do with the body of a loved one after death.

"We want to communicate that the more diverse the pool of research participants, the closer we will get to cures that can work for everyone," says Jernigan. "Through the focus groups and our dialogue with the community and tribal leaders, we are hopeful that we can identify the points of disconnection and work to build partnerships." •



Garden Discovery Walks

Savor the season and explore nature with others living with memory loss and family and friends



First Fridays, 10 a.m. – 12 p.m.

FREE!

Locations subject to change

Sept 1: Rainier Beach Urban Farm

Oct. 6: Historic Dunn Gardens, Broadview

Nov. 3: Seattle Japanese Garden, Arboretum

Enjoy a walk through a Seattle public garden, followed by a creative, nature-inspired project led by a horticulture therapist. Light refreshments provided, bring a bag lunch (optional).

Pre-registration required:

Cayce Cheairs, (206) 615-0100, cayce.cheairs@seattle.gov

Offered in partnership:







Garden Walkers Reflections on the Garden Discovery Walks

By Genevieve Wanucha

Gardens, from the rhododendron glen at the Arboretum, to the smallest oasis of nature on a city roof, are places that tell stories. They tell stories without words but rather in a language everyone knows. They talk in sensory flourishes of color, scent, and textures as soft as the flimsy silk of a poppy petal and as prickly as a borage stalk. They tell us in uncomplicated terms of renewal and impermanence, and the value of good soil. The gravel paths tell us how the garden's creators had hoped we would travel through.

Gardens tell us our own stories, by bringing back our earliest memories of nature, of tying dandelions into chains or pulling at blackberry bushes. In fact, Patty Cassidy, president of the Portland Memory Garden, says the staff intentionally plants red geraniums, daisies, and marigolds because, for some reason of history, those are the flowers that trigger memories for people who were children seven decades ago, and now live with dementia.

Every first Friday, a public garden in Seattle turns into this kind of sanctuary. The Garden Discovery Walks, a partnership of Seattle Parks & Recreation and the UW Memory and Brain Wellness Center, is a free program for people with memory loss or dementia and their partners. The group takes an exploratory tour through a garden or community P-Patch, followed by a creative nature-inspired activity.

Our first walk took place on March 3, 2017 in the display gardens of the UW Center for Urban Horticulture, where the heather buds and hellebores tuned

us into the early signs of spring growth. By now, we've visited six gardens, ranging from Magnuson Park P-Patch with its flowering quince trees, to Wallingford's Good Shepherd community garden, where one gardener taught us about compost and another picked us bouquets of her alstroemeria lilies. Yet, for the Garden Discovery Walkers, horticultural terminology matters not a whit.

"You know, I can't go around calling that a whatchamacallit, and that a wing doodle," said participant Roger Stocker, looking at rose bush—still just thorny branches in March. "But I am seeing this as it is, in the moment."

"In the garden, we are more aware of our place within the environment and ecosystem," says Cayce Cheairs, Dementia-friendly Recreation Specialist of Seattle Parks and Recreation, who co-facilitates this program. "This sense of relationship and place brings a needed sense of belonging to something larger and affirmation of self that are often threatened by the social stigma of dementia."

The other co-facilitators are Cheryl Petterson, a garden expert who oversaw the design of Bradner Gardens Park with King County Master Gardeners; Laura Rumpf, a certified horticultural therapist; and me, the science writer at the UW ADRC, who loves plants and participating in Seattle's dementia-friendly community.

At the start, we gather into a circle and turn our eyes to the 'flower of the month' specimen. We talk about what we notice upon close, mindful inspection, often suprised by a common flower's suddenly obvious majesty.

This time provides an opportunity to share an opinion, without expectation or judgment. One participant named Jim said but a few words in the circles, until June's visit to Bradner Gardens. Of a smoke bush trimming, he said a "tree growing out of a lily

"This sense of relationship and

place brings a needed sense of

belonging to something larger

and affirmation of self that are

often threatened by the social

stigma of dementia."

pad"; of the nasturtium at July's visit to the Good Shepherd garden, he saw within it "a sun setting against a red sky."

Garden Walk participants Frank Stone and his wife Susan met in a hiking organization. Susan remembers how Frank would carry a reference

book along on hikes in the Olympics and Cascades to identify plants. He now has dementia, though it hasn't impacted his love of walking in nature. In fact, he pushes his walker up inclines and over pebbles and stones on the garden paths, moving as fast as anyone.

"On these walks, Frank benefits by being out in the fresh air and getting some exercise early in the day and from being in a supportive and small group of people," says Susan. "I love the walks as a way of visiting parks and gardens that are delightful and new to me."

From poet Henry David Thoreau to 18th century physicians, many have noticed the restorative quality of being in nature. Florence Nightingale wrote in her 1859 Notes on Nursing, "It is the unqualified result of all my experience with the sick, that second only to their need of fresh air is their need of light ...Put the pale withering plant and human being into the sun, and...each will recover health and spirit."

Nurse Nightingale would surely appreciate the idea of horticultural therapy for people with memory loss and dementia. Its practitioners, such as Laura Rumpf, the horticultural therapist who designs the nature-based crafts for our walks, support the bold idea that working with plant materials in a social setting can specifically be a treatment for dementia,

as it encourages conversation and self-esteem, reminiscence, and creativity, and taps into intact motor skills.

In fact, a research study started by the Friends of the Boerner Botanical Gardens in Milwaukee County found that participants with Alzheimer's disease showed increases in social interaction with peers, self esteem, engagement in activities held at their

care facilities, interest in the future, and awareness of their environment, after eight sessions of horticultural therapy.

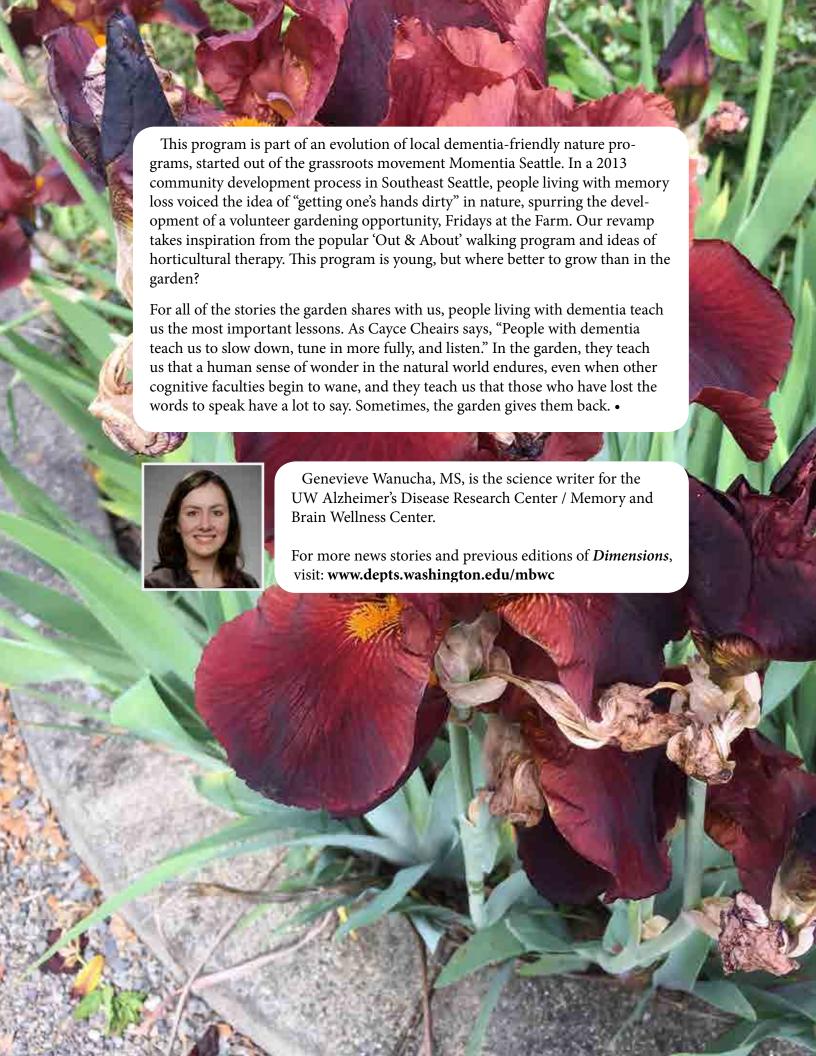
"Is it do-able?" Frank asked as Laura Rumpf brought out terracotta bowls of mint-scented geraniums, clippers, a bucket of soil, and watering can. "Yes, it sure is

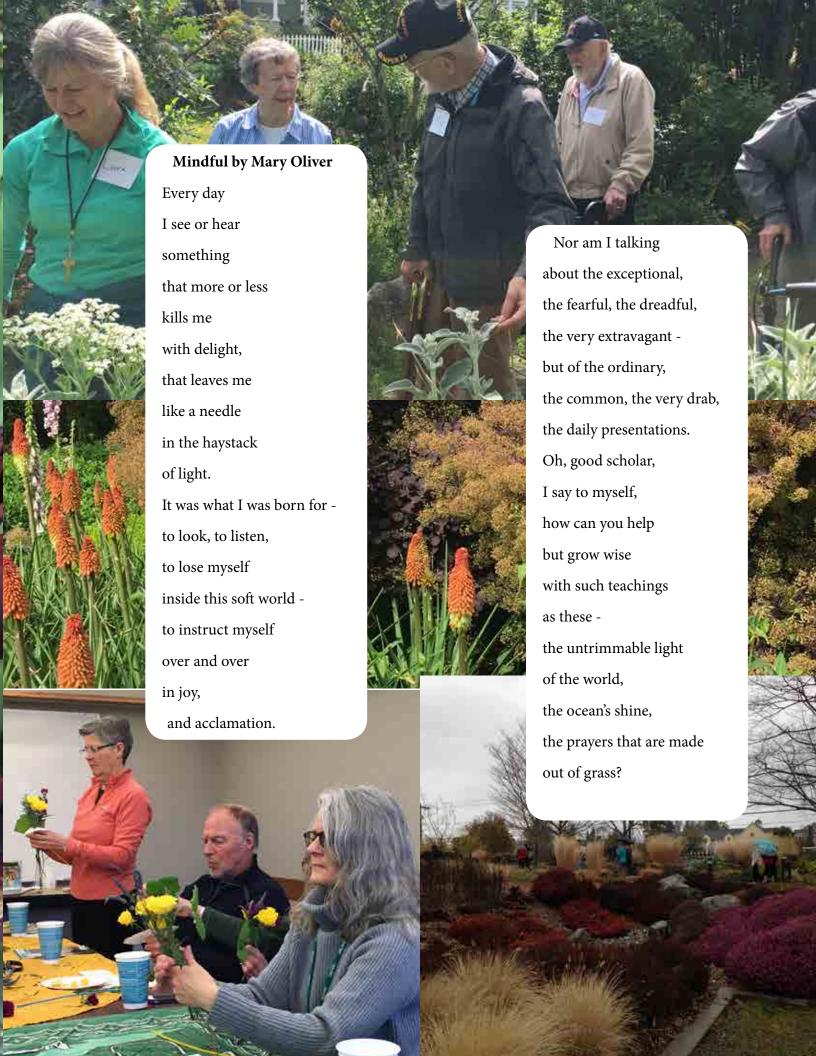
do-able," she said, and showed us how to pot cuttings of these plants to bring home and watch take root and grow. We made beautiful wreaths out of the invasive bindweed in Rainier Beach Urban Farm & Wetlands. We painted ink on homemade paper using bamboo brushes at West Seattle's Chinese Garden.

"Horticultural therapy is particularly effective for those living with memory loss because the familiarity of plants and the use of natural materials inspires reminiscence, joy and creativity while calming feelings of confusion and isolation," says Rumpf.

Time in the garden can also help care partners and family members deal with stress and worry. "Being in nature has always been my most effective de-stressor," says co-facilitator Cheryl Pettersen. "The walks provide a wonderful mix of serenity, discovery, and inspiration." In a 2015 study, Stanford scientists found that people who took a nature walk, compared to a city walk, experienced reduced rumination, or those really bad feelings when you mull over and over a problem or mistake. Brain scans revealed a calming effect on the neural pathways of negative emotion.

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