The Development of Small Primate Models for Aging Research

Kathleen E. Fischer and Steven N. Austad

Abstract

Nonhuman primate (NHP) aging research has traditionally relied mainly on the rhesus macaque. But the long lifespan, low reproductive rate, and relatively large body size of macaques and related Old World monkeys make them less than ideal models for aging research. Manifold advantages would attend the use of smaller, more rapidly developing, shorter-lived NHP species in aging studies, not the least of which are lower cost and the ability to do shorter research projects. Arbitrarily defining "small" primates as those weighing less than 500 g, we assess small, relatively short-lived species among the prosimians and callitrichids for suitability as models for human aging research. Using the criteria of availability, knowledge about (and ease of) maintenance, the possibility of genetic manipulation (a hallmark of 21st century biology), and similarities to humans in the physiology of age-related changes, we suggest three species—two prosimians (*Microcebus murinus* and *Galago senegalensis*) and one New World monkey (*Callithrix jacchus*)—that deserve scrutiny for development as major NHP models for aging studies. We discuss one other New World monkey group, *Cebus* spp., that might also be an effective NHP model of aging as these species are longer-lived for their body size than any primate except humans.

Key Words: aging; bush baby (*Galago senegalensis*); lemur (*Microcebus murinus*); longevity; marmoset (*Callithrix jacchus*); nonhuman primate (NHP); prosimian; tamarin (*Saguinus* spp.)

Introduction: Considerations for Species Selection in Aging Research

Mice and Rats

The standard mammalian models used in biomedical research are murine rodents, and from a practical perspective there are many research advantages to mice and rats: they are relatively short-lived and inexpensive to house; their genetics, biology, and husbandry are tractable and well understood; and they are early and copious breeders, making them useful, practical, and economical for many different research applications. Moreover, mice in particular have very tractable genetics, allowing specific genes to be turned off or overexpressed ubiquitously or only in specific tissues under specific conditions (more on genetic manipulation below).

But rodents are only distantly related to humans, having diverged some 84-121 million years ago (Glazko et al. 2005), and the very characteristics that make them easy to keep in the laboratory also distinguish their life histories from those of humans in important ways. Because rodents lead relatively fast (*r*-selected) lives, with low survivorship and strong selection for early and copious reproduction, there are likely to be significant differences in the biology of rodent and human aging. For instance, mice and rats experience estrus rather than menstrual cycles and so make poor models for reproductive aging (Black and Lane 2002). Similarly, mice do not suffer from atherosclerosis and other cardiovascular diseases that are important causes of morbidity and mortality among humans, and the profile of tumors they contract spontaneously is very different from that of humans (Waters and Wildasin 2006). Finally, with life histories at the opposite end of the fast-slow continuum, the evolutionary pressures that have shaped aging, such as selection of pleiotropic effects, may differ significantly between humans and rodents.

Nonhuman Primates

Animals share two kinds of traits: (1) morphological and functional characteristics that are conserved across a wide range of distantly related species (e.g., the impact of insulin/IGF [insulinlike growth factor] signaling on longevity in worms, flies, and mice; Tatar et al. 2003) and (2) idiosyncratic traits that are either shared only between more closely related species (e.g., menstrual cycles in Old World primates; Kaplan and Manuck 2008; Martin et al. 2003) or confined to a single species (e.g., Alzheimer's disease in humans; Finch and Sapolsky 1999). Because of their close phylogenetic relationship with humans, primates share a large number of both types of traits important in human aging. They also have a characteristically slow (K-selected) life history, with relatively high survivorship, delayed breeding, long interbirth interval, and low reproductive output similar to humans. Shared life history characteristics reflect similar

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selective forces and constraints, which shape aging in both humans and nonhuman primates (NHP[1]). Nonhuman primates therefore offer a logical model for age-related research and preclinical testing of aging interventions.

From an evolutionary standpoint, chimpanzees (*Pan troglodytes*) and bonobos (*P. paniscus*)—the nearest living relatives of humans—would most faithfully represent human aging. However, practical considerations of cost, ethical issues, their status as endangered species, and their long lifespan (as much as 60 years in captivity) make chimpanzees and other apes less appealing for aging research.

For largely historical reasons, Old World monkeys, particularly those in the genus *Macaca*, have been used as a compromise between evolutionary propinquity and practical concerns. Macaques and humans share many diseases of aging that affect skeletal systems (Black and Lane 2002; Jerome and Peterson 2001), cognitive function (Voytko and Tinkler 2004; Voytko et al. 2009a,b), vascular health (Appt et al. 2006, 2010; Clarkson and Mehaffey 2009; Kaplan and Manuck 2004, 2008; Register 2009; Walker et al. 2008), muscle mass (Colman et al. 2005), and reproduction (Downs and Urbanski 2006; Shideler et al. 2001; Walker and Herndon 2008).

But there are significant disadvantages associated with using macaques and other Old World monkeys for aging research, not the least of which is their long developmental period (3-5 years), low reproductive output (important for building colony size), and 30- to 40-year lifespan in captivity (de Magalhaes and Costa 2009). Costs of purchasing and housing macaques, although less than for chimpanzees, are still significant and must be multiplied across the 20-plus years it takes to produce aged monkeys. The availability of macaques is also limited, as demand for them in biomedical research is high relative to the supply of captive-bred animals. Additionally, both macaques and humans are known to carry and transmit serious zoonotic diseases, such as hepatitis A, herpes B virus, and tuberculosis (Huemer et al. 2002; Lefaux et al. 2004).

Implications of Genetic Advances

The chief feature that distinguishes modern biology from earlier research is the ability to identify and precisely manipulate patterns of gene expression. Indeed, the reason mice have largely eclipsed rats in biomedical research in recent years is the ease of genetic manipulation (Silver 1995).

Modern mouse genetics has advanced rapidly since 1981, when embryonic stem (ES) cells were first reliably produced from a few inbred mouse strains. Because these cells can be genetically manipulated in culture and then reincorporated into embryos, they represent the doorway to targeted gene manipulation (Silver 1995). Coupled with the mouse's short generation time and high fecundity, ES cells are ideal for overexpressing or knocking out the expression of specific genes. By contrast, rat ES cells eluded derivation and characterization until very recently (Buehr et al. 2008), but now that they have been well characterized, targeted genetic manipulation of rats should follow quickly.

Primates do not share the rapid development and copious reproduction characteristic of rodents, so genetic manipulation has proceeded much more slowly. More than a decade ago, researchers isolated ES cells from both the rhesus macaque (*Macaca mulatta*) and the common marmoset (*Callithrix jacchus*) (Thomson and Marshall 1998), but attention quickly shifted to the study of human ES cells, which were isolated shortly thereafter (Thomson et al. 1998). However, because small NHP species develop and reproduce relatively rapidly compared with larger species, they will likely contribute to the development and application of modern tools of molecular genetics for primates in general. Indeed, there is reason for optimism in this area as researchers recently produced a stably transgenic marmoset capable of transmitting the transgene to its offspring (Sasaki et al. 2009).

Possibly the most exciting development in cell biology in recent years is the discovery that a wide array of somatic cells can be transformed into induced pluripotent stem (iPS) cells using a cocktail of transcription factors (Okita and Yamanaka 2010). These cells, like ES cells, can be differentiated into any other cell type in the body without the complex biology necessary for isolating and culturing ES cells. Instead, genetically manipulated iPS cells can be incorporated in embryos to produce genetically manipulated animals, and such cells have been successfully generated from both rhesus macaques (Liu et al. 2008) and common marmosets (Wu et al. 2010).

The dramatic acceleration of DNA sequencing capacity means that the whole genome sequence of virtually any species can be quickly available. Of course, the more elaborate process of annotating any new genome sequence is still necessary, but rapid advances are occurring here as well. The existence of a complete genome sequence offers potential research advantages such as the development of vectors to knock down specific genes by RNA interference technology or the production of DNA microarrays to monitor gene expression profiles. Although only the human, chimpanzee, and rhesus macaque genomes have been sequenced to a high degree of coverage to date, at least eight other primate species—including small species such as the common marmoset,[2] greater galago (*Otolemur garnetti*), grey mouse lemur (*Microcebus murinus*), and Philippine tarsier (*Tarsius syrichta*)—have had a low-coverage genome sequence, and more thorough draft sequences are in development (www.genome.gov/10002154).

Small Nonhuman Primates in Aging Research

Several species of small nonhuman primates offer a compromise between the convenience and affordability of rodents

[1]Abbreviations used in this article: CITES, Convention on International Trade in Endangered Species of Wild Fauna and Flora; NHP, nonhuman primate(s)

[2]The draft (6x) coverage of the common marmoset genetic sequence is now available (ftp://hgdownload.cse.ucsc.edu/goldenPath/calJac1/); this and other websites cited in this article were accessed on December 22, 2010.

and the shared life history traits and phylogenetic proximity of Old World monkeys and apes.

Overview

Small primates, which we arbitrarily define as those weighing roughly 500 g or less, are less costly to house and maintain than larger NHP such as rhesus macaques (8-12 kg) or baboons (10-30 kg) (Raman et al. 2005). Perhaps more importantly, these smaller species also reach sexual maturity earlier and produce more offspring in a shorter period of time than do large primates, enabling more rapid research colony growth and development. Although long-lived for their body size, most small primates typically live only one or two decades in captivity, making them more tractable models for aging research. In addition, several species are known to develop age-related diseases relevant to human late-life diseases (e.g., Aujard et al. 2006; Bons et al. 2006; Brady et al. 2003; Elfenbein et al. 2007; Gilissen et al. 1999; Lemere et al. 2008; Picq 2007).

Some of the 23 small NHP species shown in Table 1 are commonly kept in captivity (e.g., *C. jacchus, M. murinus*), whereas others are not well known in captivity or even in the wild. Developing accurate information about the longevity of individual species depends on animals raised in captivity under stringent conditions that are rarely met in practice; values in Table 1 are the best available data but may not accurately reflect the maximum potential lifespan of some of these species when raised under optimal, pathogen-free conditions.

Aging research typically requires that captive animals be kept in good health and that research populations be large enough to enable comparison of age classes (young, middle-aged, and old) in cross-sectional and longitudinal studies (Austad 1997). These criteria reduce the number of species that are currently suitable subjects for aging research to those for which husbandry practices have been well developed. Even for the most commonly kept species, typical practices in zoos and other captive facilities are often not sufficient to maximize longevity, so that ages reported for captive populations often increase substantially when the animals are maintained in conditions that call for exceptional attention to their health. And, of course, improvements in both knowledge and practice continually enhance animals' lifespans; for example, the maximum reported lifespan of squirrel monkeys (*Saimiri sciureus*) increased from less than 20 years in 1960 to 30.3 years now (Austad 1997; Weigl 2005).

Limitations

As with any model, there are some drawbacks involved in using smaller primates. Small body size results in reduced samples of blood and tissue, and there is evidence that important metabolic and biochemical traits of small NHP may differ from those of humans more than is the case with larger Old World species. For example, growth hormone in the small prosimian *Galago senegalensis* is more similar to NHP growth hormone than to human growth hormone (Adkins et al. 2001); and antibodies to human proteins are much more likely to cross-react with those of macaques or baboons than with those of marmosets or galagos (Kap et al. 2009), as would be expected from their phylogenetic distance from one another.

Also, studies suggest that some responses to aging interventions such as calorie restriction (CR) may differ between primate species. For instance, squirrel monkeys subjected to CR had a lower rate of weight loss and lost a smaller proportion of their total body weight compared to rhesus monkeys under similar conditions (Weindruch et al. 1995). Likewise, nonenzymatic glycation of proteins, a deleterious post-translational modification that increases with age, is significantly lower in CR rhesus macaques compared to controls, but CR and well-fed squirrel monkeys do not differ in this parameter. Because such protein modifications have been associated with age-related diseases—and lower glycation in particular may contribute to the extension of lifespan (Sell et al. 2003)—these results suggest that CR may be less effective in mediating age-related diseases in squirrel monkeys than in rhesus macaques.

The reproductive biology of many small primates is also distinct from that of humans and Old World monkeys. Prosimians (lemurs, lorises, and galagos) and New World NHP do not experience menstrual cycles as do Old World monkeys and apes, and unlike humans several species are seasonal breeders. Furthermore, in the small New World tamarins *Saguinus oedipus* and *S. fuscicollis* ovarian aging appears to differ from that of Old World monkeys, as even postreproductive females maintain moderate circulating levels of estrogen and progesterone (Tardif and Ziegler 1992). These differences limit the utility of these species as models for human reproductive aging.

In addition, several small NHP species, such as the grey mouse lemur, appear to be particularly susceptible to stresses associated with captivity (Perret 1982) and the animals' stress can affect their physiological systems (Sapolsky et al. 1990; Wood et al. 1998) such as immune (Rogers et al. 1998) and reproductive function (Bethea et al. 2008). These effects may be due to their short history in captivity and/or less well developed husbandry techniques, or these species may have lower thresholds for stress-related responses because they are more vulnerable to extrinsic threats in nature.

Other differences among some small primates may also be important for the study of aging. For instance, prosimians and anthropoid primates appear to differ in aspects of their telomere biology—chromosomal telomere shortening is a strict barrier to cellular replicative potential in anthropoids but not in the ring-tailed lemur (*Lemur catta*) (Steinert et al. 2002). Further research is necessary to determine the importance of these distinctions.

Finally, any investigator considering the use of a primate model must consider the availability of adequate numbers of individuals at the appropriate ages. All primates are listed in Appendix I or II of the Convention on International Trade in

Endangered Species of Wild Fauna and Flora (CITES[1]). CITES, and particularly Appendix I, which covers the most endangered species (e.g., many tamarins), places significant limits on the trade and use of animals and their blood and tissues in research (Parsons 1983). Captive breeding programs address some of these concerns, but primate species well represented in captive breeding colonies are in high demand in many fields of biomedical research, making the acquisition of study subjects more challenging than with most rodent models.

Some Candidate Species for Aging Research

We consider all the major groups of NHP species that weigh 500 g or less: prosimians (lemurs, lorises, and galagos or bush babies), New World callitrichids (marmosets and tamarins), and tarsiers[3] (Figure 1). Of these, we have identified those suitable to varying degrees for development in aging research based on their size, fecundity, rapid life cycle, and ease of maintenance and reproduction in captivity. These species could quickly produce large research colonies and enable the completion of NHP aging studies in less than 10 years. As with all research involving NHP, it is essential to consider factors such as conservation status, numbers already in captivity, and well-developed husbandry in assessing species suitability for aging studies.

Prosimians (strepsirrhines), the primates most distantly related to humans, diverged from the other primates (haplorrhines) approximately 60-70 million years ago.[4] The New and Old World monkeys diverged 26-43 million years ago; the first fossil evidence of primates in South America dates to approximately 26 million years ago (the Oligocene epoch), but molecular data generally support an earlier divergence (Chatterjee et al. 2009; Wildman et al. 2009).

Prosimians

Among the prosimians listed in Table 1, all are small (up to about 450 g) nocturnal animals that reach sexual maturity in the first breeding season after birth. Females may come into estrus once or twice during a breeding season and generally produce twins (*G. senegalensis* and *Arctocebus calabarensis* are exceptions). In contrast to most primates, these species "park" their young in nests or tree hollows and females return frequently during the night to nurse them (Bearder 1986).

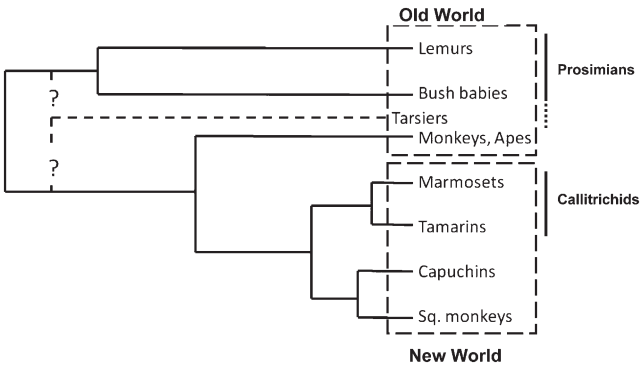

Figure 1 Phylogeny of selected small nonhuman primates. Branch lengths are proportional to estimated divergence times. (The phylogenetic position of the tarsiers is still in dispute as shown by the question marks and dashed lines to the two families.) Sq. monkeys = Squirrel monkeys (genus *Saimiri*). Adapted from Chatterjee et al. (2009) and Fabre et al. (2009).

Prosimians have traditionally been considered solitary foragers, but this notion is the subject of increasing debate as more evidence accumulates (e.g., Gursky 2000b, 2005; Nekaris 2003a,b, 2006). Dietary breadth varies among these species but most consume significant quantities of arthropods, plant exudates, and fruit.

Females generally have overlapping home ranges and may share nest sites (Bearder 1986; Richard 1986). Reproductively active males tend to overlap their home ranges with those of several females and to exclude other males (Bearder 1986; Richard 1986). Individuals with overlapping home ranges maintain contact through scent marking and vocal communication. Some of these animals may be more amenable to the solitary housing necessary for some experimental studies as long as they have vocal and olfactory contact with others.

The Grey Mouse Lemur

The grey mouse lemur, which at 60 to 110 g is among the smallest of all primates, is one of two particularly promising candidates for aging research (Austad 1997). The genus *Microcebus* is a diverse group of small lemurs that live in dry forest environments in Madagascar; they have a varied diet that includes fruit and flowers, leaves, sap, arthropods, and vertebrates.

The chief advantages of *M. murinus* are its exceptionally small size and rapid life cycle. Because it reaches sexual maturity in less than 1 year and has two to three offspring per year, research colonies can expand rapidly. *M. murinus* has been successfully raised in captivity since 1953, and large colonies have been developed from founding populations in France since the 1970s (Bons et al. 2006; Cayetanot et al. 2005). More than 20 primate facilities and zoos throughout the world maintain mouse lemurs.

[3]Because tarsiers are seriously threatened with extinction and their slow reproductive rate and poorly developed captive husbandry make them impractical for aging or other biomedical research, we do not consider them further.

[4]The position of the tarsiers is controversial: some authors claim they are a sister group to the prosimians, with an estimated divergence date of roughly 64 million years ago (Chatterjee et al. 2009), whereas others position them as a sister group of the haplorrhines (Bininda-Emonds et al. 2007; Fabre et al. 2009; Yoder 2003).

Table 1 Traits of selected small (up to ~500 g) nonhuman primate species

Species	Weight (g)	Age at maturity (months)	Litter size	Captive maximum longevity (years)	Family	Source
Prosimians						
Arctocebus calabarensis	150-320	8-10	1	13	Lorisidae	Bearder 1986; de Magalhaes and Costa 2009; Harvey et al. 1986
Loris tardigradus	227-355	10-13	1-2	19.3	Lorisidae	Bearder 1986; de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Nycticebus pygmaeus	370-460	9	1-2	16.5	Lorisidae	de Magalhaes and Costa 2009; Bearder 1986; Weigl 2005
Galago moholi	180-215	10	2	16.5	Galagidae	de Magalhaes and Costa 2009; Weigl 2005
Galago senegalensis	190-240	7-10	1-2	>16.5[a]	Galagidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Galagoides demidoff	46-88	8-10	1-2	13.4	Galagidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Bearder 1986
Cheirogaleus major	395-400	12	2	13.4	Cheirogaleidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Cheirogaleus medius	180-380	12	2	23.4	Cheirogaleidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Mirza coquereli	300-331	10-11	1-2	17.4	Cheirogaleidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Microcebus murinus	60-110	7-12	1-2	18.2	Cheirogaleidae	de Magalhaes and Costa 2009; Dal-Pan et al. 2010; Weigl 2005
Tarsius bancanus	122-128	13-30	1	>16.3	Tarsiidae	Bearder 1986; de Magalhaes and Costa 2009; Weigl 2005
Tarsius spectrum	100-200	14	1	12	Tarsiidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Tarsius syrichta	120-130	n.a.[b]	1	14.2	Tarsiidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Tamarins						
Saguinus fuscicollis	370-460	18-24	1-2	24.9	Callitrichidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Saguinus geoffroyi	500-510	18	2	>16.8	Callitrichidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Saguinus imperator	519	18-24	2	>21	Callitrichidae	de Magalhaes and Costa 2009; Weigl 2005
Saguinus mystax	544	16-18	2	20	Callitrichidae	de Magalhaes and Costa 2009; Weigl 2005

Table 1 (continued)

Species	Weight (g)	Age at maturity (months)	Litter size	Captive maximum longevity (years)	Family	Source
Saguinus nigricollis	460-520	28	2	20.2	Callitrichidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Saguinus oedipus	445-510	17-18	2	>26.2	Callitrichidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005
Callitrichids						
Callithrix jacchus	350-450	12-16	2	16.5	Callitrichidae	de Magalhaes and Costa 2009; Smucny et al. 2004 Weigl 2005
Callithrix argentata	343	10-11	2	16.5	Callitrichidae	de Magalhaes and Costa 2009; Weigl 2005
Callithrix humeralifera	355	10-11	2	15	Callitrichidae	de Magalhaes and Costa 2009; Weigl 2005
Callithrix pygmaea	124-150	21-24	2	18.7	Callitrichidae	de Magalhaes and Costa 2009; Harvey et al. 1986; Weigl 2005

[a]This individual animal was still alive at last report.
[b]Age at maturity is not known for this species.

M. murinus enters a daily torpor under a short-day photoperiod (8L:16D) in captivity and has been much studied for its circadian rhythm and seasonal changes in metabolic rate (Schmid and Speakman 2000). Although its maximum reported longevity of 18.2 years is greater than that of many other NHP species (Table 1), it may actually be among the most rapidly aging primates if senescence is measured by functional decline. With a life expectancy in captivity of 8 to 10 years, substantial cognitive decline by 10 years of age (Bons et al. 2006; Picq 2007), and cataracts by age 7 in half of individuals (Beltran et al. 2007), *M. murinus* shows—at exceptionally young ages for any NHP species—age-related symptoms similar to those of aging humans. It is also susceptible to a wide range of tumors at later ages (Remick et al. 2009).

Researchers have used *M. murinus* in aging studies and found that the acceleration of seasonal cycles accelerates some age-related changes in this species. Aujard and colleagues (2001) demonstrated changes in melatonin production and cellular response (as measured by Fos expression) to photic stimulus in the suprachiasmatic nucleus in both chronologically aged and artificially accelerated *M. murinus*. Similarly, Cayetanot and colleagues (2005) and Aujard and colleagues (2006) showed that animals subject to accelerated (5-month) seasonal cycles from birth exhibited accelerated changes in age-related locomotor patterns comparable to those of chronologically aged animals (5-9 years), and both accelerated and aged groups showed significant differences from young to middle-aged adult controls (2-4½ years old). Chronologically aged (5-9 years) and artificially accelerated animals (2-4½ years old, 5-9 seasonal cycles) exhibited decreased nocturnal activity, increased diurnal activity, and weakened circadian rhythms compared to controls (2-4½ years old) (Aujard et al. 2006; Cayetanot et al. 2005). These disrupted patterns of wakefulness, sleep, and fragmented activity patterns are similar to those observed in aging humans.

M. murinus can be a useful model for research on normal human brain aging and Alzheimer's disease as investigators have reported pathological changes in the brains of some aged *M. murinus* that closely resemble those in the aging human brain. These changes include rapid localized atrophy and diffuse deposits of Aβ (the protein believed responsible for Alzheimer's disease in humans; Dhenain et al. 2000, 2003). Bons and colleagues (2006) reported that about 80% of the animals in their study exhibited normal brain aging and 20% showed symptoms similar to those of Alzheimer's patients: impaired cognitive function, aggressive behavior, decreased social interactions, and disrupted biorhythms. Associated with these behavioral changes in older animals are changes in the brain such as deposits of Aβ and hyperphosphorylated tau (the major component of intracellular, fibrillar "tangles" that are particularly prevalent in humans with Alzheimer's disease); however, the distribution of lesions is distinct from that found in humans (Bons et al. 2006).

Aging *M. murinus* also show decays in specific types of learning and memory skills comparable to those that affect humans: procedural memory appears to be conserved,

whereas declarative memory and executive function decline (Picq 2007). Memory and cognitive impairment in aged animals varies by individual—some older animals perform tasks as well as young adults (Picq 1995, 2007).

Olfactory memory does not appear to be affected by age—although it decreases in some aged individuals, in most it does not and there is no consistent age-related pattern of decline (Joly et al. 2006).

One serious caveat concerning the use of *M. murinus* is that because it is listed in CITES Appendix I, animals cannot be taken from the wild and international trade of captive individuals is highly regulated. This means that work at existing colonies can proceed, but establishing new colonies will present a challenge and may limit research on this species.

The Galago or Northern Lesser Bush Baby

The second prosimian species that may be worthy of development as an aging model is the Northern lesser bush baby (*G. senegalensis*; Austad 1997). Lesser bush babies are nocturnal, like mouse lemurs, but weigh about three times as much (Table 1). They tend to be solitary foragers (eating arthropods and plant exudates), but apparently sleep gregariously, nesting in dense vegetation, tree forks, or hollows (Bearder 1986; Nash 2003; Pullen et al. 2000). They are polygynous and typically breed twice a year (Bearder 1986); females cycle year-round under captive conditions, with an estrous cycle of 29 to 39 days (Darney and Franklin 1982). Twin births are the norm and females may produce two litters a year (Bearder 1986). Females park their young at night while they forage and return to the nest periodically to nurse them.

Lesser bush babies are frequently kept in zoos, so their husbandry is reasonably well developed (for descriptions of caging, diet, reproductive management, and medical problems, Wright 1989). They are also in CITES Appendix II, rather than Appendix I, so trade restrictions are far less extensive.

Although reports describe work on the anatomy and biomechanics of *G. senegalensis* (MacLatchy and Muller 2002; Njogu et al. 2006; Ryan and van Rietbergen 2005; Schaefer and Nash 2007), there are no reports of research on aging and age-related diseases.

The major advantage of this species compared with *M. murinus* is that its CITES listing makes it potentially more widely available. But the lack of information on virtually anything having to do with aging is a serious hindrance to determining its potential as an informative model for human aging.

Callitrichids: Marmosets and Tamarins

The callitrichid primates comprise four neotropical genera and about 20 species commonly known as marmosets and tamarins (*Saguinus* and *Leontopithecus* spp.) (Wildman et al. 2009). They are small (<1 kg) diurnal, arboreal primates that live in family groups (with one breeding pair) and feed on arthropods, fruit, small vertebrates, plant exudates, and nectar (Goldizen 1986). They are the most social of the small primates we consider here.

Female callitrichids appear to be continually (rather than seasonally) sexually receptive—copulation may occur even during pregnancy and lactation as well as after the weaning of the young (Goldizen 1986; Savage et al. 1997). Males contribute substantially to offspring care, and reproductive pairs and their offspring cooperate in defending home territories, raising young, and foraging.

Callitrichids generally produce twins (*Callimico goeldii* is an exception), but litters of one or three offspring are not uncommon, although a maximum of two is reared in the wild. In captivity, callitrichids appear capable of producing two litters per year. Young mature around 12 to 18 months of age, but in nature often remain within their parents' territory providing care for the next generation of offspring. Neonates are a significant percentage of maternal body weight (14-24%) and parental care provided by males and siblings is essential for successful reproduction (Clapp and Tardif 1984; Goldizen 1986; Jaquish et al. 1996).

Some species exhibit chimerism in both somatic and germline tissues, a feature that makes them unique among primates and may help to explain the species' social organization and reproductive patterns (Haig 1999; Ross et al. 2007).

Husbandry for several species is well developed and there has been much progress in developing the common marmoset as a model for aging. (For more details about callitrichid biology and the use of common marmosets in aging research, Tardif et al. 2011.) Marmosets and tamarins deserve consideration because of their demographic suitability and wide use in various types of biomedical research, even though they are several times larger than mouse lemurs or bush babies.

We focus here on the cottontop tamarin (*S. oedipus*), which is the most widely studied. Tamarins, like marmosets, are diurnally active and live in social groups that include only a single breeding pair (Burrell and Altman 2006). They are chiefly of interest because they are so commonly kept in captivity and their husbandry is well developed (Clapp and Tardif 1984). Most research in captive colonies to date has focused on cognition, reproduction, and social behavior as it relates to reproduction (Abbott et al. 2003; Almond et al. 2008; Snowdon et al. 2010; Ziegler and Snowdon 2000; Ziegler et al. 2000). Several degenerative diseases with human analogues have also been reported (Lemere et al. 2008; Wood et al. 1998). There are two potential drawbacks of tamarins compared to marmosets: first is their substantially longer life, but, given the extensive characterization of their behavior, they may be useful for cognitive aspects of primate aging; second, the fact that they are critically endangered in the wild (IUCN 2010) presents logistical issues for the development of new research colonies.

Squirrel Monkeys and Capuchins

Finally, two larger NHP species warrant mention here. Squirrel monkeys (*Saimiri* spp.), which weigh 500 to 1100 kg and live up to 30 years, have been used extensively in biomedical and aging research, to study the impact of calorie restriction on aging (Ingram et al. 1990; Qin et al. 2006; Roth et al. 1991, 2000; Sell et al. 2003), age-related cognitive decline (Bading et al. 2002; Brady et al. 1992; Elfenbein et al. 2007; Levy et al. 1995; Lyons et al. 2004, 2007; Mackic et al. 1998; Morelli et al. 1996; Price et al. 1991; Qin et al. 2006; Sawamura et al. 1997; Walker 1993, 1997; Walker et al. 1987, 1990), heart and vascular disease (Brady et al. 1991, 2003; Heddings et al. 2000; Nudo et al. 2003; Tolwani et al. 2000), and reproductive changes during aging (Williams 2008). In addition, squirrel monkeys show age-related declines in memory tasks as well as abnormalities in the brain that are similar to those in humans, and may be suitable models for atherosclerosis.

Capuchin monkeys (*Cebus* spp.) command some attention because of their extreme longevity vis-à-vis body size: they weigh about 2.5 kg and have a maximum recorded lifespan of more than 50 years in captivity (de Magalhaes and Costa 2009). The record is 55 years, which makes *C. capuchinus* virtually as long-lived for its body size as humans (based on our longevity quotient; Austad and Fischer 1991). The extreme longevity of this species suggests that it might be a useful model for exploring mechanisms of successful aging in small primates. The drawback is that few captive colonies exist and even these consist of relatively few animals.

Conclusions

The development of small nonhuman primate models for aging research has considerable advantages: lower costs per animal, greater potential for rapid colony growth, relatively close phylogenetic relationships to humans, and, perhaps most attractively, much shorter lifespan compared with more commonly used NHP species. Indeed, there has been significant progress in aging research using *Microcebus* and *Callithrix* in the past decade. Other species may hold promise for development of aging models, particularly if challenges in husbandry can be addressed. The species reviewed here are those that have been most extensively studied and for which captive individuals are most readily available. They are certainly not the only suitable species and other species may be more appropriate for particular questions in aging research (see, for example, Austad 2011; Edrey et al. 2011; Waters 2011).

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