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PERSPECTIVE

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Bats as instructive animal models for studying longevity and aging

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Abstract

Bats (order Chiroptera) are emerging as instructive animal models for aging studies. Unlike some common laboratory species, they meet a central criterion for aging studies: they live for a long time in the wild or in captivity, for 20, 30, and even >40 years. Healthy aging (i.e., healthspan) in bats has drawn attention to their potential to improve the lives of aging humans due to bat imperviousness to viral infections, apparent low rate of tumorigenesis, and unique ability to repair DNA. At the same time, bat longevity also permits the accumulation of age-associated systemic pathologies that can be examined in detail and manipulated, especially in captive animals. Research has uncovered additional and critical advantages of bats. In multiple ways, bats are better analogs to humans than are rodents. In this review, we highlight eight diverse areas of bat research with relevance to aging: genome sequencing, telomeres, and DNA repair; immunity and inflammation; hearing; menstruation and menopause; skeletal system and fragility; neurobiology and neurodegeneration; stem cells; and senescence and mortality. These examples demonstrate the broad relevance of the bat as an animal model and point to directions that are particularly important for human aging studies.

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INTRODUCTION

With over 1400 species, bats comprise the second-largest order (Chiroptera) of mammals, and are the only mammals that execute true self-powered flight.[1] Bats display an incredible diversity of physiologies, including variations in diet (e.g., fruit, blood, nectar, insects),[2,3] presence or absence of hibernation,[4,5] and short and long life spans.[5,6] In general, lifespan is highly correlated with body mass; however, bats demonstrate exceptional longevity for their body size. Some bat species can live 20–40 years, three to 10 times longer than size-comparable terrestrial nonflying mammals.[5,7–13] Using DNA from tissue sampled from captive and wild bats of known age, epigenetic clocks can accurately estimate the chronological age of any bat.[14] Bats thus offer opportunities as novel models for aging research. First, bats may provide new perspectives on healthspan, as many bat species enjoy decades of good health, free from diseases and disability.[5,11–13] Second, bats allow the study of aging on a timescale like that of primates, in contrast to common animal models with lifespans of only weeks to a few years. This article highlights (1) specific examples of the advantages of bats for studies of longevity and aging and (2) suggests opportunities to increase their impact as an animal model for biomedical research (Figure 1).

GENOME SEQUENCING, TELOMERES, AND DNA REPAIR

The Bat1K initiative is a global effort that began over 10 years ago with a goal of sequencing, assembling, and annotating reference-quality, chromosomal level genomes of all living bat species.[15,16] These reference-quality genomes allow for large, detailed analyses of the molecular adaptations that evolved in bats and are the basis for future functional comparative analyses. Phase one of the Bat1K project has been achieved (assembly of >100 bat genomes representing all bat families), and these genomes are being analyzed to elucidate the longevity adaptations in bats versus other mammals, in short-lived bats versus longer-lived bats, and the role of key aging processes across bat species. These analyses complement (1) ongoing bat mark-recapture aging studies documenting chronological change in biomarkers of aging in wild and captive bats; (2) the comparative *ex vivo* bat cellular assays used to study stress and physiological responses; and (3) inform and direct functional validation studies.

Telomeres are regions of hundreds of 5′-TTAGGG-3′ DNA repeats that cap chromosomes.[17] In eukaryotic somatic cells, these regions shorten with cell replication.[18] Longer telomeric caps are thought to help maintain the stability of the genome.[19] Shortening of telomeres with age has been associated with inflammation, oxidative stress, cellular senescence, and age-related diseases.[19–21] Telomeres do not shorten with age in the longest-lived genus of bats, *Myotis*.[22] Instead, the *Myotis* genome and transcriptome show changes consistent with modifications in telomere maintenance and DNA repair activity.

Beyond genomic machinery, lifestyle can also influence telomere length in bats. For example, hibernation is associated with a lengthening of telomeres in long-lived bats (e.g., some *Rhinolophus* species) suggesting a dynamic process[23] that holds potential for antiaging therapeutics. However, not all bats hibernate (e.g., fruit bats in the wild or some bats in captivity) or maintain telomere length as they age,[22] suggesting that more than one healthspan adaptation has evolved in bats.

Bats are also unusual in that some species mitigate aspects of the age-related increases in DNA damage that occur in most mammals.[16,24] Genomic analyses reveal that some long-lived bats, such as *Myotis* species, may display duplications of *p53*, a tumor suppressor gene that regulates cell division (Athar et al., in review). Some bats also show upregulation of genes associated with DNA repair (e.g., *UVRAG*), inhibition of cell proliferation and tumor formation (miRNA-16 and miRNA-143), and suppression of tumors (e.g., miRNA-101, *BRCA1*, *BRCA2*), as well as downregulation of a tumorigenesis promoter, miRNA-221.[25,26] Moreover, some *Myotis* may benefit from

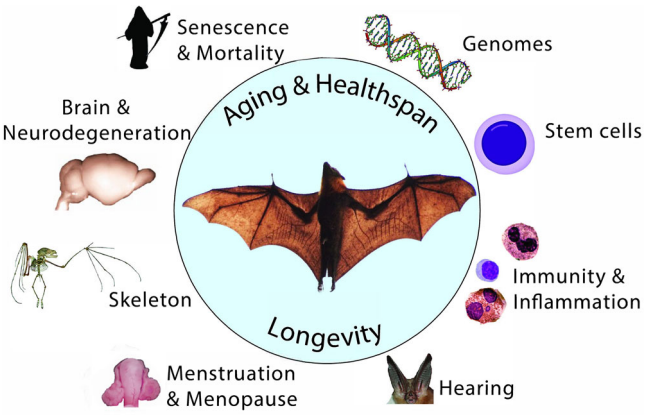

FIGURE 1 Bats are the focus of longevity studies as they may have naturally evolved mechanisms to prevent or delay the onset of age-related changes to their genome, cells, and specific organ systems. Other advantages of bats as a model system relate to their similarities to primates (e.g., neurobiology, reproductive physiology). The availability of some bat species in captive colonies can facilitate controlled studies of aging. Taken together, bats are an exceptional model for understanding the aging process and healthspan, and their study may lead to therapeutics to further human health. Images from vecteezy.com, Wikicommons, the Cooper Lab at NEOMED, and the Orman lab at SUNY Downstate.

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downregulation of genes involved in tumor cell proliferation, especially *HIF1A*, a transcription factor that regulates the expression of genes associated with energetics and angiogenesis.[27,28] Some *Myotis* exhibit age-related transcriptome changes suggesting that their ability to maintain and repair the integrity of their DNA, as well as regulate the cell cycle,[29] increases with age. This could be a mechanism driving the negligible rates of cancer in some bats, which is interesting given they can also maintain telomere length without expected cancer rates. Taken together, these studies suggest that bats may employ diverse and differing mechanisms for mitigating the accumulation of DNA damage with age.

Key areas for future research include:

- Fine-scale and deep comparative genomics to thoroughly understand the genomic mechanisms underlying the ability of diverse bat species to resist cancer and aging.
- Functional tests of genomic novelties based on bat cellular model systems.
- Ongoing mark–recapture and captivity studies of long-lived wild bats to sample individuals of known age to validate genomic predictions.
- Integration and functional validation of findings through studies in traditional models like *Caenorhabditis elegans* and mice (e.g., knock-ins of bat genes and predicted regulators of bats' extended healthspan).

BAT STEM CELLS

Research on bat stem cells has focused on characterizing stem/progenitor cell populations in various tissues. Early studies identified mesenchymal stem cells, neural stem cells, and hematopoietic stem cells in bats, demonstrating their capacity for multilineage differentiation.[30]

Bats display unique transcriptional programs and signaling pathways compared to other mammals.[31,32] Current research explores the physiological properties of bat stem cells, including their responses to stressors, contributions to tissue regeneration, and their potential role in longevity.[31,33–40] For example, fibroblasts of some bats, which can form the basis of some cell lines, do not undergo replicative senescence and display elevated transcript levels of *p53* (work in progress), and are more resistant to cellular stress when challenged with heavy metals, peroxides, and heat.[41–43] Ongoing investigations are also revealing the regenerative capacities of bat tissues, such as their ability to regenerate damaged organs and appendages.

The establishment of bat organoid cultures allows for the recapitulation of complex tissue interactions that are more similar to in vivo physiologies, including responses to viral challenges.[44–47] The future use of bat-derived organoids, including chimeras, may allow for the testing of therapeutics such as mRNA and small proteins that may influence our future pandemic readiness and facilitate the development of therapeutics for human diseases.[44]

Key areas for future research include:

- Comprehensive mapping of bat stem cell populations and their regulation across different tissues.
- Elucidation of the molecular pathways and cellular mechanisms underlying bat stem cell maintenance, self-renewal, and stress resistance.
- Investigation of the contributions of bat stem cell responses to cellular stressors and damage, and their function in tissue regeneration, repair, and longevity.

IMMUNITY AND INFLAMMATION

Bats have extraordinary potential as a translational model for immune therapies.[44] Some bats have an unusual immune tolerance of viruses that are typically lethal in humans but do not cause clinical symptoms (e.g., Ebola, MERS, Marburg, Nipah, SARS-CoV, Hendra, etc.).[26,48–55] The interferon pathway is an essential part of immune surveillance and antiviral defense in mammals. Many bats display constitutively high levels of interferon-α in circulation, which in humans is an inducible gene in response to the activation of pattern recognition receptors, providing antiviral immunity and may allow bats to coexist with viruses without developing pathologies.[54,55] A better understanding of the mechanism of high immune tolerance in bats may provide us with innovative approaches for the treatment of viral infections and future pandemics.

The molecular mechanisms underlying bat immunity have been functionally tested in a cell culture experiment in which macrophages derived from a long-lived *Myotis* bat were challenged with mimics of bacterial (lipopolysaccharide) and viral infections. After an acute proinflammatory response to the mimics, cells from the bats differed from mice in that they eventually showed high levels of the anti-inflammatory cytokine interleukin-10, which may have helped neutralize the proinflammatory response.[56] This anti-inflammatory response could be contributing to a bat's ability to regain homeostasis rather than suffering a cytokine storm or chronic inflammation. Mice with a knock-in of the bat gene *Asc2*, a potent negative regulator of inflammasomes, showed increased survival when challenged with influenza A infection compared to wild-type mice.[57] In addition, the *Asc2* knock-in suppressed inflammasome activation associated with SARS-CoV-2. Bat *Asc2* was highly expressed as mRNA and translated into protein in both humans and mice, where it functioned to inhibit inflammasomes. Because aging is associated with chronic inflammation,[58] some bats that are able to inhibit inflammasomes are probably avoiding aspects of age-related diseases and potentially increasing lifespan.

Immune function shifts during hibernation in bats. In the long-lived bat *Rhinolophus ferrumequinum*, hibernation is associated with decreased immune response and metabolic suppression; however, late hibernating bats showed enhanced expression of genes associated with immune function.[23,59] These results suggest caution in choosing study taxa for immune-related research.

The immune system also plays a key role in the suppression of tumors. The cells of bats are more vulnerable to oncogenic hits for

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malignant transformations compared to humans or mice (work in progress), and yet tumors are rarely found in bats.[60,61] Instead of relying solely on cell cycle and DNA repair signaling, bats may utilize their sophisticated immune surveillance to identify and destroy cancerous cells.

Key areas for future research include:

- Development of bat-based immune cellular model systems.
- Development of novel therapeutics that modulate inflammasomes.
- Elucidation of the molecular pathways that underlie chronic disease in mammals.
- Approaches to promote immune health.

HEARING

The aging mammalian auditory system experiences a gradual accumulation of damage over a lifetime of exposure to sound, leading to the progressive, irreversible loss of hearing sensitivity over time.[62–64] Age-related hearing loss (ARHL) is the most common sensory deficit[65] and the leading cause of disability in people 70 years of age and older.[66] In humans and animal models, ARHL is associated with peripheral sensorineural damage, including loss of cochlear hair cells and their afferent and efferent neurons,[64,67–70] as well as degeneration of the stria vascularis, a structure that maintains the endocochlear potential.[71,72] Although rodent models have provided key insights into the mechanistic basis of hearing loss, intrinsic limitations linked to their short lifespans have constrained our ability to investigate what physiological and molecular mechanisms may support hearing health over a long lifespan and into old age.

Recently, echolocating bats have emerged as potential models for ARHL, not only due to their extremely long lifespans but also because the maintenance of auditory sensitivity is critical for effective foraging, navigation, and obstacle avoidance.

Many bat species adjust their sonar behavior to achieve spectral, temporal, or spatial release from noise[73–76]; however, bats are resistant to noise even when they are unable to behaviorally mitigate its masking effects.[77] Evidence of cochlear resistance to noise exposure[74,78] indicates that bats may possess specializations to reduce noise-induced hair cell damage.[64] For example, previous studies suggest that the auditory efferent system may contribute to preserving hearing sensitivity in bats, with evidence for tonic efferent activation in response to chronic noise exposure (e.g., in bats that live in dense communal roosts[79]) and phasic activation in response to high-intensity, self-generated acoustic signals.[79,80]

Although bats are not always immune to hearing loss,[81] the links between age, hearing status, and auditory structural damage in bats remain relatively unexplored. Recent work has shown evidence for ARHL in the Egyptian fruit bat, *Rousettus aegyptiacus*[82]; however, bats are differentially susceptible to noise-induced cochlear damage in which echolocating insectivorous species show greater resistance to noise-induced hair cell damage than visually dominant frugivores.[78] Preliminary data from the insectivorous big brown bat (*Eptesicus fuscus*) indicate that these auditory specialists are more resistant to cochlear aging than *R. aegyptiacus*. Not only does *E. fuscus* retain good hearing sensitivity into old age, but aging bats do not show structural evidence of cochlear aging characteristic of mammalian ARHL such as loss of inner or outer hair cells or afferent presynaptic ribbons (work in progress).

ARHL can also cause shifts in the entire auditory neuroaxis, including central processing centers.[83] The inferior colliculus, a key midbrain structure for processing auditory temporal and frequency information, has been shown to change with age in humans and mice, and presumably would shift in bats that undergo ARHL (e.g., *Rousettus*) but perhaps not in bats that show resistance to noise and ARHL (e.g., *Eptesicus*). Recordings of neuronal activity in the inferior colliculus of echolocating bats show that they can process complex parallel echolocation streams,[84–86] and disruption of this ability could be a strong selection factor against age-related declines in central auditory processing.

Although the bat auditory system mediates highly specialized biosonar behaviors, it is not fundamentally different from the cell types, structures, and pathways observed in other mammals. Bats, therefore, represent powerful models with great potential to provide important insights into the protective mechanisms supporting healthy cochlear function into old age.

Key areas for future research include:

- Characterization of the cochlear transcriptome in echolocating bats could indicate what factors may confer resistance to acoustic overstimulation and help identify potential therapeutic targets.
- Investigation of bat cochlear cytoarchitecture (e.g., of the stria vascularis, cochlear hair cells, their stereociliary bundles, and their synaptic interface with afferent and efferent neurons) could reveal adaptive structural variation that maintains functional integrity into old age.
- Behavioral and physiological studies could incorporate neuromodulatory tools (e.g., viral vector-based chemogenetics or optogenetics) to probe auditory function, plasticity, and resistance to noise across the lifespan in bats.

MENSTRUATION AND MENOPAUSE

There remains much to understand about the physiological changes in the reproductive system over a lifetime, including the cyclical cessation of endometrial shedding (menstruation), age-related shifts in nonovarian reproductive tissues, and the transition to menopause.

Historically, small laboratory animals (e.g., mice, rats, rabbits, etc.) have represented foundational models for human health. However, unlike humans, these species have bicornuate, V-shaped uteri that support multiple implantation sites and fetuses.[87] Although nonhuman primates are a robust model for studying human reproduction, a national shortage of these animals limits potential reproductive studies and prioritizes translational research efforts.[88,89]

Bats have a simplex uterus, menstruate, and produce 1–2 offspring annually.[90,91] Like humans, bats also can develop adenomyosis and

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endometrial hyperplasia.[92] However, similar to small mammals, bats have a shorter time (1–2 years) to sexual maturity.[93] With this suite of reproductive characteristics, bats are an excellent model to examine the developmental origins of health and disease of the reproductive system.

During gestation, exposure to sex-steroid hormones is critical for proper development of the reproductive system. Because some reproductive disorders coincide with altered hormone profiles and signaling pathways,[94–96] it is possible that alterations to the endocrine system during development can lead to various reproductive conditions. The ability to influence sex-steroid exposure of bats in utero may elucidate the etiology of reproductive conditions. In addition, this model could provide foundational knowledge for the physiology of intersex people and gender-affirming care prior to, during, and after sexual maturation.

In sexually mature individuals, menstruation can coincide with pathological conditions associated with uterine bleeding, including adenomyosis, endometrial hyperplasia, endometriosis, and polycystic ovarian syndrome. Because *Carollia* can develop some of these pathologies naturally,[92] they provide a platform to investigate the etiologies, pathophysiologies, and contributing factors associated with abnormal uterine bleeding.

Bats age at a slower rate compared to similar-sized species,[31] and, therefore, may offer insights into age-related reproductive conditions such as infertility, complications associated with advanced-aged pregnancies, and senescence. Studies that examine age-related alterations in fertility are lacking in bats. To date, the one published study in greater horseshoe bats (*R. ferrumequinum*) found that reproductive capacity did not decrease with age.[97] Although more studies need to be performed to confirm this finding in other bat species, it is possible that some bats may escape complications associated with advanced-age pregnancies.

An individual's direct reproductive output will eventually be zero, often due to mortality, but may also occur due to reproductive aging and menopause. In a few rare species that are menopausal, reproductive output is augmented by increasing the survival of progeny via prosocial behaviors such as food sharing.[98] In some populations of species that menopause, there are relatedness asymmetries because males disperse to a greater extent than females. Vampire bats (*Desmodus*) is one genus that display both these characteristics,[99,100] and, therefore, may undergo menopause. Across a lifespan, reproductive changes are poorly understood, and the inclusion of bats as a model will allow for a detailed understanding of reproductive physiology, health, and senescence.

Key areas for future research include:

- Define the reproductive consequences associated with alterations in sex-steroid exposure during development.
- Elucidate the etiology, pathophysiology, and contributing factors associated with abnormal uterine bleeding.
- Determine if bats alter reproductive output or strategy with age.

SKELETAL SYSTEM AND FRAGILITY

Bone fragility and osteoarthritis are common age-related diseases of the skeleton in the elderly, and effective prevention remains elusive.[101,102] Historical breakthroughs in treating bone fragility have been based on models that also experience age-related bone fragility (e.g., mice,[103,104] nonhuman primates,[105,106] sheep, dogs, goats, pigs, rabbits, and cows[107,108]). Decades of research with these models have produced therapies that slow or compensate for the degeneration of bone tissue, but none have led to the prevention of age-related bone fragility. Despite billions of dollars invested in joint replacement therapies every year,[109] therapeutic approaches that prevent the development of bone fragility and age-related loss in joint cartilage are still lacking.

The bone tissues of bats may offer new paradigms in our understanding of skeletal health and function with age. For long-lived insectivorous bats (e.g., *Eptesicus*) that require functional wings to feed, maintenance of bone integrity is likely a key selection factor. While the bones of mice and humans act as stiff supports for locomotion, the wing bones of bats are elongated and normally bend and flex with wingbeats.[110–112] These bones can bend more before they break compared to the more rigid limb bones of humans and mice, where age-related bone fragility would likely be fatal. Additionally, preliminary tests show that the *Eptesicus* wing bones may not become more brittle with age and maintain youthful levels of collagen gene expression and synthesis (work in progress). Experiments based on limb-derived stem cells of *Carollia* and *Eptesicus* showed that, unlike those of mice, osteoprogenitor cells successfully differentiated into osteoblasts/osteocytes, produced a less mineralized matrix, and showed reduced transcripts of mineral-related genes.[113] Compared to mice, adult bats display novel collagen fiber orientations within their bone matrix, which may offer some resilience to fragility with age.[114]

Beyond the matrix of bone, maintenance of the integrity of articular cartilage and skeletal muscle is critical for the survival of bats. Cartilage protects the bones, provides a smooth gliding surface for movement, and serves as a shock absorber. Studies of the osteoarthritic knee, hip, and glenohumeral joints of mice and humans show a reduction in the number of chondrocytes and articular cartilage thickness, degeneration of the cartilage extracellular matrix, and an overall decline in subchondral bone integrity with age.[115–119] For proper flight in the elderly, bats may display mechanisms to avoid cartilage degradation and sarcopenia with age.

Key areas for future research include:

- Quantify phenotypes of bone, cartilage, and muscle cells and tissues across the lifespan of bats.
- Identify and quantify the molecular pathways bats utilize to maintain musculoskeletal health with age.
- Experimentally quantify senescence, or lack thereof, in the mechanosensitivity of musculoskeletal cells across the extended lifespan of bats.

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NEUROBIOLOGY AND NEURODEGENERATION

Bat and primate brains are structurally similar in cortical and subcortical brain regions, and, therefore, the bat brain offers multiple advantages for translational studies of the neurobiology of aging.

In the brain of Seba's short-tailed bat (*Carollia perspicillata*), the narrow cell layer of the hippocampal formation area CA3 and broad cell layer of area CA1 in the bat resembles the primate brain,[120–124] and is structurally opposite of rodents[125] (broad CA3 and narrow CA1; Figure 2). *Carollia* possesses a clear prosubiculum in its hippocampal formation, a region located between area CA1 and the subiculum.[120] A prosubiculum is readily identifiable in primate brain and rarely or never identified in the rodent brain.[126,127] Its physiological function, thus, has never been established. The retrosplenial cortex[128] is well-defined in the *Carollia* brain, and it possesses immunohistochemical features that clearly group areas 29ab separately from areas 29c and 30.[129] The hippocampal and parahippocampal cortices are not only known for their role in memory and navigational behavior, but these areas are among the earliest and hardest hit in neurodegeneration.[130–133]

Additional similarities between the bat and primate brain are obvious in brain atlases, even if they have not been studied in detail.[121,125,134] For example, the *Carollia* striatum has a distinct caudate nucleus and putamen separated by an internal capsule (Figure 2), as seen in the primate brain.[121,124] The caudate nucleus is a structure associated with motor function[135–137] and reward recognition,[138–141] and is a known target of Alzheimer's disease (AD) and Parkinson's disease (PD).[142–146] The putamen is heavily affected in neurodegenerative disease as well.[145,147,148] In contrast, the rodent striatum does not have a distinct caudate nucleus and putamen[149]; the cells of both are blended together in a single nucleus.[125]

Neurodegeneration occurs in normal aging and is accelerated in disorders such as AD or PD. An established convergence point for the different mechanisms of neurodegeneration and cell death is calcium dysregulation.[150–155] Calcium regulation is critical for the normal physiology of inhibitory neurons. Calcium dysregulation may account for inhibitory neurons being among the earliest losses in neurodegenerative diseases such as AD.[156–158] Reports from animal models of AD have described: preferential loss of calretinin (CR) interneurons,[156] combined losses of CR and parvalbumin (PV) interneurons,[159,160] loss of PV interneurons,[161] and preservation of CR interneuron activity.[162] Reported hyperactivity of excitatory neurons could result from PV interneuron loss and/or from abnormal CR interneuron activity.[163,164]

Another advantage of *Carollia* is found in subcortical structures such as the claustrum, amygdala, and paraventricular and supraoptic nuclei of the hypothalamus, where the relative sizes of these structures are larger than the rat brain[121] (see Ref. 171 for the claustrum). This size advantage offers access for anatomical and physiological studies. The function of the claustrum has been pursued for decades. Despite speculations that it is central to consciousness and high-level cognitive processing,[165–170] functional studies have been hampered due to its thin shape and/or small size in rodents and primates.[171] Relative to the forebrain size, the claustrum in *Carollia* is larger than the claustrum in other mammals. The size advantage of the claustrum in *Carollia* has enabled a detailed definition of multiple inhibitory neuron populations based on calcium-binding protein expression, with distinct distributions in the claustral core or claustral shell,[172] a key to studies of the claustrum's intrinsic circuitry.[173]

The amygdala and hypothalamic structures, such as the paraventricular and supraoptic nuclei, show similar relative size advantages in *Carollia*.[121] Preliminary studies demonstrate rich connectivity between these two hypothalamic nuclei. Coupled with similarities in the urogenital and reproductive systems of humans and bats, *Carollia* may be advantageous for studies of conditions such as nocturia, a significant problem of the elderly.[174–179]

Key areas for future research include:

- Localize and define the time course of any neurodegenerative changes that occur in bats.
- Identify functional biomarkers of inhibitory activity in normal or abnormal circuits in brain areas where inhibitory cell loss is one of the earliest signs of neurodegenerative disease in humans.

SENESCENCE AND MORTALITY

The fact that older bats eventually die indicates that physiological senescence does take place as they age. So far, however, we know very little about age-related degenerative changes in bats. One piece of the puzzle has been uncovered by comparing the transcriptomes of wild, long-lived bats like *Myotis* at different ages: they exhibit typical age-related declines in gene expression associated with adaptive immunity and mitochondrial activity, accompanied by compensatory increases in DNA damage signaling and repair.[29] Fully untangling senescence in bats will require longitudinal studies that are more easily conducted with captive colonies. Notably, the lifespan of captive bats can be significantly longer compared to wild bats. For example, vampire bats live to 15–17 years in the wild,[180,181] but their lifespan can extend to ~30 years in captivity.[182] Table 1 contrasts the published lifespans of several bat species in the wild versus captivity, although notably little is yet known about the longevity of captive bats (maximum recorded lifespans are currently available online at https://genomics.senescence.info/species/index.html for 112 bat species, with 34 species recorded from captivity[183]).

Captive breeding colonies are thus becoming an increasingly important resource to unlock the full potential of bats as animal models for aging. Their expansion avoids the depletion of natural populations, enables hypothesis-driven studies of identified individuals under controlled conditions, and allows for more efficient tissue sampling under resource-sharing plans modeled after those for primate facilities. Colony size, format, and husbandry specifics vary by species and university. Husbandry guidance is available from multiple sources, including *Bats in Captivity* (3 volumes)[184–186] and Skrinyer et al.[187]

Key areas for future research include:

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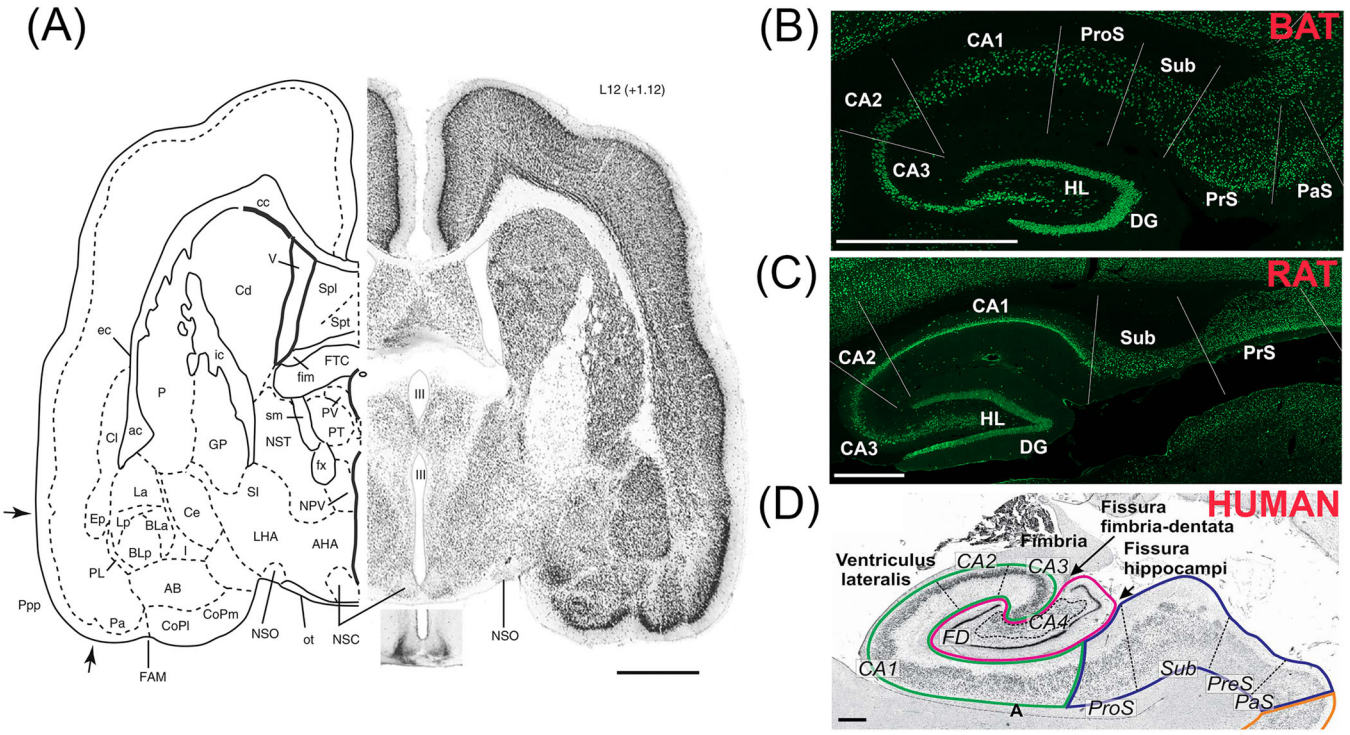

FIGURE 2 Neuroanatomical features of the bat brain. (A) Coronal section of a bat (*Carollia perspicillata*) brain to demonstrate features of caudate nucleus, putamen, amygdala, and some hypothalamic regions. Reproduced with permission from Ref. 123. Comparison of hippocampal cytoarchitecture in (B) bat (*Carollia perspicillata*), (C) rat (Sprague Dawley), and (D) human. The cytoarchitecture of the hippocampal formation of the bat resembles the human hippocampal formation and contrasts with the rat hippocampal formation. In particular, note: (i) the thicker and more dispersed strip of cell bodies in bat and human CA1, as opposed to the thinner and denser strip in rat CA1; (ii) the thinner strip of cell bodies in CA3 relative to CA1 in bat and human, as opposed to the thicker strip in CA3 relative to CA1 in the rat; and (iii) the existence of a prosubiculum in the bat and human but not in rat. (B) Sagittal bat brain section from tiled 63× confocal images. NeuN labeling in green is a neuronal-specific marker. The sagittal plane of this section was determined to be 2.5 mm from the lateral edge and 2.1 mm from the midline. (C) NeuN labeling of sagittal rat brain section from tiled 20× confocal images. This section is 2.8–3.0 mm lateral to the midline (corresponding to plates 82–83 from Paxinos and Watson, *The Rat Brain in Stereotaxic Coordinates, 2nd edition*, Academic Press, 1986). (D) Silver-stained coronal human brain section (magnification and imaging details not available). Subregional boundaries are drawn as white lines in the panels B and C and with color or dotted lines in the panel D. Abbreviations: AB, accessory basal amygdaloid complex (basomedial nuclei); ac, anterior commissure; AHA, anterior hypothalamic area; BLa, basolateral amygdaloid nucleus (anterior); BLp, basolateral amygdaloid nucleus (posterior); CA1, regio superior of cornu Ammonis; CA2, part of regio inferior of cornu Ammonis; CA2, part of regio inferior of cornu Ammonis; CA3, part of regio inferior of cornu Ammonis; cc, corpus callosum; Cd, caudate nucleus; Ce, central amygdaloid nucleus; Cl, claustrum; CoPl, posterolateral cortical amygdaloid nucleus; CoPm, posteromedial cortical amygdaloid nucleus; DG/FD, dentate gyrus (also known as fascia dentata); ec, external capsule; Ep, endopyriform nucleus; FAM, amygdaloid fissure; fim, fimbria, FTC, transverse cerebral fissure, fx, fornix, GP, globus pallidus, HL/CA4, dentate hilus (according to Blackstad or CA4 according to Lorente de No); I, intercalated mass; III, third ventricle; ic, internal capsule; La, lateral amygdaloid nucleus (pars anterior); LHA, lateral hypothalamic area; Lp, lateral amygdaloid nucleus (pars posterior); Me, medial amygdaloid nucleus; NPV, paraventricular nucleus of the hypothalamus; NSC, suprachiasmatic nucleus; NSO, supraoptic nucleus; NST, nucleus of the stria terminalis; ot, optic tract; P, putamen; Pa, periamygdaloid area, PaS, parasubiculum; PL, paralaminar nucleus (amygdala); Ppp, posterior pyriform area; ProS, prosubiculum; PrS/PreS—presubiculum; PT, paratenial nucleus (thalamus); PV, paraventricular nucleus of hypothalamus; SI, substantia innominata; sm, stria medullaris; Spl, lateral septal nucleus; Spt, triangular septal nucleus; Sub, subiculum; V, lateral ventricle. Dorsal is at the top of every panel. Rostral is to the left for panels B and C. Lateral is to the left for the panel D. Calibration bar in the lower left of every panel = 1 mm. Credits: (B) Reproduced, cropped, and relabeled from Fig. 2 of Stewart et al.[120] (C) Original data from Orman, R., von Maydell, K., and Stewart, M. (D) Reproduced and cropped from Fig. 2 of Kedo et al.[189]

- Can the lifespan of long-lived species be extended by living in captivity?
- How do the major organ systems of bats age?
- In cellular model systems, do bat cells show signs of senescence and when?

CONCLUSIONS

Bats have much to offer biomedical research. Their value in longevity research is currently being established at multiple levels, from sub-cellular mechanisms to whole-organ and systemic studies of the

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TABLE 1 Longevity of some bats and their associated colony locations in the United States.

Bat species	Colony location	Documented lifespan (years)	
		Wild	Captive
Artibeus jamaicensis	Colorado State	9 (max)	>10 (max)
	Virginia Tech		19.2 (max)
Carollia perspicillata	Johns Hopkins	10 (max)	12.4 (avg) 17 (max)
	SUNY Downstate		
	University of Illinois, Chicago		
Desmodus rotundus	Princeton	17 (max)	19.5 (avg) 29.2 (max)
Eptesicus fuscus	Brown	5.7 (avg) 19 (max)	Not available
	Johns Hopkins		
	NEOMED		
Rousettus aegyptiacus	Johns Hopkins	9 (avg) 22.9 (max)	22 (avg)
	University of California, Los Angeles		
	University of Illinois, Chicago		
	University of California, Berkeley		
Tadarida brasiliensis	Texas A&M	8 (avg)	12 (avg)
	University of Arizona		
	University of California, Riverside		

Note: Longevity data are compiled from Refs. 10, 181, 183, and 190, and web resources (animaldiversity.org, genomics.senescence.info). Outside of the United States, some colonies include *Phyllostomus discolor* (Max Plank Institute for Ornithology) and *Eptesicus* (McMaster University).

mammalian aging process. Here, we present several vignettes demonstrating the advantages of bats as an animal model. We highlight the importance of exploring the latter portion of their life that has been understudied. We expect the similarities bats share with primates to be especially valuable in aging studies. The availability of reliable epigenetic clocks, molecular tools,[188] and captive colonies of a number of species will permit the following of lifespan, healthspan, and aging to the end of life in diverse bat species. Studies leveraging bats as an animal model have consistently revealed surprising adaptations supporting increased healthspan in a remarkably long-lived mammal, with informative variation that reflects the richness of this group.

AUTHOR CONTRIBUTIONS

L.N.C. and R.O. conceptualized, contributed original text, reviewed, and edited the manuscript. M.Y.A., G.C., A.G., A.M.L., C.F.M., M.S., E.C.T., R.C.W., and T.P.Z. contributed original text, reviewed, and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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