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Marmosets as a Translational Aging Model – Introduction

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Abstract

The life history of the common marmoset (*Callithrix jacchus*) points to this species as a premiere nonhuman primate aging model. In order to take advantage of these features, we require an expanded and refined understanding of aging in this species. The papers in this special issue move this field forward substantially by providing exciting new findings about the aging of the common marmoset and the potential this species offers for revealing aging's secrets and improving the lives of aging humans.

Humans have a fascination with the process of aging and it has long been noted that aging represents the single most important risk factor for the majority of chronic human diseases. As the Center for Disease Control (CDC) estimates that by the year 2050 the number of people over the age of 65 will double (Weir et al., 2015), studies to understand aging and develop interventions that may ameliorate its effects take on increased importance.

Studies of aging have largely focused on model organisms with extremely short life spans, such as yeast, *Caenorhabditis elegans*, and *Drosophila melanogaster*. Even in mammalian models, which are more closely related to humans, the focus has been on a species that has evolved a shorter than average life-span – *Mus musculus* (i.e. the mouse). These short-lived organisms have allowed for relatively rapid answers to many basic questions regarding aging, and they are particularly well-suited for longitudinal studies. However, they have limitations in how they inform us about primate – including human - aging. Therapeutics and interventions developed around the findings from short-lived animal models have a very high failure rate in clinical trials, creating a "translational gap" between human and animal studies (Cummings et al., 2014; Sabbagh et al., 2013). One possible reason for these failures is the phylogenetic distance and evolved differences between these short-lived model organisms and the lineage in which humans evolved, that being primates. Austad and Fischer (1992) proposed that focusing virtually all studies of anti-aging mechanisms in models which have demonstrably poor defenses against aging – i.e. species selected for short life spans – may provide an obviously biased view of aging overall (see also Miller, 1997; Ungvari and Phillips, 2011).

Primates have a longer than expected life span relative to mammals of similar body size. A useful tool to understand relative life span is the longevity quotient [$LS_{actual}/LS_{expected}$, with $LS_{expected}$ determined from least-squares linear regression of ln life-span (LS) versus ln

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adult weight for all mammals for which acceptable data available] with values < 1.0 indicating a shorter life span than expected relative to body size while values > 1.0 indicate a longer than expected life span. The average LQ for primates is 1.92 (Austad and Fischer, 1992), indicating that primates live almost twice the life span that would be expected for a mammal of similar body size. Studies of aging in nonhuman primates are challenged by these long life spans. The primate species most commonly used in translational research – macaques (genus *Macaca*), baboons (*Papio hamadryas*) and vervet monkeys (*Chlorocebus aethiops*) have maximum life spans that range from 30.8 to 40 years (http://genomics.senescence.info/species/). Because primates show the predicted relationship between body size and life span, there has been a developing interest in the use of the smallest primates to study aging. The smallest of the nonhuman primates are the mouse lemurs. The gray mouse lemur (*Microcebus murinus*) has a maximum life span of 18.2 years (http://genomics.senescence.info/species/), and there are studies that suggest the species displays age-related brain pathology that may be similar to the changes seen in Alzheimer's Disease (Bons et al., 2006; Mestre-Frances et al., 2018). However this species is rarely used in translational studies, with limited availability in captivity. In addition, mouse lemurs exhibit a marked seasonal metabolic pattern akin to a torpor or modified hibernation (Terrien, et al., 2018). While this is a fascinating phenomenon, in and of itself, it may raise issues regarding the mouse lemur's use as a translational aging model.

The common marmoset (*Callithrix jacchus*) is a small-bodied neotropical primate that is studied extensively in a broad arrays of research areas, including infection, vision, audition, social behavior, cognition, and reproduction (Carrion and Patterson, 2012; Kishi et al., 2014; Mitchell and Leopold, 2015; Miller, et al., 2016). There is a growing and intense interest in the potential of this species in the area of gene editing and transgenic production, related to its high fertility relative to other nonhuman primates (Sasaki, et al., 2009). The maximum life span recorded for the common marmoset is 22.8 years (http://genomics.senescence.info/species/), 57% of that of the rhesus macaque, but only 4.6 years longer than that of the less well-characterized and less available mouse lemur.

The life history of the common marmoset, combined with the growing body of research on this species in diverse research areas points to it as a premiere nonhuman primate aging model. In order to take advantage of these features, we require an expanded and refined understanding of aging in this species. To use the marmosets to understand aging, we must answer the following questions: What is an "old marmoset"? Can we manage marmosets in captivity so that we are witnessing aging? What does aging look like in a marmoset?

As studies of aging in marmosets began, there were suggestions that we did not yet have a good handle on what was "old" in a marmoset. As an example, timing of occurrence of amyloid accumulation in the brain varies in different marmoset colonies and this difference was associated with apparent differences in age-specific mortality, raising the fascination question of whether aging might be occurring at different rates in different colonies (Geula, et al., 2002; Ridley, et al., 2006; Tardif, et al., 2011). A 37% increase in the maximum reported marmoset life span in 2012 (Nishijima, et al. 2012), suggests that historical marmoset findings are affected by significant non-age-related mortality.

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One of the standard and highly valued aspects of an aging model is the ability to manage it in ways that minimize non-aging-related deaths (Miller, 1997). This minimization is generally established by some form of barrier housing that reduces exposure to infections and toxins, something that is difficult and exceedingly expensive to achieve with large-bodied, long-living Old World monkeys. Another benefit of the marmoset as an aging model is the potential to affordably maintain group-housed animals in such a barrier setting. Ross et al (2017) recently reported on demographic outcomes from such housing, finding that a barrier maintained population had significantly lower early adult mortality than the population from which it was derived. Therefore, populations of socially housed marmosets can be managed under barrier conditions to produce a better aging model

In the past decade, we have published three reviews of available findings on aging in common marmosets (Tardif, et al., 2011; Ross, et al., 2012; Ross, 2018). These reviews report findings on potential biomarkers that change with aging in marmosets in a fashion parallel to that observed in humans (e.g. serum albumin; beta-amyloid deposition in the brain). They also suggest areas in which the marmoset may be an aging model of particular interest, such as cardiovascular function, displaying increased blood pressure and arteriosclerosis with increasing age. However, they also point to the substantial limitations in our knowledge.

The papers in this special issue move this field forward substantially by providing exciting new findings about the aging of the common marmoset and the potential this species offers for revealing aging's secrets and improving the lives of aging humans.

References:

Austad SN and Fischer KE, 1992 Primate longevity: its place in the mammalian scheme. American Journal of Primatology, 28(4), pp.251–261.

Bons N, Rieger F, Prudhomme D, Fisher A and Krause KH, 2006 Microcebus murinus: a useful primate model for human cerebral aging and Alzheimer's disease?. Genes, Brain and Behavior, 5(2), pp.120–130.

Carrion R Jr and Patterson JL, 2012 An animal model that reflects human disease: the common marmoset (Callithrix jacchus). Current opinion in virology, 2(3), pp.357–362. [PubMed: 22709521]

Cummings JL, Morstorf T and Zhong K, 2014 Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's research & therapy, 6(4), p.37.

Geula C, Nagykery N and Wu CK, 2002 Amyloid-β deposits in the cerebral cortex of the aged common marmoset (Callithrix jacchus): incidence and chemical composition. Acta neuropathologica, 103(1), pp.48–58. [PubMed: 11837747]

Kishi N, Sato K, Sasaki E and Okano H, 2014 Common marmoset as a new model animal for neuroscience research and genome editing technology. Development, growth & differentiation, 56(1), pp.53–62.

Mestre-Frances N, Trouche SG, Fontes P, Lautier C, Devau G, Lasbleiz C, Dhenain M and Verdier JM, 2018 Old Gray Mouse Lemur Behavior, Cognition, and Neuropathology In Conn's Handbook of Models for Human Aging (Second Edition) (pp. 287–300).

Miller CT, Freiwald WA, Leopold DA, Mitchell JF, Silva AC and Wang X, 2016 Marmosets: a neuroscientific model of human social behavior. Neuron, 90(2), pp.219–233. [PubMed: 27100195]

Miller RA, 1997 When will the biology of aging become useful? Future landmarks in biomedical gerontology. Journal of the American Geriatrics Society, 45(10), pp.1258–1267. [PubMed: 9329491]

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Mitchell JF and Leopold DA, 2015 The marmoset monkey as a model for visual neuroscience. Neuroscience research, 93, pp.20–46. [PubMed: 25683292]

Nishijima K, Saitoh R, Tanaka S, Ohsato-Suzuki M, Ohno T and Kitajima S, 2012 Life span of common marmoset (Callithrix jacchus) at CLEA Japan breeding colony. Biogerontology, 13(4), pp.439–443. [PubMed: 22752736]

Ridley RM, Baker HF, Windle CP and Cummings RM, 2006 Very long term studies of the seeding of β-amyloidosis in primates. Journal of Neural Transmission, 113(9), p.1243. [PubMed: 16362635]

Ross CN, Davis K, Dobek G and Tardif SD, 2012. Aging phenotypes of common marmosets (Callithrix jacchus). Journal of Aging Research, 2012.

Ross CN, Austad S, Brasky K, Brown CJ, Forney LJ, Gelfond JA, Lanford R, Richardson A and Tardif SD, 2017 The development of a specific pathogen free (SPF) barrier colony of marmosets (Callithrix jacchus) for aging research. Aging (Albany NY), 9(12), p.2544. [PubMed: 29227963]

Ross CN 2018 Marmosets in Aging Research In The Marmoset in Biomedical Research, Marini R, Mansfield K, Tardif S, Wachtman L and Fox J, editors, American College of Laboratory Animal Medicine Series, Elsevier.

Sabbagh JJ, Kinney JW and Cummings JL, 2013 Animal systems in the development of treatments for Alzheimer's disease: challenges, methods, and implications. Neurobiology of aging, 34(1), pp. 169–183. [PubMed: 22464953]

Sasaki E, Suemizu H, Shimada A, Hanazawa K, Oiwa R, Kamioka M, Tomioka I, Sotomaru Y, Hirakawa R, Eto T and Shiozawa S, 2009 Generation of transgenic non-human primates with germline transmission. Nature, 459(7246), p.523. [PubMed: 19478777]

Tardif SD, Mansfield KG, Ratnam R, Ross CN and Ziegler TE, 2011 The marmoset as a model of aging and age-related diseases. ILAR journal, 52(1), pp.54–65. [PubMed: 21411858]

Terrien J, Gaudubois M, Champeval D, Zaninotto V, Roger L, Riou JF and Aujard F, 2018 Metabolic and genomic adaptations to winter fattening in a primate species, the grey mouse lemur (Microcebus murinus). International Journal of Obesity, 42(2), p.221. [PubMed: 28925409]

Ungvari Z and Philipp EE, 2010 Comparative gerontology—from mussels to man. Journal of Gerontology: Biological Sciences, 66A(3), pp. 295–297.

Weir HK, Thompson TD, Soman A, Moller B, Leadbetter S, White MC, 2015 Meeting the Healthy People 2020 Objectives to Reduce Cancer Mortality. Prev Chronic Dis 12, E104. [PubMed: 26133647]