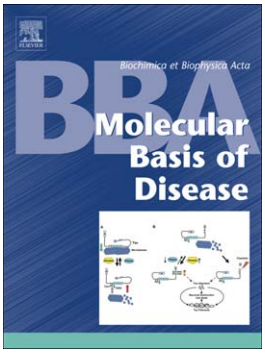

Non-human primates as a model for aging

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Non-human primates as a model for aging

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ABSTRACT

There has been, and continues to be, a dramatic shift in the human population towards older ages necessitating biomedical research aimed at better understanding the basic biology of aging and age-related diseases and facilitating new and improved therapeutic options. As it is not practical to perform the breadth of this research in humans, animal models are necessary to recapitulate the complexity of the aging environment. The mouse model is most frequently chosen for these endeavors, however, they are frequently not the most appropriate model. Non-human primates, on the other hand, are more closely related to humans and recapitulate the human aging process and development of age-related diseases. Extensive aging research has been performed in the well-characterized rhesus macaque aging model. More recently, the common marmoset, a small non-human primate with a shorter lifespan, has been explored as a potential aging model. This model holds particular promise as an aging disease model in part due to the successful creation of transgenic marmosets. Limitations to the use of non-human primates in aging research exist but can be mitigated somewhat by the existence of available resources supported by the National Institutes of Health.

HIGHLIGHTS

- Expansion of the aging human population necessitates development of aging models.
- Non-human primates replicate the human aging process.
- Rhesus monkeys are a well characterized and extremely useful aging model.
- The common marmoset is a developing aging model that holds great promise.
- Resources exist to assist those wanting to use non-human primate aging models.

Keywords: Non-human primate, aging, animal model, rhesus monkey, common marmoset

1. Need for aging models

According to the United Nations Population Fund, population aging is one of the most significant trends of the 21st century [1]. Globally, the proportion of older people is growing at a faster rate than the general population and more people are living to more extreme ages than ever before [2]. Currently, one in nine people worldwide is 60 years of age or older and this proportion is projected to increase to one in five by 2050 [1]. This expanding aging population is a considerable challenge for healthcare systems as 80% of older adults have at least one chronic condition and 70% have at least two [3]. This speaks to the urgent need for biomedical research targeting better understanding of biological aging as well as the biology and treatment of specific age-associated diseases and conditions.

2. Modeling human aging

Ideally all human relevant biomedical research would be performed in humans but clearly this is impractical due to numerous ethical and technical considerations. Therefore, it is necessary to model the human aging process in non-human systems. Much of this can be done without the use of animals, for example, through the use of computer models or in vitro systems. While often useful these systems are incapable of reproducing the complex and multifaceted in vivo physiology of aging. While many different non-human models have been used to explore the aging process (e.g. yeast, roundworm, fruit fly, rat), mice are routinely the model of choice.

The mouse is the most often used biomedical model for various reasons. Practically, they are small in size, have a short generation time and an accelerated lifespan. These characteristics translate to lower cost and reduced space and time requirements than are generally associated with the use of larger animal models. Most importantly perhaps, is the fact that the mouse genome is similar to humans (overall 92% similarity on average and 85% similarity between human and mouse coding regions [4]) and can be readily manipulated. In addition, mice are

biologically similar to humans exhibiting many of the same diseases and conditions, there are well validated reagents and methods available and it is a well-established experimental model. However, several key differences between humans and mice limit their potential as an aging model. Among these disadvantages are the fact that mice are only distantly related to humans having diverged approximately 84-121 million years ago [5], they don't develop several important age-related diseases naturally (e.g. atherosclerosis and diabetes), their small size can be limiting, they are nocturnal, they have estrous not menstrual cycles and behavioral compliance can be an issue. These issues draw attention to the need for models that more closely mimic humans.

3. Non-human primate models for aging research

Although rodent models offer several distinct advantages [6, 7], fundamental differences in the aging process between rodents and humans have hindered direct translation of findings in rodents to humans. Non-human primates on the other hand, are a vital link between basic research and clinical application in that findings from non-human primate studies are highly translatable to human health issues. Non-human primates are an ideal translational model because they share strikingly similar genetic, physiological, and behavior traits with humans [6-10]. They also exhibit naturally occurring (i.e. no genetic manipulation required) age-associated diseases that present in a realistic time frame with a developmental course that nicely replicates human conditions. In addition, like humans, non-human primates are outbred and therefore exhibit a similar degree of inter-individual variability and have patterns of comorbidity that mirror humans. Also similar to humans, non-human primates exhibit unusually long average life spans that are nearly 4-fold higher than those of most other mammals relative to their body sizes [11]. Unlike in human studies, non-human primate studies allow for complete control over the experimental environment including housing, environmental conditions, diet and social interactions. Non-human primate studies offer an excellent trade-off between the limitations of

both rodent and human studies. Nevertheless, there are very few studies using non-human primate aging models likely because of the challenges associated with the model, including limited availability of aged animals, specialized care required, the high cost associated with their use and potential ethical concerns [6].

A primate is defined as a mammal of the order Primates. The Primates include prosimians (tarsiers and lemurs), monkeys (new world monkeys and old world monkeys), apes (lesser apes and greater apes) and humans. While several different types of primates have been used to model human aging, old world monkeys, specifically rhesus macaques, are historically the most frequently studied. Recently, there has been increased interest in the use of a small new world primate, the common marmoset, in aging studies. As it is not possible to fully review all non-human primates used in aging research, following a brief overview of the use of prosimians and apes in aging research, the remainder of this review will focus on the most commonly used species, the rhesus macaque, and the newly developing model, the common marmoset (see Tables 1 and 2 for additional information on some of the more commonly studied species).

3.1 Prosimian models of aging, the grey mouse lemur

The use of prosimians as aging models is limited. The most frequently used prosimian in this field is the grey mouse lemur (*Microcebus murinus*), a small (average body weight 60-120g), nocturnal species with a relatively short lifespan (8-12 years) and strong seasonality of body weight and physical activity that uses daily torpor to save energy during seasonal periods of resource scarcity [12]. Prosimians are the most phylogenetically distant non-human primate from humans having diverged from the human lineage approximately 60-70 million years ago [13, 14], and are considered to have more primitive characteristics. Nonetheless, the grey mouse lemur has been used for studies of age-related changes in the central nervous system and cognition [15-17], vision [18, 19], olfaction [20-22], circadian rhythm [23-25], motor function

[26, 27], immune function [28], and energy metabolism [29]. There are drawbacks associated with the use of this model including restricted specimen sampling related to their small body size, their scarcity in captivity which translates to limited information being available regarding basic husbandry practices and physiological differences between mouse lemurs and humans owing to their phylogenetic distance from humans. There is an opportunity however, to take advantage of these differences. For example, given their use of seasonal daily torpor, the grey mouse lemur offers a unique potential opportunity to study the effects of aging on thermoregulation and metabolism.

3.2 Ape models of aging, the chimpanzee

Chimpanzees have been the most common ape used in biomedical research. Physiologically and genetically similar to humans, they have greater than 98% DNA sequence homology with humans [30]. The vast majority of the aging specific research in apes has also been in chimpanzee (Pan troglodytes), a species known to develop many of the same age-related diseases and conditions as humans (e.g. metabolic syndrome, cardiovascular disease, renal dysfunction) and in proportions similar to aged humans [31, 32]. Aging research in this species has focused mainly on brain aging and reproductive senescence. For example, Chen et al [33] found that grey matter volume decreased with age in chimpanzees and that there was a trend towards decreased white matter volume with age but that this decrease occurred proportionally later in the chimpanzee lifespan than in humans. In line with this, only limited cognitive and motor function decline with age has been detected and only towards the end of lifespan [34]. Similarly, menopause is a late-life event in chimpanzee [35]. Use of chimpanzee aging models has historically been limited by their long lifespan in captivity, high cost, ethical considerations and challenges associated with their housing and maintenance.

More recently, the use of chimpanzees in biomedical research has been limited by a June, 2013 decision by the National Institutes of Health (NIH) to significantly reduce the use of chimpanzees in agency-supported biomedical research. At that time, NIH planned to identify 50 chimpanzees that would be retained to support biomedical research. Such research would have to meet strict ethical principles established by the Institute of Medicine and accepted by the NIH. Furthermore, on June 16, 2015, the United States Fish and Wildlife Service announced that it had designated captive chimpanzees as endangered. This declaration put in place a requirement to receive a permit for the use of captive chimpanzees in research. No such permits were requested. On November 17, 2015, NIH Director Francis Collins announced that they would no longer maintain the colony of 50 animals for future biomedical research. These decisions have led to a loss of access to chimpanzees for biomedical research [36, 37].

3.3 Old world monkey models of aging, the rhesus macague

Old world monkeys diverged from the human lineage approximately 20-35 million years ago [13, 38]. The old-world monkey genus, Macaca with its' 23 recognized species, is the most geographically widespread non-human primate genus and the most widely used in biomedical research. Within the genus Macaca, rhesus monkeys (Macaca mulatta) are the most commonly used in biomedical aging research [39, 40]. Rhesus monkey share ~93% sequence identity with the human genome [41, 42], and this similarity extends to numerous aspects of their anatomy, physiology, neurology, endocrinology, immunology, and behavior [43, 44]. Confirming their utility as a model of human aging, rhesus monkeys exhibit a spectrum of age-associated diseases that are similar to those in humans [43-45].

A key component of a good aging model is a realistic aging course in conjunction with some degree of time compression. Rhesus monkeys age in similar ways to humans at a rate of approximately two and a half to three times that of humans [46, 47]. They have a lifespan

measured in decades [44, 48, 49] with median lifespan in captivity of approximately 26 years and maximum lifespan under standard husbandry of approximately 40 years. Rhesus monkeys are generally considered old after approximately 20 years of age and show significant signs of physical decline such as decreased mobility, skin atrophy and coat greying/thinning by their late 20s. At these later ages, they also develop many of the disorders common in older humans, including cancer, cataracts, osteopenia, and cardiovascular disease [50].

Macaques may offer the best compromise between phylogenetic and physiologic relatedness to humans, cost efficiency, lifespan, availability, expertise in animal husbandry practices, and translation of results to humans. Unlike in human studies, environment, dietary intake and medical history can be fully described, and studies can be designed to assure comprehensive subject monitoring and strict protocol adherence. Unlike rodents, rhesus monkeys display patterns of eating and sleeping behavior that mirror those of humans, have a lifespan measured in decades, and develop and age in similar ways to humans.

The value of the rhesus monkey aging model extends to a multitude of different aging systems, treatments and interventions. To cover all in detail is not possible within the scope of this review. The remaining sections on rhesus monkey will therefore focus on the musculoskeletal system, menopause, and the effects of caloric restriction on aging.

3.3.1 Rhesus macaque musculoskeletal aging

Frailty is a state of increased vulnerability for adverse health outcomes; a higher risk of disability, falls, hospitalization, and mortality [51]. The prevalence of frailty increases with increasing age [52]. Given the worldwide increase in the number of elderly, the total worldwide population of frail elderly is predicted to dramatically increase [53]. Degradation of the musculoskeletal system with advancing age contributes to increased frailty. Macaques are very

useful for modeling age-related changes in the human musculoskeletal system because they develop muscle loss and bone loss during aging that very closely recapitulate the human conditions [54-56].

3.3.1.1 Sarcopenia

Sarcopenia is the loss of skeletal muscle mass and function during the aging process [57-61]. Sarcopenia becomes increasingly common with advancing age, and is associated with muscle weakness, disability, falls, and fractures, as well as increases in morbidity and mortality [57-61]. Healthcare costs attributed to sarcopenia are estimated at ~$18.5 billion annually in the US, and costs are only expected to rise with the worldwide increase in life expectancy [62]. Unfortunately, the underlying molecular mechanisms in sarcopenia, and sex-specific differences in the pathophysiology, remain poorly understood–precluding the development of therapies to combat sarcopenia [57, 58, 60, 63].

The rhesus monkey is the optimal model for human sarcopenia. Unlike rodents where significant muscle mass loss occurs later in life [64], the dynamics of sarcopenia in rhesus monkeys matches that in humans, with onset at mid-age and a gradual loss thereafter. A reduction in muscle fiber cross sectional area significantly contributes to the muscle mass loss and an age-dependent increase in muscle fibers developing mitochondrial enzyme abnormalities due to mitochondrial DNA deletion mutations has been observed [56, 65, 66]. In addition, skeletal muscle makes up a greater proportion of total body mass in primates compared to rodents, and is a great consumer of energy expenditure.

3.3.1.2 Osteoporosis

Osteoporosis is a major health and economic issue worldwide. Osteoporosis is characterized by low bone mass, deterioration of bone tissue, disruption of bone architecture, and compromised

bone strength, all of which increase the risk of fracture. As the population ages worldwide, the overall number of osteoporotic fractures is growing substantially. In 2010, the estimated prevalence of osteoporosis among U.S. men and women aged 50 years and older was 10.3% [67] and an estimated 200 million women worldwide are affected by the osteoporosis. An estimated 50% of women and 20% of men in the United States will sustain an osteoporotic fracture in their lifetime [68]. These fractures are accompanied by increased morbidity and mortality [69].

Although often used, the mouse is not an ideal model for human osteoporosis. Human cortical bone reflects continuous remodeling throughout life. Mouse cortical bone rarely undergoes Haversian remodeling and thus does not usually contain osteons [70]. The cortex consists primarily of circumferential lamellae laid down on the outer surface as the bone grows. Unlike in humans, bone acquisition and longitudinal bone growth continue in mice after sexual maturity and in many strains, bone growth continues up to advanced age [71]. In addition, mice do not undergo a true menopause. While they may experience irregular cycling beginning at ~10 months of age, estrogen levels are still maintained and uterine weight, an indicator of functional estrogen exposure, is maintained at normal levels up to advanced age [72]. Similarly, male mice maintain testosterone levels with advancing age [73].

On the other hand, macaques, and other old world monkeys, are an excellent model for human osteoporosis because they have haversian osteonal remodeling of cortical bone, and a similar reproductive endocrine system that affects bone metabolism. Following peak bone mass at approximately 10 years of age [10], macaques reliably develop increased skeletal turnover and bone loss with advancing age as well as following natural or surgically-induced estrogen depletion [10, 55, 74]. This is not surprising in view of their striking similarities to humans in

menstrual cycle, occurrence of natural menopause, and bone remodeling processes in both cancellous and cortical bone [74].

3.3.1.3 Osteoarthritis

Osteoarthritis has the highest prevalence of all forms of arthritis in the world and is the leading cause of chronic disability due to pain [75]. The economic costs of OA are high, including those related to treatment and lost work productivity. Approximately 27 million adults in the United States are estimated to have the disease [76]. This prevalence combined with our limited knowledge of the pathogenesis of osteoarthritis highlights the need for significant research efforts aimed at better understanding the development and progression of osteoarthritis with the goal of developing successful treatment regimens.

Non-human primates such as the rhesus macaque present a special case for studying naturally occurring osteoarthritis. Because spinal osteoarthritis manifests similarly in humans and monkeys and macaque monkeys age at approximately three times the rate of humans, macaque models offer opportunities for longitudinal study that are difficult in humans. For example, an 11-year longitudinal examination of rhesus macaques determined that similar to the human condition, age and body mass both significantly predicted variability in osteoarthritis [77]. This study clarified the roles of age and body mass in osteoarthritis and established the rhesus monkey model.

3.3.2 Rhesus macaque menopause

Menopause can be defined as a natural consequence of the aging process in which human females gradually lose the ability to reproduce. This loss in fertility involves eventual complete cessation of ovulation and menstruation and is accompanied by functional and structural changes in the hypothalamic-pituitary-ovarian axis. The importance of studying menopause in a

model species cannot be overstated. Not only are there negative effects related directly to menopause but the altered hormonal milieu associated with the menopausal state translates to an increased risk for age-related diseases and conditions including musculoskeletal and cardiovascular disease. More globally, a positive correlation between menopause and epigenetic aging measured in blood has recently been established [78].

Although previously thought to be a uniquely human trait [79], macaques, baboons and the great apes undergo a true menopause that mimics the physiological changes accompanying the human condition. Likely given the extensive use of rhesus monkeys in biomedical research, reproductive senescence has been more thoroughly characterized in this species than in any other non-human primate. Early studies in rhesus macaques were complicated by the fact that in the wild rhesus monkeys are seasonal breeders. More recent studies taking seasonal breeding into account and more completely examining the multiple facets of the hypothalamic-pituitary-ovarian axis, have conclusively determined that rhesus monkeys undergo menopause at approximately 25-26 years of age [80]. While physiologically similar to human menopause, the timing with respect to lifespan is later. In humans, the average age of menopause is approximately 50 years, though it varies based on race, ethnicity, demographic region and lifestyle factors [81], with maximum lifespan estimated to be approximately 122 years [82]. This translates to humans having the potential to experience nearly 60% of their lifespan in a post-reproductive state. Maximum lifespan in rhesus monkeys is approximately 40 years [46] translating to approximately 40% of their potential lifespan that may be spent in a post-reproductive state. Evolutionary theories exist attempting to explain the length of the post-reproductive human lifespan [83] though a consensus explanation has not been reached.

3.3.3 Calorie restriction (CR) in rhesus monkeys

A primary challenge in the study of aging arises from the biological complexity of the aging process itself. Over 80 years ago, a deceptively simple approach of reducing calorie intake was

shown to delay aging and the onset of age-associated disease in rodents [84]. Since then, CR, the sustained reduction of caloric intake without malnutrition, has been shown to be the most robust and consistent intervention that delays aging in diverse species [85-87] and is the only environmental intervention that repeatedly and strongly increases maximum lifespan and delays biological aging in laboratory rodents [87]. Two studies designed to test CR in non-human primates are ongoing; one by intramural scientists at NIA [88] and the other at the Wisconsin National Primate Research Center [89-91]. Although of differing design, both trials indicate that long-term CR can be carried out safely and is associated with evidence of improved health [92]. The proven success of this paradigm in non-human primates strongly supports the use of CR as an important tool for understanding the biology of aging [89].

This CR review will focus on the ongoing study at the Wisconsin National Primate Research Center. The Wisconsin study began with 30 male rhesus monkeys in 1989 and added an additional 30 females and 16 males in 1994 [91]. At entry into the study all animals were adults between 6 and 14 years of age. Animals were evenly randomized to either Control or CR groups and have been maintained continuously as such since that time. Since entry into the study, comprehensive health data has been routinely collected on these animals. Numerous beneficial effects of CR have been described. Selected findings from the last approximately five years will be summarized here.

As described earlier in section 3.3.1, rhesus monkeys are an excellent model for musculoskeletal aging. Bone and muscle health has long been an area of concern in the context of CR. In response to long-term CR, bone mass and bone density declined over time with generally higher levels in Control compared to CR animals while circulating serum markers of bone turnover were not different between groups. Given the smaller overall body size of the CR animals, a reasonable interpretation of these results is that the lower bone mass in CR animals

reflects the smaller body size of these animals and not pathological osteopenia [93]. Building on previous work showing maintenance of skeletal muscle mass in monkeys on CR [65] investigators determined that muscle fiber density was preserved in old CR animals based on fiber counts of intact rectus femoris muscles. They interpreted the data from this study to suggest that muscle fibers from CR animals are better poised to endure and adapt to changes in muscle mass than those of Control animals [94].

Short-term (<1 year) CR has been reported to decrease physical activity and metabolic rate in humans and non-human primate models; however, studies examining the long-term (>10 year) effect of CR on these parameters were lacking. Recently, the metabolic and behavioral adaptations to long-term CR were evaluated longitudinally in rhesus macaques. The results suggest that long-term CR decreases basal metabolic rate, but maintains higher physical activity with lower metabolic cost of movements compared with Control animals [95].

The paradigm in aging interventions has shifted over the past decade from evaluation of the extension of lifespan to the extension of healthspan, or the healthy period of life. Frailty, the state of high vulnerability for adverse health outcomes, is a central component of healthspan. Frailty has been an area of increasing interest in human clinical research [96] and an adaptation of a commonly used human frailty index for use in non-human primates has recently been published. Yamada et. al. [97] utilized metabolic and physical activity data from the Wisconsin CR study to establish a novel set of measurable criteria of frailty in non-human primates, and using these criteria, showed that CR reduces the incidence of frailty and increases healthy lifespan in rhesus monkeys.

A group of studies examined the effects of long-term CR on brain structure and function in rhesus monkeys finding overall beneficial effects of a reduced calorie diet. A brief summary of

these findings follows. High stress reactivity predicted lower volume and microstructural tissue density in brain regions involved in emotional processing and modulation. The CR diet reduced stress reactivity and regional associations with neural modalities [98]. Data from other studies suggested that CR may ameliorate the influence of homocysteine on several important age-related parameters of parenchymal health [99], CR improved glucose regulation and may positively influence specific brain regions and motor task performance [100], and consumption of a CR diet lowered proinflammatory and increased anti-inflammatory cytokine concentrations, which lessened the statistical association between systemic inflammation and the age-related alterations in important brain regions including the hippocampus [101]. In a study examining the association between cognitive and motor performance and anatomic and microstructural brain integrity, brain-behavior correlations for a motor task were attenuated in CR animals compared to Controls, indicating a potential protective effect of CR [102]. In a preliminary, postmortem histological analysis of the effects of CR on brain health, CR was found to affect levels of glial fibrillary acid protein expression but not amyloid plaque load. This finding implies that at the microstructural level the benefits of CR may be achieved by offsetting the increased load of oxidatively damaged proteins [103]. Finally, a new study determined that the regional and metabolic heterogeneity of the hippocampus is non-uniformly impacted by age and CR. This study revealed cell-type and regional specificity in the metabolic response to age and delayed aging by CR and suggests that key regulators of energy metabolism play a role in implementing the neuroprotective program induced by CR [104].

More generally, the Wisconsin CR study set out to test the overall hypothesis that CR will slow aging in a primate species. Two important milestones in this study have been reached. First, the effect of CR in reducing disease onset was significant with age-related diseases detected in Control animals at approximately 3 times the rate that they were detected in CR animals. Animals on CR, thus, appeared to be biologically younger than normally fed animals [89].

Second, the effect of CR on mortality was significant indicating that at any point in time the Control animals had 1.8 times the rate of death from any cause when compared to animals under CR. These data demonstrate the conservation of the beneficial effect of in primates [90].

3.4 New world monkey models of aging, the common marmoset

New world monkeys diverged from the human lineage 26-43 million years ago [105, 106]. Among the new world monkeys, the common marmoset holds the most promise for aging research. Similar to the rhesus monkey, common marmosets share ~93% sequence identity with the human genome [107] and they develop similar age-related diseases and conditions as humans including diabetes, cardiovascular disease and cancer [108, 109]. The marmoset is an established model for neuroscience, infectious disease, behavioral research, obesity, and reproductive biology [110]. Like other primates, marmosets are not as genetically tractable as mice but stable transgenic marmosets capable of transmitting the transgene to their offspring have been generated [111, 112] and investigators are actively pursuing new technologies (e.g. CRISPR) for the creation of disease-specific genetically modified marmosets. This makes the marmoset a particularly attractive model for neurodegenerative diseases such as Parkinson's.

A major advantage of marmosets compared to macaques is their shorter lifespan and rapid life history. They are reproductively competent at approximately 1.5 years of age, produce litters of 2-3 offspring every 5-6 months, and are considered aged at 8 years of age (Table 2) [113, 114]. In captivity, mortality increases from 35% to 85% between 5 and 10 years of age [109]. This translates into the ability to assess animals longitudinally from young adulthood to old age within the timeline of a typical NIH grant. This abbreviated time course reduces the risk associated with lack of control over study variables, including equipment and personnel availability, over the course of an aging study. A second major advantage of the marmoset model is its high fecundity [115] and the fact that littermates are hematopoietic chimeras. This chimerism offers

several potential benefits including the ability to limit variability between control and experimental groups and the opportunity to study the effects of early environment on later life outcomes. Other advantages associated with the use of common marmosets include their human-like cooperative breeding structure and the fact that do to their small size they are generally easier to handle and maintain and require smaller vivarium space than macaques. Importantly, unlike macaques, marmosets do not have any zoonotic diseases of particular concern to humans. Marmosets may strike the perfect balance between similarity to humans and abbreviated aging course.

There are some disadvantages to the marmoset aging model. While antibodies, assays, and other experimental resources are readily available for rodents and macaques, there are fewer commercially available options for marmosets, although this has been improving [116]. There is also a lack of evidence-based, standardized procedures for marmoset captive management, especially regarding diet and feeding husbandry. Aging marmosets are prone to systemic amyloidosis and chronic inflammatory conditions of the intestine, gall bladder, and kidney, all of which remain ill-defined. Obesity along with dyslipidemia and altered glucose metabolism leading to hepatomegaly, hepatic steatosis, diabetes, atherosclerosis, cardiomyopathies, and stroke is becoming a more frequent finding in captive marmosets [117, 118], age-related increases in insulin resistance have been detected [109] and potential biomarkers of aging have been identified in the plasma metabolome [119]. These facts have led to interest in a marmoset aging model of obesity and metabolic syndrome.

3.4.1 The common marmoset model for neurodegenerative diseases

Marmosets are a popular model for neurodegenerative diseases including Parkinson's, Alzheimer's, Huntington's and multiple sclerosis, due to a combination of their small size, their brain similarities to humans and the availability of validated behavioral, surgical and imaging

techniques [120]. These similarities include evidence of age-related decreases in neurogenesis that occur prior to old age [121]. The small body size of marmosets is particularly attractive for early stage pharmaceutical testing where smaller amounts of the substance would need to be produced than if using a larger bodied model. Marmosets have been particularly useful as a neurotoxin induced model of Parkinson's disease [122] and more recently genetic models of Parkinson's disease have been developed [123].

3.4.2 Aging interventions in common marmosets

Overwhelming evidence supports the maintenance of cellular proteostasis as one of the key processes in ensuring longevity and there is growing appreciation for the role that the mechanistic target of rapamycin (mTOR) plays in regulating this process. Rapamycin, an inhibitor of mTOR, is used for human immunosuppression therapy following transplant. Rapamycin was first shown to extend lifespan in yeast cells [124] and has since been shown to have a beneficial effect on lifespan in nematodes, flies, mice and human cells [125, 126]. Of interest, lifespan extension has even been detected in mice that began rapamycin treatment in advanced age [127]. Studies in the common marmoset are currently underway to determine the effect of rapamycin on lifespan in a non-human primate species. Both short and long term oral rapamycin was well tolerated in marmosets and led to suppression of the mTOR pathway [128] with only minor metabolic consequences [129]. Further study showed rapamycin-induced tissue-specific upregulation of some components of the mechanisms that regulate protein homeostasis in marmosets [130]. These studies are proof that the common marmoset is an excellent model for investigating long term aging interventions.

4. Non-human primate aging resources

Lack of access to older animals is likely the largest limitation of aging research with non-human primates. In addition to animal colonies that may be available to interested investigators through

the network of National Primate Research Centers, two excellent aging non-human primate resources exist. Over 10 years ago, the National Institute on Aging developed the internet Primate Aging Database and the Aged Non-Human Primate Tissue Bank. The internet Primate Aging Database was developed to collect data on normal aging in a wide range of non-human primate species. Blood chemistry measurements and body weight data have been collected for healthy non-human primates across the lifespan, from primate colonies across the country. The database currently includes over 1,000,000 data points from over 40 species and is available for use by the aging research community. The Aged Nonhuman Primate Tissue Bank was established to archive tissues that might otherwise be discarded, and to provide that tissue to investigators undertaking research on normal aging and age-related diseases. This bank serves as a central repository for rare and valuable samples that would be too expensive to maintain in multiple facilities. The collection is predominantly from rhesus macaques and baboons and contains fresh-frozen specimens, slides containing sections of formalin-fixed tissue and OTC-embedded fresh-frozen specimens.

5. Conclusion

The vast majority of aging research occurs in non-primate species. There is great value to this work, but non-human primates offer a combination of a tractable model that very closely mimics human anatomy, physiology, and behavior and develops and ages similarly to humans. Ideally, age-related diseases and conditions would be studied in an aged model thereby replicating the aging environment present in the human condition. In longer lived species such as macaques this can be problematic. Importantly, resources exist to attenuate the numerous challenges involved in maintaining animals until old age. Utility of the common marmoset aging model is primed to increase as methods and resources are further developed and the full value of transgenic marmosets is realized.

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Table 1. Advantages and limitations of most commonly used non-human primates in aging research.

Species	Scientific Name	Classification	Advantages	Limitations
Grey Mouse lemur	*Microcebus murinus*	Prosimian	Small body size, short lifespan, interesting model for thermoregulation research	Small body size, availability, nocturnal, solitary, phylogenetic distance from humans, lack of commercially available resources
Common Marmoset	*Callithrix jacchus*	New World monkey	Small body size, reasonably short lifespan, short generation time, social structure, fecundity	Small body size, aging process needs further description, lack of standardized husbandry procedures, lack of commercially available resources
Squirrel monkey	*Saimiri spp.*	New World monkey	Small body size, somewhat realistic aging course	Long lifespan for body size, lack of commercially available resources
Macaques	*Macaca sp.*	Old World monkey	Well characterized, closely related to humans, large body size, realistic aging course	Long lifespan, availability of aged animals may be limited, zoonotic concerns
Vervet monkey	*Chlorocebus pygerythrus*	Old World monkey	Closely related to humans, large body size, realistic aging course	Long lifespan, limited availability of aged animals
Baboon	*Papio hamadryas*	Old World monkey	Closely related to humans, large body size, realistic aging course	Long lifespan, limited availability of aged animals, housing requirements
Chimpanzee	*Pan troglodytes*	Great ape	Closest human relative, realistic aging course, large body size	Long lifespan, housing requirements, imposed limitations on research, ethical considerations

Table 2. Average adult weight and lifespan in captivity of commonly used non-human primate models of aging.

Model	Average Adult Weight (kg)	Average Lifespan (years)	Maximum Lifespan (years)
Grey mouse lemur	0.06-0.12	8-10 [131]	18 [132]
Common marmoset	0.35-.040	7-8 [133]	21 [133]
Squirrel monkey	.60-1.30	20 [131]	30 [38, 134]
Macaque species	5-10	26 [46]	40 [46]
Vervet monkey	3-7	20 [131]	31 [135]
Baboon	12-25	30 [136]	38 [135]
Chimpanzee	40-65	30 [1]	65 [1]

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