

Toward Precision Medicine, January 9, 2017

Dr. Matt Kaeberlein, PhD, Professor, UW Department of Pathology, ADRC Project 1 Leader. *Preventing Alzheimer's disease by targeting the hallmarks of aging.*

Dr. Matt Kaeberlein shared his perspective on Alzheimer's disease as a disease of aging. Aging from 40 years to 85, the largest risk factor for AD, hasn't been a focus of AD clinical research because of the traditional view that aging is not malleable. To counter this assumption, Kaeberlein pointed out that research has uncovered genetic, environmental, and pharmacological compounds that modify the aging process in lab models and humans (metformin). He is now pursuing the use of these modifiers of aging to prevent or slow AD progression.

Kaeberlein's talk focused on the FDA-approved drug rapamycin, the best example of a drug that definitively increases lifespan in every lab model system. He has found that, for mice, rapamycin seems to improve all the tested measures of health during aging, including reduced rates of cancer, obesity, improved cognitive function during the normal aging process, and delayed aging. His study published in *E-life* shows that a 3-month treatment from 20-23 months of age is enough to increase life expectancy after treatment by 60%, suggesting that starting the treatment in middle age is enough to give a significant increase in lifespan, at least in mice. Rapamycin improves cardiac function in dogs and the immune response to the flu vaccination in elderly humans.

Kaeberlein posed a big question: Why isn't there a clinical trial of rapamycin in AD? Rapamycin is available in generic versions and the side effect profile, known from its use in transplant recipients, has been tolerable for transplant recipients. He thinks that there could be a lack of communication between basic scientist and clinicians and a general lack of appreciation of rapamycin studies.

In the group discussion, attendees discussed the possible barriers to a rapamycin clinical trial for AD prevention. They pointed out a hurdle in identifying the proper population of study participants at a manageable cost. Specifically, because researchers would want to start rapamycin as early as possible in aging adults, the trial would be difficult to differentiate from an anti-aging trial considering that rapamycin acts on mechanisms of aging.

As the discussion into the field's current challenges continued, Kaeberlein noted that the AD research falls down in its reliance on testing therapies in young mice. He said he doubts that rapamycin could restore function in older mice. These findings may not hold relevance to questions about how the aging human brain would respond to rapamycin.

He also gave an update on his lab's use of the *Caenorhabditis elegans* roundworm as a biological model system for investigating Alzheimer's proteinopathy. These worms are genetically manipulated to express the human amyloid beta protein or tau, and they eventually become paralyzed by the toxic effects of these proteins. His lab team is testing out a new robotic system to screen for modifiers of toxicity in these worms. In the short term, postdoctoral associate Josh Russell will finish characterizing the transgenic lines and study extracellular vesicles.