National Institute of Aging

2019 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, developing the marmoset as a model for human aging has the potential to advance the NIA mission in a number of 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 a number of 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 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 an increase in abnormally phosphorylated tau, 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 aspects of marmoset biology position the species as an excellent primate model for advancing our understanding of AD. In addition, the development of genetically modified marmosets may lead to new 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 including, but not limited to, AD. 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 as a model 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 health span. The advantages of

marmosets for studies of age-related diseases have positioned this emerging model system to advance the core mission of the NIA.

Breadth of Current Research. Ongoing research in the marmoset investigates age-related changes in a wide range of systems and multiple levels of analysis (81). Several studies examine age-related physiological and structural changes in this species to understand how aging of the metabolome may increase diabetes and cardiovascular diseases risk (82) or to identify factors promoting osteoporosis resistance in females (83), for example. At the CNS level, much work is focused on characterizing normal age-related changes in the brain (15), perception, cognition, and motor function (84, 85) as well as the neuroendocrinology of these processes (81). A rapidly growing area of research focuses on establishing marmoset models for age-related brain disorders, including for AD, Parkinson's disease, Huntington's disease, multiple sclerosis, and stroke (86). Efforts are also ongoing to characterize the effects of pharmacological (e.g, rapamycin; (87)) and life-style (e.g., exercise;(88)) interventions on health span in this species.

The Future. Offering key advantages for aging research, the marmoset provides unique tools 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. 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. In addition, the development of genetically modified models for neurodegenerative diseases that apply recent revolutionary approaches such as CRISP/Cas9 gene editing will provide new tools for understanding the mechanisms underlying neurodegeneration and designing new treatment strategies with high translational potential to humans. Due to its short lifespan, 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 will offer the opportunity study the mechanisms by which social influences impact the aging process.

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