National Institute of Aging

2021 Marmoset Community White Paper

The core mission of the National Institute of Aging (NIA) is to support and conduct genetic, biological, clinical, behavioral, and social research on aging. Common marmosets (*Callithrix jacchus*) share with other primates, including humans, many aspects of physiology, a complex brain organization, and sophisticated social and cognitive behaviors, facilitating translational research on human conditions. With an average lifespan of about 10 years and a maximum lifespan of 21, marmosets are also among the shortest-lived anthropoid primates. This characteristic makes them uniquely suited for studies of aging, as the dynamics of the aging process can be studied longitudinally throughout the entire lifespan, an approach not feasible in more long-lived primates. Thus, marmoset models of human aging have the potential to advance the NIA mission in multiple areas. First, the short lifespan of the marmoset provides the opportunity to track the progression of normal aging and age-related disorders and study their underlying mechanisms in order to achieve better prevention and prognosis. Interestingly, marmosets develop several age-related changes of specific relevance to human late-life phenotypes. For example, they exhibit age-related declines in basic biological markers, such as a decrease in lean muscle mass, that are similar to those observed in humans. They also show a marked age-related increase in cancers, amyloidosis, pathogenic tau accumulation, diabetes and renal diseases, typical of human late-life disorders. Many aspects of functional decline during normative aging in marmosets are also similar to those of humans, with marmosets exhibiting hearing loss as well as declines in cognitive and motor function with increased age. Aging is the greatest risk factor for many diseases including Alzheimer's Disease (AD), and understanding how age-related changes at both the system and cellular levels predispose the primate brain to these diseases will be critical to developing effective prevention and treatment strategies. Of particular interest, aged marmosets spontaneously develop β-amyloid deposition and tauopathies, both implicated in the pathogenesis of AD. Because the high rate of failure in AD clinical trials has been ascribed, in part, to the inadequacy of rodent models that recapitulate only limited aspects of AD pathology, these features of marmoset biology position the species as an excellent primate model for advancing our understanding of AD. In addition, advances in genetic engineering are leading to the generation of genetically modified marmosets as models for AD and other age-related neurodegenerative conditions, such as Parkinson's disease. Thus, the marmoset has substantial potential for the development of novel strategies to prevent and treat neurological diseases of aging. Moreover, because the marmoset is a highly social primate who forms long-lasting bonds and can be maintained in a social group in the laboratory, it should also prove particularly valuable to study social influences on the aging process and their impact on the pathogenesis of age-associated diseases. Finally, this short-lived primate offers the opportunity to test the safety and efficacy of interventions against age-related burden in a compressed time-frame relative to long-term studies in macaques or humans, thus allowing for the evaluation of specific interventions to extend human healthspan.

Breadth of research. Recent work in the marmoset has documented age-related changes in a wide range of biological systems (168), including the microbiome (169) immune system (170) and metabolome (171), likely to have important consequences for aging trajectories. At the CNS level, efforts are ongoing to characterize age-related changes in the marmoset brain (172, 173), associated changes in perception, cognition and motor function (174, 175), and their neuroendocrine mechanisms (176, 177). A rapidly growing area of research focuses on developing genetically modified marmosets to model AD (178), Parkinson's disease (11) and other age-related brain disorders (8). Capitalizing on the relatively short lifespan of the marmoset,

research evaluating the effects of pharmacological (e.g, rapamycin, (179) metformin and acarbose (180)) and environmental (e.g., exercise (181)) interventions on healthspan in this species is underway.

Future. Offering key advantages for aging research, the marmoset provides a unique model to advance our understanding of aging at multiple levels of analysis. Studies focused on the basic biology of aging will help elucidate how age-related changes in immune function, mitochondrial function, DNA damage repair and epigenetic processes may increase the brain's vulnerability to neurodegeneration. Complementary *in vitro* studies of marmoset neuron and astrocyte cultures (182) will enable better understanding of the basic processes involved in aging and neurodegenerative disorders. At the system level, advances in neuroscience techniques applicable to behaving marmosets, such as chemogenetics, optogenetics, 2-photon imaging, and high field functional MRI, will be critical to identify the neural changes that underlie perceptual and cognitive deficits in healthy and pathological aging. Longitudinal studies integrating behavioral, physiological and neural assessments in naturally aging marmosets, marmosets with induced pathology, and genetically modified models for neurodegenerative diseases will provide better tools for understanding the mechanisms underlying neurodegeneration and designing new treatment strategies with high translational potential to humans. The marmoset will also be an ideal animal model to study the effects of early life interventions (e.g., diet, caloric restriction) on the development of late-life diseases. Finally, the rich social behavior of the marmoset, now amenable to functional neuroimaging (108), will offer the opportunity to study the mechanisms by which social influences impact the aging process. Given the unique advantages of the marmoset model for advancing fundamental questions of human aging, we urge NIA to support aging marmoset colonies, to facilitate their distribution to Investigators and to support marmoset aging research.

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