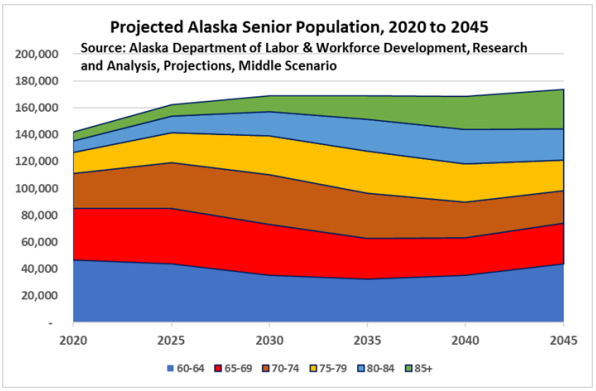
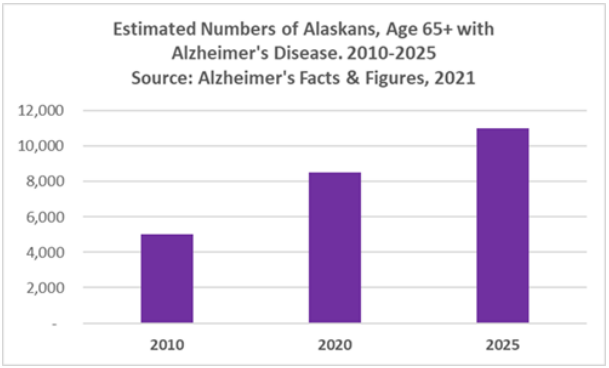
UA Center for Transformative Research in Metabolism (TRiM): Translating Hibernation Research to Improve Human Health, Adding Life to Years

What is the compelling need for research focused on age-related diseases?

- Older adults, the fastest growing age demographic in Alaska and on the planet, are at risk for frailty and age-related diseases attributed to chronic metabolic health disorders. Stroke (#5), diabetes (#8), and Alzheimer's disease (#9) are the leading causes of death for Alaskans age 65+ (CDC National Center for Health Statistics, Stats of the State of Alaska).
- Alaska is the state identified having the top senior growth rate in the U.S. that increased 72% over the last decade (2020 Profile of Older Americans, Administration on Aging). In 2020, Alaska's 60+ population totaled 142,099, projected to increase by more than 30,700 by 2045 at which time, 21% of the state's population will be seniors. Persons age 85+ will be the fastest growing age segment of the older Alaskan population requiring medical intervention and daily supports (Alaska Department of Labor & Workforce Development, Research and Analysis, Middle Scenario; Alaska State Plan for Senior Services, FY2020 to FY2023).



- People age 65+ spend more on health care per capita than other age groups because they are most at risk for frailty, chronic disease, and cognitive impairments (Alaska State Plan for Senior Services, FY2020 to FY2023).



- Alzheimer's is the most underrecognized threat to public health because the burden is large and the impacts are significant for families and the public health care system. Alaska ranks #5 among states for a projected increase in the number of seniors, age 65+ with Alzheimer's disease, when the number of older adults with Alzheimer's is forecasted to climb 29.4%. (Alzheimer's Facts and Figures, 2021)
- Alzheimer's disease was the sixth leading cause of death in Alaska in 2019 claiming 131 Alaskans that year. (Alaska Division of Public Health, Health Analytics and Vital Records, 2020)
- Alaska Medicaid, the primary funder of long-term services and supports, paid $76 million to cover the cost of care for older Alaskans with Alzheimer's. Medicare paid $26,474 per beneficiary annually for Alaskans with dementia who received care in the Emergency Department and hospital re-admissions (Alzheimer's Facts and Figures, 2021).

What is needed to improve health care for Alaska's aging population? Innovative solutions to address metabolic disorders that underly many chronic diseases affecting older adults, threatening their ability to live independently as contributing members to their family and community.

- The UA Center for Transformative Research in Metabolism (TRiM) is an interdisciplinary biomedical research center at the University of Alaska funded through a five-year grant from the National Institutes of Health, National Institute of General Medical Sciences (P20GM130443) using the Centers of Biomedical Research Excellence (COBRE) funding mechanism.
- The Center, a collaboration between UAF (lead institution) and UAA (partner institution), employs arctic mammalian hibernating species as a comparative platform to study the metabolic extremes exhibited in

hibernation through pre-clinical and clinical research initiatives that connect hibernation discoveries to innovative treatments for metabolic disease and related disorders.

- Scientists at the UA Center for Transformative Research in Metabolism (TRiM) are working to identify the metabolic mechanisms underlying the physiological changes in mammalian hibernation to address metabolic disease and frailty including type 2 diabetes, cardiovascular disease, obesity, disuse muscle atrophy, sarcopenia, osteoporosis, and brain disorders associated with Alzheimer's disease and vascular dementia.
- Hibernation, a specialized metabolic adaptation, allows arctic mammals to conserve energy and withstand long periods of harsh environmental conditions as evidenced by the hibernating arctic ground squirrel and black bear. They modify their metabolic pathways to provide essential nutrients that build up muscle and other tissues during their long hibernating period of fasting and immobility and arouse in the spring with no negative effects. In this way, they completely avoid a cycle of malnutrition and inactivity that in humans would lead to frailty and the need for long-term nursing home care.

How can translating hibernation research be used to inform treatments that will improve human health?

- Alzheimer's Disease – Brains of hibernating mammals and Alzheimer's patients undergo similar structural and metabolic changes including increased hyperphosphorylation of the tau protein and hypoxia in brain tissue. Researchers have observed that unlike the Alzheimer's tau-produced tangles that appear in humans, these structures disappear among small mammal hibernators and the process is fully reversed upon arousal.
- Vascular Dementia – In humans, stroke is the result of reduced blood flow and oxygen to the brain causing death of brain cells that may lead to vascular dementia. In contrast, small hibernating mammals are highly resistant to hypoxia and glucose deprivation and utilize these conditions to stimulate neuron regeneration, based on electrophysiological analysis. TRiM scientists are working to identify molecular targets that when activated in response to limited blood flow stimulate neuron regeneration in the arctic ground squirrel. These molecular targets are being further studied to develop new therapies to treat vascular and other forms of dementia.
- Disuse Muscle Atrophy – Frailty and loss of muscle/bone tissue is a significant health problem for people in long-term convalescent settings. TRiM's scientists are working to identify the mechanisms in the post-transcriptional regulation of genes involved in the skeletal muscle metabolism of the arctic ground squirrel and black bear that promote protein production, and allow the animals to arouse fit and trim in the spring, without losing muscle.
- Canine Aging Model – In addition to using arctic hibernating mammals as a discovery platform, TRiM's researchers are using the sled dog/canine model as an intervention platform to test novel treatments to prevent or reverse brain aging. Because canines age faster, but with similar risks for cognitive dysfunction as humans, the canine platform returns clinically relevant results within months while a human trial could take years to demonstrate benefit. We are currently working with Neuronascent Inc., a biotech company to demonstrate that we have unique infrastructure, not available at larger institutions outside of Alaska, to support veterinary clinical trials. Once we demonstrate proof-of-concept for our capacity to conduct these trials we will test a novel treatment for canine cognitive dysfunction. Veterinary clinical trials will benefit our furry companions and, importantly, are stepping-stones to human clinical trials

TRiM's overall research goal is to use animal models, such as hibernation and canine cognitive dementia, to advance development of diagnostics and treatments that will reduce the incidence of chronic diseases related to metabolic disorders across the lifespan. Alaska has a special niche because of access to animals with unique adaptations and models that are not available at other research institutions.

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