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Emerging technologies for advancing molecular and cellular research in bats

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ABSTRACT

Bats represent a remarkable mammalian lineage, distinguished by the evolution of powered flight, sophisticated echolocation, exceptional longevity, and robust resistance to viral infections. These adaptations have contributed to their rapid and extensive diversification over a short evolutionary period. Extensive research on bat biology has elucidated key aspects of species diversity, adaptive evolution, and the molecular frameworks that confer resistance to viral pathogens. Recent integration of high-resolution multi-omics, single-cell transcriptomics, and advanced three-dimensional culture systems has significantly expanded exploration of bat biology at the molecular and cellular levels. This review consolidates current advances in our understanding of bat species diversification, development, and immunological adaptations with relevance to human health. Emphasis is placed on emerging technologies and methodologies that have transformed the study of bat physiology and host-pathogen interactions. Prospective avenues for research are also outlined, including the development of new animal models and the application of cutting-edge biotechniques. These advances are anticipated to expand the utility of bats as a critical platform for biomedical and evolutionary insight.

Keywords: Bat; Evolution; Adaptation; Organoid; Artificial Intelligence

INTRODUCTION

Bats within the order Chiroptera represent one of the most ecologically diverse and evolutionarily distinctive groups within Mammalia, encompassing more than 1400 recognized species and accounting for over 20% of known mammalian diversity, ranking second only to rodents in terms of species richness (Simmons & Cirranello, 2025; Teeling et al., 2018). This extraordinary lineage has attracted extensive scientific attention across multiple disciplines, including comparative genomics, evolutionary developmental biology, immunology, pathogen ecology, and conservation biology, owing to a suite of rare adaptations not observed in other mammalian taxa.

The evolution of powered flight, a trait unique among mammals, represents a defining innovation in bats. Highly elongated forelimb digits, extended by a thin membranous wing, enable efficient exploitation of the aerial environment, facilitating long-range foraging and predator evasion (Hedenström & Johansson, 2015). This innovation profoundly shaped their life histories, catalyzing their rapid diversification and enabling broad ecological expansion across diverse habitats (Simmons et al., 2008). In addition to flight, bats possess a refined echolocation system, involving the emission and interpretation of high-frequency sound pulses for navigation and prey detection in complete darkness (Jones, 2005). This sophisticated sensory adaptation provides access to nocturnal aerial niches rarely accessible to other vertebrates. The combined evolution of flight and echolocation has enabled exceptional evolutionary flexibility, driving repeated adaptive radiations and a wide diversity of feeding ecologies (Kunz & Fenton, 2005).

The antiviral defenses of bats have attracted intense scientific interest due to their capacity to harbor a wide range of viruses while exhibiting minimal clinical symptoms

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(Banerjee et al., 2021; Irving et al., 2021). Numerous viruses detected in bats, including rabies, Ebola, Marburg, Nipah, Hendra, SARS-CoV-1, MERS-CoV, and SARS-CoV-2, are highly pathogenic in humans (Teeling et al., 2018; Zhao et al., 2022; Zhou et al., 2020b). This extraordinary viral tolerance is hypothesized to reflect strong evolutionary pressures, such as elevated metabolic demands imposed by flight and heightened pathogen exposure in densely populated roosts (Guo et al., 2024; Purushotham et al., 2025; Tian et al., 2025). As a result, bats' capacity to serve as asymptomatic reservoirs for diverse viral taxa has positioned them as critical models for investigating host-pathogen dynamics and the emergence of zoonotic diseases (Temmam et al., 2022).

In parallel with their biomedical relevance, bats perform vital ecological functions across natural and agricultural landscapes. As nocturnal predators of insects, they contribute substantially to pest control, saving the global agriculture industry billions of dollars annually (Kunz et al., 2011; Song et al., 2025; Wang et al., 2025a). Additionally, many frugivorous and nectarivorous species act as pollinators and seed dispersers, supporting the reproductive cycles of a wide range of plants, including economically important crops (Fleming et al., 2009; Song et al., 2025). These ecosystem services are essential for maintaining biodiversity, food security, and human well-being.

Over the past several decades, research on bats has expanded well beyond classical taxonomy to encompass molecular biology, functional genomics, bioinformatics, and innovative biotechnological platforms. Comparative genome sequencing has yielded unprecedented insight into the genetic architecture underlying defining traits of bats, such as flight, echolocation, and antiviral immunity (Jebb et al., 2020; Morales et al., 2025; Parker et al., 2013; Tian et al., 2025; Zhang et al., 2013). Concurrently, the development of induced pluripotent stem cells (iPSCs) (Déjosez et al., 2023; Qin et al., 2023) and organoid systems (Banerjee et al., 2020; Zhou et al., 2020a) has transformed functional studies, enabling controlled modeling of bat-specific cellular processes, including immune regulation, metabolic adaptation, and virus-host interactions.

This review summarizes major advances in molecular and cellular investigations of bats, emphasizing the impact of emerging technologies on our understanding of their unique biological traits and relevance to public health and biomedical research. Applications of high-throughput sequencing have enabled the discovery of previously unrecognized species and the identification of genes linked to key adaptations. Single-cell transcriptomic approaches have provided insight into the cellular architecture of bat wing development, while organoid systems have enabled the study of antiviral defense mechanisms in physiologically relevant contexts (Figure 1). The integration of artificial intelligence (AI), multi-omics platforms, single-cell technologies, iPSC-derived models, and organoid cultures is reshaping the research landscape. This

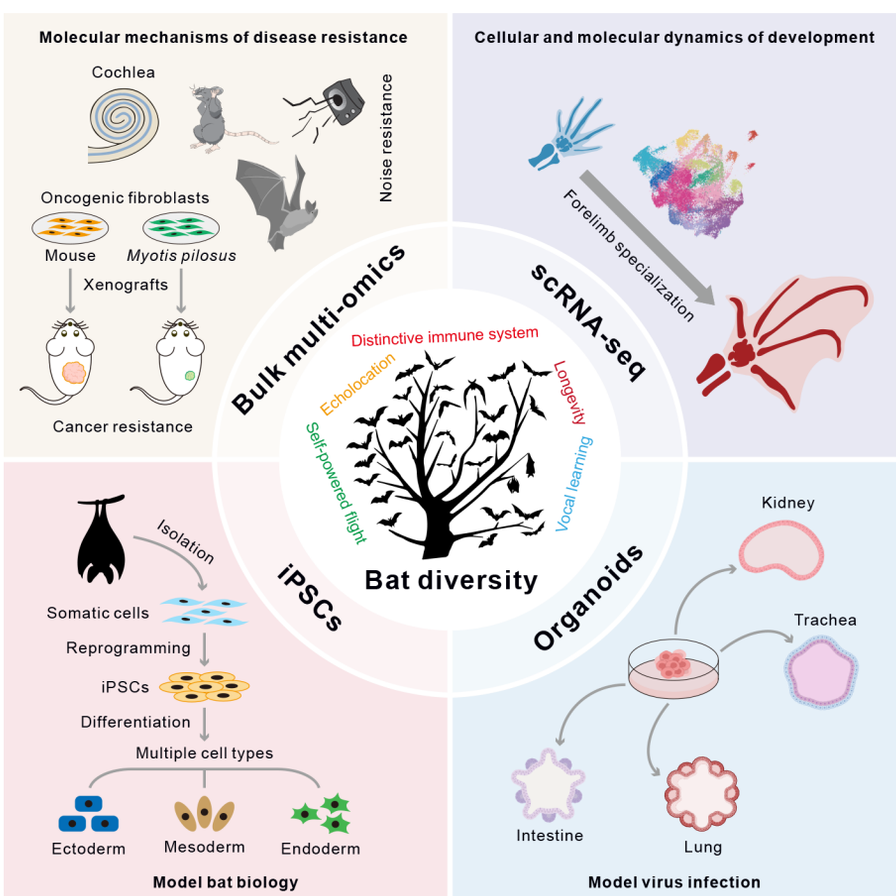

Figure 1 Emerging technologies accelerating mechanistic insights into bat biology

Systematic investigation of bat biodiversity establishes a crucial foundation for elucidating the evolutionary and molecular mechanisms underlying complex traits in bats. Recent advances in bulk multi-omics, single-cell RNA sequencing (scRNA-seq), induced pluripotent stem cells (iPSCs), and organoid systems are rapidly transforming mechanistic research in bat biology.

review also outlines future directions expected to accelerate discovery in bat genomics, disease ecology, and conservation biology. By integrating advanced technologies with established approaches, new opportunities are emerging to resolve the molecular and cellular complexities of bat biology, generate powerful genetic and cellular tools, and drive interdisciplinary research spanning biodiversity conservation, global health, and ecosystem sustainability. Broader domains such as behavioral ecology and flight biomechanics, although important, lie beyond the scope of this review.

RECENT ADVANCES IN BAT SPECIES DIVERSITY

Updated catalog of bat species in China

Understanding the evolutionary origins of complex bat traits depends fundamentally on accurate documentation of species diversity. Recent advances in integrative taxonomy, driven by the combination of morphological characterization and molecular diagnostics—especially through low-cost, high-throughput sequencing—have substantially refined current knowledge of bat diversity. These efforts have revealed many cryptic taxa that were previously indistinguishable based on morphology alone (Novaes et al., 2025). Importantly, targeted surveys of previously underexplored regions have also led to a marked increase in the discovery of new species. For instance, although the Gaoligong Mountains have a long history of mammalogical investigation, bat communities have primarily been overlooked in favor of other taxa (Li et al., 2024). A focused two-year survey recently identified four new bat species, *Rhinolophus yuaner*, *Arielulus jinmao*, *Murina maojiao*, and *Murina duanjiao*, based on morphological analysis and high-throughput sequencing (Luo et al., 2025b). In a parallel effort on the southeastern Qinghai-Tibetan Plateau, five new *Murina* species were described: *M. beibengensis*, *M. medogensis*, *M. milinensis*, *M. yadongensis*, and *M. chayuensis* (Luo et al., 2025a, 2025c). These findings underscore the extent to which bat species richness remains underestimated in under-surveyed areas. Incorporating these newly described taxa and recent literature (Li et al., 2025a; Luo et al., 2025b), an updated checklist of bat species in China was compiled, totaling 172 species across 38 genera and eight families (Table 1).

Table 1 The updated checklist of bats in China

Family	Species name	Common name	IUCN Red List	China's Red List of Biodiversity	Genome assembly
Pteropodidae	*Cynopterus brachyotis*	Lesser dog-face fruit bat	LC	VU	GCA_009793145.1
Pteropodidae	*Cynopterus sphinx*	Cynopterus bat	LC	NT	GCA_030015415.1
Pteropodidae	*Eonycteris spelaea*	Dawn bat	LC	VU	GCA_003508835.1
Pteropodidae	*Macroglossus sobrinus*	Hill long-tongued fruit bat	LC	EN	GCA_004027375.1
Pteropodidae	*Megaerops ecaudatus*	Tailless fruit bat	LC	DD	NA
Pteropodidae	*Megaerops niphanae*	Ratanaworabhan's fruit bat	LC	DD	NA
Pteropodidae	*Pteropus dasymallus*	Ryukyu flying fox	VU	EN	NA
Pteropodidae	*Rousettus amplexicaudatus*	Geoffroy's rousette	LC	VU	NA
Pteropodidae	*Rousettus leschenaultii*	Leschenault's rousette	NT	NT	GCA_015472975.1
Pteropodidae	*Sphaerias blanfordi*	Blanford's fruit bat	LC	VU	NA
Hipposideridae	*Aselliscus stoliczkanus*	Stoliczka's trident bat	LC	NT	GCA_033961575.1
Hipposideridae	*Aselliscus dongbacanus*	Dong Bac trident bat	NT	DD	NA
Hipposideridae	*Coelops frithii*	Tail-less leaf-nosed bat	NT	VU	NA
Hipposideridae	*Hipposideros armiger*	Great leaf-nosed bat	LC	LC	GCA_001890085.1
Hipposideridae	*Hipposideros cineraceus*	Ashy roundleaf bat	LC	NT	NA
Hipposideridae	*Hipposideros fulvus*	Fulvous leaf-nosed bat	LC	DD	NA
Hipposideridae	*Hipposideros gentilis*	Exotic leaf-nosed bat	LC	LC	NA
Hipposideridae	*Hipposideros larvatus*	Horsfield's leaf-nosed bat	LC	LC	GCA_031876335.1
Hipposideridae	*Hipposideros lylei*	Shield-faced leaf-nosed bat	LC	VU	NA
Hipposideridae	*Hipposideros pratti*	Pratt's roundleaf bat	LC	NT	NA
Rhinolophidae	*Rhinolophus nippon*	Greater horseshoe bat	LC	LC	GCA_004115265.2
Rhinolophidae	*Rhinolophus xinanzhongguoensis*	Middle kingdom horseshoe bat	NT	DD	NA
Rhinolophidae	*Rhinolophus affinis*	Intermediate horseshoe bat	LC	LC	GCA_040057535.1
Rhinolophidae	*Rhinolophus malayanus*	Malayan horseshoe bat	LC	DD	NA
Rhinolophidae	*Rhinolophus stheno*	Lesser brown horseshoe bat	LC	NT	NA
Rhinolophidae	*Rhinolophus pearsonii*	Pearson's horseshoe bat	LC	LC	NA
Rhinolophidae	*Rhinolophus yunanensis*	Dobson's horseshoe bat	LC	VU	NA
Rhinolophidae	*Rhinolophus episcopus*	Big-eared horseshoe bat	LC	LC	NA
Rhinolophidae	*Rhinolophus marshalli*	Marshall's horseshoe bat	LC	NT	NA
Rhinolophidae	*Rhinolophus rex*	King horseshoe bat	EN	NT	GCA_041825415.1
Rhinolophidae	*Rhinolophus schnitzleri*	Schnitzler's horseshoe bat	DD	DD	NA
Rhinolophidae	*Rhinolophus siamensis*	Thai horseshoe bat	LC	DD	NA
Rhinolophidae	*Rhinolophus shortridgei*	Blyth's horseshoe bat	DD	DD	NA
Rhinolophidae	*Rhinolophus monoceros*	Formosan lesser horseshoe bat	DD	VU	NA
Rhinolophidae	*Rhinolophus pusillus*	Least horseshoe bat	LC	LC	NA

Continued

Family	Species name	Common name	IUCN Red List	China's Red List of Biodiversity	Genome assembly
Rhinolophidae	*Rhinolophus sinicus*	Chinese horseshoe bat	LC	LC	GCA_001888835.1
Rhinolophidae	*Rhinolophus thomasi*	Thomas's horseshoe bat	LC	NT	NA
Rhinolophidae	*Rhinolophus formosae*	Formosan woolly horseshoe bat	LC	NT	NA
Rhinolophidae	*Rhinolophus perniger*	Woolly horseshoe bat	LC	NT	GCA_043748905.1
Rhinolophidae	*Rhinolophus osgoodi*	Osgood's horseshoe bat	LC	DD	NA
Rhinolophidae	*Rhinolophus yuaner*	Yuaner horseshoe bat	DD	DD	NA
Megadermatidae	*Lyroderma lyra*	Greater false vampire	LC	VU	GCA_004026885.1
Megadermatidae	*Megaderma spasma*	Lesser false vampire bat	LC	DD	GCA_043880595.1
Emballonuridae	*Taphozous melanopogon*	Black bearded Tomb bat	LC	LC	GCA_044509165.1
Emballonuridae	*Taphozous theobaldi*	Theobald's tomb bat	LC	NT	NA
Molossidae	*Chaerephon plicatus*	Wrinkle-Lipped free-tailed bat	LC	DD	NA
Molossidae	*Tadarida insignis*	East Asian free-tailed bat	DD	NT	NA
Molossidae	*Tadarida latouchei*	La Touche's free-tailed bat	EN	NT	NA
Miniopteridae	*Miniopterus fuliginosus*	Asian long-fingered bat	NE	NT	GCA_051201465.1
Miniopteridae	*Miniopterus magnater*	Large long-fingered bat	LC	NT	NA
Miniopteridae	*Miniopterus pusillus*	Small long-fingered bat	LC	NT	NA
Vespertilionidae	*Kerivoula furva*	Dark woolly bat	LC	DD	NA
Vespertilionidae	*Kerivoula picta*	Painted bat	NT	NE	NA
Vespertilionidae	*Kerivoula titania*	Titania's woolly bat	LC	NT	NA
Vespertilionidae	*Kerivoula kachinensis*	Kachin woolly bat	LC	DD	NA
Vespertilionidae	*Kerivoula depressa*	Flat-skulled woolly bat	LC	DD	NA
Vespertilionidae	*Kerivoula dongduongana*	Indochina's woolly bat	LC	DD	NA
Vespertilionidae	*Harpiocephalus harpia*	Hairy-winged bat	LC	NT	NA
Vespertilionidae	*Harpiola isodon*	Formosan golden tube-nosed bat	LC	DD	NA
Vespertilionidae	*Murina aurata*	Little tube-nosed bat	DD	NT	GCA_004026665.1
Vespertilionidae	*Murina bicolor*	Yellow-chested tube-nosed bat	LC	DD	NA
Vespertilionidae	*Murina chrysochaetes*	Golden-haired tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina cyclotis*	Round-eared tube-nosed bat	LC	NT	NA
Vespertilionidae	*Murina eleryi*	Elery's tube-nosed bat	LC	NT	NA
Vespertilionidae	*Murina fanjingshanensis*	Fanjingshan tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina feae*	Fea's tube-nosed bat	LC	DD	NA
Vespertilionidae	*Murina fusca*	Dusky tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina gracilis*	Taiwanese little tube-nosed bat	LC	DD	NA
Vespertilionidae	*Murina harrisoni*	Harrison's tube-nosed bat	LC	DD	NA
Vespertilionidae	*Murina hilgendorfi*	Hilgendorf's tube-nosed bat	LC	LC	NA
Vespertilionidae	*Murina huttoni*	Hutton's tube-nosed bat	LC	LC	NA
Vespertilionidae	*Murina jinchui*	Jinchu's tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina leucogaster*	Rufous tube-nosed bat	LC	LC	NA
Vespertilionidae	*Murina liboensis*	Libo tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina lorelieae*	Lorelie's tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina puta*	Taiwanese tube-nosed bat	DD	NT	NA
Vespertilionidae	*Murina recondita*	Faint-golden little tube-nosed bat	LC	DD	NA
Vespertilionidae	*Murina rongjiangensis*	Rongjiang tube-nosed bat	LC	DD	NA
Vespertilionidae	*Murina shuipuensis*	Shuipu tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina ussuriensis*	Ussurian tube-nosed bats	LC	DD	NA
Vespertilionidae	*Murina yushuensis*	Yushu tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina yuanyang*	Yuanyang tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina lvchun*	Lvchun tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina maojiao*	Maojiao tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina duanjiao*	Duanjiao tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina beibengensis*	Beibeng tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina medogensis*	Medog tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina milinensis*	Milin tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina yadongensis*	Yadong tube-nosed bat	DD	DD	NA
Vespertilionidae	*Murina chayuensis*	Chayu tube-nosed bat	DD	DD	NA
Vespertilionidae	*Eudiscopus denticulus*	Disk-footed bat	LC	DD	NA

Continued

Family	Species name	Common name	IUCN Red List	China's Red List of Biodiversity	Genome assembly
Vespertilionidae	*Myotis altarium*	Szechwan myotis	LC	NT	NA
Vespertilionidae	*Myotis annectans*	Hairy-faced bat	LC	NT	NA
Vespertilionidae	*Myotis badius*	Bay myotis	DD	DD	NA
Vespertilionidae	*Myotis blythii*	Lesser mouse-eared bat	LC	NT	NA
Vespertilionidae	*Myotis bombinus*	Far eastern myotis	NT	NT	NA
Vespertilionidae	*Myotis brandtii*	Brandt's bat myotis	LC	NT	GCA_000412655.1
Vespertilionidae	*Myotis chinensis*	Chinese myotis	LC	NT	NA
Vespertilionidae	*Myotis csorbai*	Csorba's myotis	DD	DD	NA
Vespertilionidae	*Myotis dasycneme*	Pond bat	NT	LC	NA
Vespertilionidae	*Myotis davidii*	David's myotis	LC	LC	GCF_000327345.1
Vespertilionidae	*Myotis fimbriatus*	Fringed long-footed myotis	LC	NT	NA
Vespertilionidae	*Myotis formosus*	Hodgson's bat	LC	VU	NA
Vespertilionidae	*Myotis frater*	Fraternal myotis	LC	DD	NA
Vespertilionidae	*Myotis hasseltii*	Lesser marge-footed bat	LC	VU	NA
Vespertilionidae	*Myotis horsfieldii*	Horsfieldii's myotis	LC	LC	NA
Vespertilionidae	*Myotis ikonnikovi*	Ikonnikov's myotis	LC	LC	NA
Vespertilionidae	*Myotis indochinensis*	Indo-Chinese myotis	DD	DD	NA
Vespertilionidae	*Myotis laniger*	Chinese water myotis	LC	LC	NA
Vespertilionidae	*Myotis macrodactylus*	Big-footed myotis	LC	NT	NA
Vespertilionidae	*Myotis mystacinus*	Whiskered bat	LC	DD	GCA_964094495.2
Vespertilionidae	*Myotis myotis*	Mouse-eared bat	LC	DD	GCF_014108235.1
Vespertilionidae	*Myotis taiwanensis*	Taiwanese myotis	DD	NT	NA
Vespertilionidae	*Myotis montivagus*	Burmese whiskered myotis	DD	LC	NA
Vespertilionidae	*Myotis muricola*	Nepalese whiskered myotis	LC	NT	NA
Vespertilionidae	*Myotis nipalensis*	Nepal myotis	LC	DD	NA
Vespertilionidae	*Myotis pequinius*	Peking myotis	LC	LC	NA
Vespertilionidae	*Myotis petax*	Eastern Daubenton's bat myotis	LC	DD	NA
Vespertilionidae	*Myotis pilosus*	Rickett's big-footed myotis	VU	NT	GCA_036010255.1
Vespertilionidae	*Myotis rufoniger*	Reddish-black myotis	LC	DD	NA
Vespertilionidae	*Myotis siligorensis*	Himalayan whiskered bat	LC	NT	NA
Vespertilionidae	*Myotis aurascens*	Steppe whiskered bat	LC	DD	NA
Vespertilionidae	*Myotis longicandatus*	Long-tailed myotis	DD	DD	NA
Vespertilionidae	*Submyotodon latirostris*	Taiwan broad-muzzled myotis	LC	DD	NA
Vespertilionidae	*Submyotodon moupinensis*	Baoxing broad-muzzled myotis	DD	DD	NA
Vespertilionidae	*Arielulus circumdatus*	Bronze sprite	LC	VU	NA
Vespertilionidae	*Arielulus jinmao*	Jinmao sprite	DD	DD	NA
Vespertilionidae	*Thainycteris aureocollaris*	Collared sprite	LC	DD	NA
Vespertilionidae	*Thainycteris torquatus*	Necklace sprite	DD	DD	NA
Vespertilionidae	*Barbastella beijingensis*	Beijing barbastelle	DD	DD	NA
Vespertilionidae	*Barbastella leucomelas*	Eastern barbastelle	LC	VU	NA
Vespertilionidae	*Barbastella darjelingensis*	Asian barbastelle	LC	DD	NA
Vespertilionidae	*Eptesicus serotinus*	Serotine house bat	LC	LC	NA
Vespertilionidae	*Eptesicus gobiensis*	Gobi serotine	LC	DD	NA
Vespertilionidae	*Eptesicus nilssoni*	Northern serotine	LC	LC	GCA_030846915.1
Vespertilionidae	*Eptesicus pachyomus*	Oriental serotine	LC	NE	NA
Vespertilionidae	*Eptesicus pachyotis*	Thick-eared serotine	LC	LC	NA
Vespertilionidae	*Hypsugo alaschanicus*	Alashanian pipistrelle	LC	DD	NA
Vespertilionidae	*Hypsugo cadornae*	Cadorna's pipistrelle	LC	DD	NA
Vespertilionidae	*Hypsugo pulveratus*	Chinese pipistrelle	LC	NT	NA
Vespertilionidae	*Hypsugo savii*	Savi's pipistrelle	LC	NT	NA
Vespertilionidae	*Hypsugo mordax*	Pungent pipistrelle	DD	DD	NA
Vespertilionidae	*Hypsugo affinis*	Chocolate pipistrelle	LC	LC	NA
Vespertilionidae	*Mirostrellus joffrei*	Joffre's pipistrelle	DD	NE	NA
Vespertilionidae	*Ia Io*	Great evening bat	NT	NT	GCA_025583905.1
Vespertilionidae	*Nyctalus aviator*	Birdlike noctule	NT	NT	GCA_036971965.2
Vespertilionidae	*Nyctalus noctula*	Common noctule	LC	NT	NA

Continued

Family	Species name	Common name	IUCN Red List	China's Red List of Biodiversity	Genome assembly
Vespertilionidae	*Nyctalus plancyi*	Chinese noctule	LC	LC	NA
Vespertilionidae	*Pipistrellus abramus*	Japanese pipistrelle	LC	LC	GCA_044885105.1
Vespertilionidae	*Pipistrellus ceylonicus*	Kelaart's pipistrelle	LC	LC	NA
Vespertilionidae	*Pipistrellus coromandra*	Indian pipistrelle	LC	LC	NA
Vespertilionidae	*Pipistrellus javanicus*	Javan pipistrelle	LC	NT	NA
Vespertilionidae	*Pipistrellus paterculus*	Mount popa pipistrelle	LC	LC	NA
Vespertilionidae	*Pipistrellus pipistrellus*	Common pipistrelle	LC	LC	GCA_903992545.1
Vespertilionidae	*Pipistrellus savii*	Alpine pipistrelle	LC	NT	NA
Vespertilionidae	*Pipistrellus montanus*	Mountain pipistrelle	DD	DD	NA
Vespertilionidae	*Pipistrellus taiwanensis*	Taiwanese pipistrelle	DD	DD	NA
Vespertilionidae	*Pipistrellus tenuis*	Least pipistrelle	LC	NT	NA
Vespertilionidae	*Plecotus austriacus*	Grey long-eared bat	NT	NT	NA
Vespertilionidae	*Plecotus auritus*	Long-eared bat	LC	LC	NA
Vespertilionidae	*Plecotus ognevi*	Ognev's long-eared bat	LC	DD	NA
Vespertilionidae	*Plecotus taivanus*	Taiwan big-eared bat	NT	NT	NA
Vespertilionidae	*Plecotus homochrous*	Himalayan long-eared bat	DD	DD	NA
Vespertilionidae	*Plecotus kozlovi*	Kozlov's long-eared bat	LC	DD	NA
Vespertilionidae	*Scotomanes ornatus*	Harlequin bat	LC	LC	NA
Vespertilionidae	*Scotophilus kuhlii*	Lesser Asiatic yellow bat	LC	LC	NA
Vespertilionidae	*Scotophilus heathii*	Greater Asiatic yellow bat	LC	LC	NA
Vespertilionidae	*Tylonycteris fulvida*	Indiamalayan bamboo bat	NE	LC	NA
Vespertilionidae	*Tylonycteris pygmaeus*	Pygmy bamboo bat	DD	DD	NA
Vespertilionidae	*Tylonycteris tonkinensis*	Tonkin greater bamboo bat	NE	NE	NA
Vespertilionidae	*Vespertilio murinus*	Eurasian particolored bat	LC	LC	GCA_963924515.1
Vespertilionidae	*Vespertilio sinensis*	Asian particolored bat	LC	LC	NA

CR: Critically Endangered; EN: Endangered; VU: Vulnerable; NT: Near Threatened; LC: Least Concern; DD: Data Deficient; NE: Not Evaluated. NA: Not available.

The discovery of new species extends well beyond taxonomic interest, holding significant implications for biodiversity conservation. Many recently described bats occupy extremely narrow ranges and habitats increasingly threatened by deforestation, mining, and agricultural encroachment. Most are known from only a few localities, suggesting that some could be at risk of extinction before their ecological requirements, population sizes, or conservation needs are properly assessed (Frick et al., 2020). This emerging recognition is reshaping conservation assessment strategies, prompting more frequent updates to IUCN Red List classifications for newly resolved taxa (Xiao et al., 2025). In parallel, expanded species discovery has enhanced our understanding of the crucial roles bats play in ecosystems, including pollination, seed dispersal, and insect regulation. These insights underscore both the transformative power of high-throughput sequencing in revealing cryptic biodiversity and the urgent need to protect newly identified bat species and their habitats, especially in the face of accelerating environmental change.

Expanded genomic resources enhance resolution of bat phylogeny

Accurate reconstruction of species-level phylogenies is fundamental for estimating divergence times, inferring speciation and extinction dynamics, and interpreting the evolution of phenotypic, behavioral, and genomic traits (Guo et al., 2021; Nei & Kumar, 2000). Bats were historically classified into two suborders based on morphological features: Microchiroptera (echolocating microbats) and Megachiroptera (non-echolocating megabats) (O'Leary et al., 2013). However, subsequent molecular phylogenetics using multi-locus datasets revealed a different topology, supporting a sister relationship between laryngeally echolocating bats of the superfamily Rhinolophoidea and non-echolocating Old World fruit bats (Pteropodidae), which together form the new suborder Yinpterochiroptera (Guan et al., 2025; Teeling et al., 2000, 2005), with the remaining laryngeally echolocating lineages grouped into the suborder Yangochiroptera. Rapid expansion of genomic resources, ranging from low-coverage assemblies to reference-grade genomes, has enabled increasingly robust reconstructions of bat phylogeny (Jebb et al., 2020; Parker et al., 2013; Tian et al., 2025). Ambitious efforts are now underway to generate chromosome-level assemblies for all extant bat species (Teeling et al., 2018). These datasets, encompassing broad taxonomic and geographic representation, have substantially improved the resolution of deep and shallow branches in the bat phylogenetic tree and enabled more precise estimation of divergence times. By integrating prior phylogenetic analyses (Liu et al., 2023; Teeling et al., 2005) with molecular dating from the TimeTree database (Kumar et al., 2022), a time-calibrated phylogeny was reconstructed for the eight families and 38 genera of bats present in China (Figure 2).

Despite these advances, several phylogenetic relationships remain poorly resolved, particularly among subfamilies within Vespertilionidae and Phyllostomidae, as well as at deeper nodes of the bat tree. These unresolved branches are largely due to incomplete lineage sorting (ILS), introgression, horizontal gene transfer, and extensive convergence (Guo et al., 2021; Hahn & Nakhleh, 2016; Hu et al., 2025), all of which are exacerbated by the rapid radiation of major bat

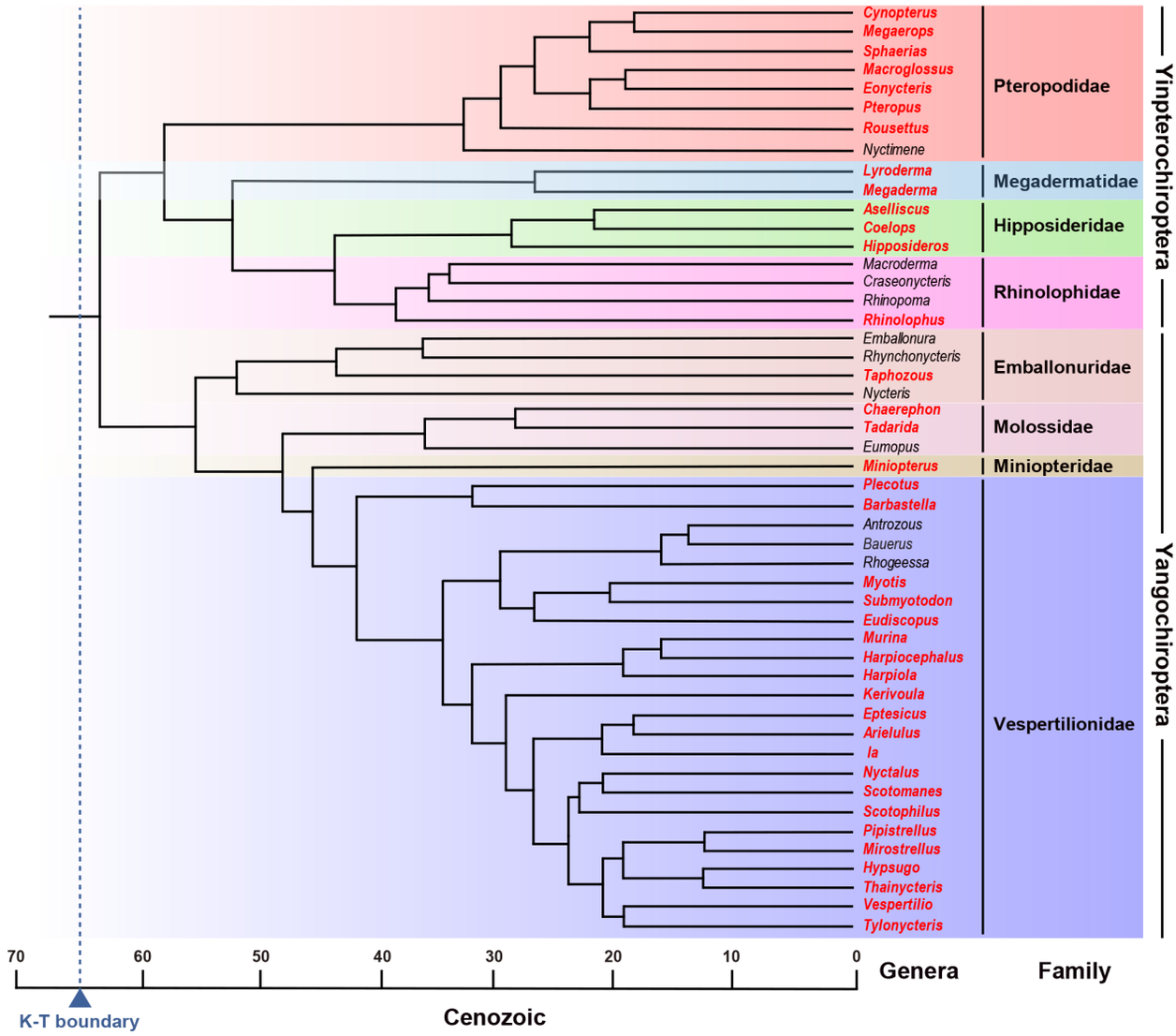

Figure 2 Phylogeny and divergence times of bat families and genera in China

The tree represents a consensus phylogeny with estimated divergence times synthesized from previously published studies. Genera highlighted in red indicate taxa with confirmed distributions in China.

lineages approximately 50–60 million years ago (Guan et al., 2025; Teeling et al., 2005). Resolving these persistent conflicts will likely require large-scale analyses of molecular evolution based on chromosome-level genomic datasets (Wang et al., 2025). In parallel, AI, including machine learning, offers promising tools for extracting phylogenetically informative morphological, molecular, and chromosomal characters among bat species (Mo et al., 2024). The integration of AI-driven inference with high-resolution genomic data is anticipated to advance the reconstruction of a fully resolved and comprehensive species tree for bats.

MOLECULAR EVOLUTION OF ADAPTIVE TRAITS IN BATS

Bats are among the most evolutionarily remarkable mammals, displaying a unique set of adaptive traits that have allowed them to thrive across a wide variety of ecological niches (Teeling et al., 2018). Foremost among these adaptations is powered flight, a capability unique among mammals and central to their evolutionary success. In addition, the emergence of sophisticated echolocation systems has allowed bats to specialize in nocturnal insectivory, navigate complex landscapes, and engage in acoustically mediated social interactions (He et al., 2021; Jones & Teeling, 2006). Technological advances and integrative approaches have greatly expanded understanding of the molecular mechanisms underpinning these adaptations. This section highlights recent insights into the molecular evolution of flight, echolocation, dietary specialization, and longevity in bats (Figure 3).

Single-cell transcriptomics elucidate mechanisms of bat wing development

The evolution of powered flight in bats, which originated approximately 56 million years ago, is well supported by fossil evidence displaying traits such as elongated digits and membranous wings (Simmons et al., 2008). These structural innovations have spurred extensive research into the molecular and developmental mechanisms underlying bat forelimb morphogenesis. Histological analyses have revealed that developing bat forelimbs display enlarged regions of chondrocyte proliferation compared to mouse models (Sears et al., 2006). Maintenance of interdigital membranes in bats is achieved through a balance of enhanced fibroblast growth factor (FGF) signaling and reduced bone morphogenetic

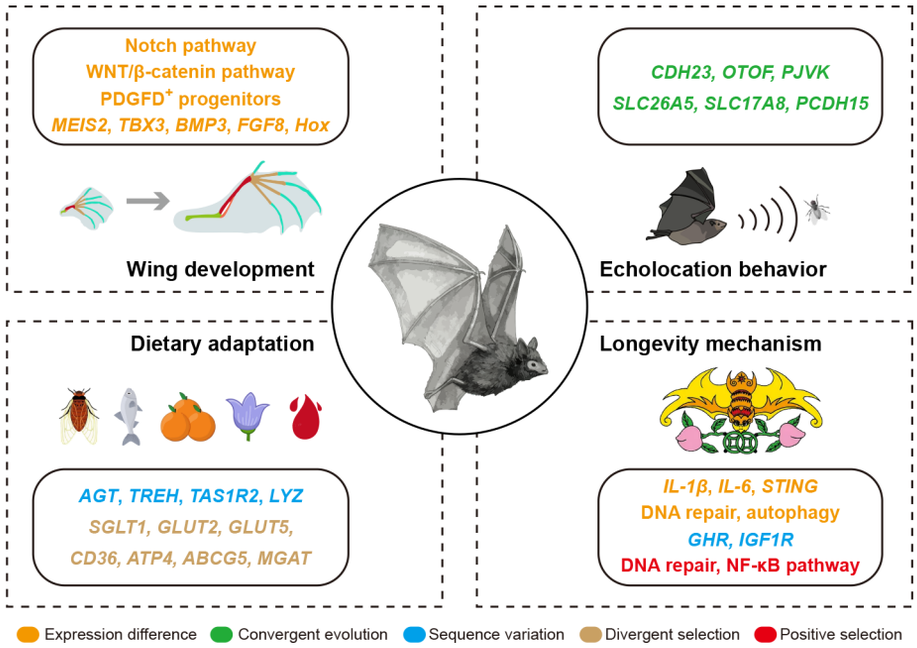

Figure 3 Genes associated with key adaptive traits in bats

Diagram showing genes linked to representative adaptive traits. Genes identified by different analytical approaches are color-coded accordingly.

protein (BMP) activity (Weatherbee et al., 2006). Transcriptomic profiling has further identified elevated expression of genes including *MEIS2*, *TBX3*, *BMP3*, *FGF8*, and multiple *Hox* family members in bat forelimbs relative to hindlimbs (Eckalbar et al., 2016; Wang et al., 2014).

The emergence of single-cell RNA sequencing (scRNA-seq) has enabled cell-type-specific resolution of gene expression dynamics, advancing understanding of bat wing development beyond what bulk transcriptomics could provide (Pomaville et al., 2024). In *Rhinolophus sinicus*, scRNA-seq revealed a distinct population of PDGFD$^+$ mesenchymal progenitors in the forelimb, which promote interdigital web retention and skeletal elongation via secretion of lineage-specific growth factors (Lyu et al., 2025). These developmental processes are characterized by prolonged chondrogenesis and delayed ossification, orchestrated by activated Notch signaling and suppression of WNT/β-catenin pathways. In *Carollia perspicillata*, stage-resolved scRNA-seq analysis of limb development identified conserved cell populations and shared gene expression patterns between bats and mice, while also delineating the developmental origin of the chiropatagium (Orkney et al., 2025). While scRNA-seq has illuminated key aspects of bat wing specialization, certain features remain poorly understood, such as the earlier development of bat hindlimbs compared to other mammals (Nojiri et al., 2023). These questions present promising targets for future scRNA-based approaches. Collectively, these studies demonstrate that bat wing evolution involves both the emergence of novel cellular populations and the reconfiguration of ancestral regulatory networks. Deciphering the developmental basis of bat limb morphology provides critical insight into the evolutionary adaptability of mammalian limb structures and offers important clues about the drivers of morphological novelty and potential mechanisms of limb malformations in humans (Teeling et al., 2018).

Interdisciplinary insights into the origin and evolution of echolocation in bats

Echolocation is a complex adaptive behavior involving the production of acoustic signals and interpretation of returning echoes to support navigation, obstacle avoidance, and prey capture (He et al., 2021; Jones, 2010). In toothed whales, converging lines of evidence suggest a single evolutionary origin of echolocation in their last common ancestor (Churchill et al., 2016; Liu et al., 2018; Park et al., 2016). In contrast, the origin of echolocation in bats remains controversial. Two main hypotheses have been proposed: one posits a single origin of laryngeal echolocation in the common ancestor of all bats, followed by secondary loss in non-echolocating Old World fruit bats (Pteropodidae); the other suggests independent evolution of echolocation in the two echolocating suborders, Yinpterochiroptera and Yangochiroptera (Teeling et al., 2000, 2005).

The bat fossil record offers limited resolution, especially for pteropodids, which lack approximately 98% of expected material, including transitional forms (Brown et al., 2019; Eiting & Gunnell, 2009; Teeling et al., 2005). Morphological studies of extant adults generally support a single origin of echolocation among bats (Hand et al., 2023; Veselka et al., 2010). However, several lines of morphological evidence—including unique postcranial traits in rhinolophids and differences in inner-ear structure between yangochiropterans and yinpterochiropterans—suggest the possibility of independent origins (Davies et al., 2013; Eick et al., 2005). Several researchers have suggested that traits such as enlarged cochleae and multi-harmonic social calls in pteropodids may represent vestiges of primitive echolocation (Springer et al., 2001). One study reported similar prenatal bony labyrinth sizes across bat lineages, aligning with the hypothesis of a single origin of laryngeal echolocation; however, its narrow taxonomic scope and limited sample size have drawn criticism (Nojiri et al., 2018; Wang et al., 2017). In contrast, another study identified distinct laryngeal structural differences between rhinolophid and yangochiropteran bats, suggesting that advanced laryngeal echolocation may have evolved independently in these groups (Usui et al., 2024).

Given the limitations of morphological data and the potential

for homoplasy (Zou & Zhang, 2016), molecular evidence has become central to this debate (Andersson & Georges, 2004; Hirschhorn & Daly, 2005; Stinchcombe & Hoekstra, 2008). Multiple studies have identified convergent amino acid substitutions in hearing-related genes across echolocating lineages of bats and other echolocating mammals (Davies et al., 2012; He et al., 2021; Li et al., 2010; Liu et al., 2011, 2018; Parker et al., 2013; Shen et al., 2012). Genome-wide analyses have revealed enriched convergence in auditory genes along the ancestral branches of all bats and echolocating clades, but not in pteropodid lineages (Liu et al., 2022b). Functional studies of *prestin*, a gene essential for cochlear amplification, suggest that bats with ancestral *prestin* alleles had superior high-frequency hearing and outer hair cell function compared to those with pteropodid-derived variants, supporting a secondary loss of echolocation in Old World fruit bats (Liu et al., 2022b). Fossil evidence (Hand et al., 2023), as well as molecular and functional data, suggest that laryngeal echolocation originated once in the common ancestor of bats, with subsequent loss in pteropodids. However, developmental studies present an alternative scenario. Notably, Nojiri et al. (2021) proposed that the common ancestor of bats possessed only a rudimentary echolocation system, with fully developed laryngeal echolocation evolving independently in rhinolophids and yangochiropterans. Their conclusions, based on embryonic morphological comparisons, are limited by restricted sample size and developmental stages. In contrast, Liu et al. (2022b) used broader taxon sampling and gene-editing approaches to provide genomic and functional evidence favoring a single origin followed by loss in select lineages. These competing perspectives underscore the ongoing uncertainty surrounding the evolutionary origin of laryngeal echolocation in bats. Resolving this question will require integrative approaches that combine fossil, morphological, developmental, and comparative genomic data—potentially supported by AI—to generate a definitive explanation.

Molecular basis of dietary adaptations in bats

Bats exhibit the broadest dietary range of any vertebrate group, exploiting ecological resources that include insects, small vertebrates, fruits, nectar, and even blood. Although approximately 70% of extant bat species are insectivorous (Kunz et al., 2011), ancestral state reconstructions suggest an omnivorous origin, supported by the retention of functional ancestral sweet taste receptors (Li et al., 2023). This molecular versatility may have enabled repeated evolution of specialized diets across divergent bat lineages. Recent advances in genome and transcriptome sequencing, along with functional assays, have provided new insight into the genetic underpinnings of these dietary adaptations (Xu et al., 2024).

Taste receptor genes represent key molecular entry points for dietary specialization. The sweet taste receptor, encoded by *TAS1R2*, is required for detecting sugars in nectar and fruit and has been independently pseudogenized in several obligate piscivorous and sanguivorous species, resulting in the loss of sweet taste perception (Hong & Zhao, 2014; Zhao et al., 2010). In contrast, frugivorous and nectarivorous bats retain intact and functional *TAS1R2* genes. Similarly, bitter taste receptors encoded by the *TAS2R* family—critical for toxin detection—are markedly reduced in bats relative to other mammals. Among bats, vampire species exhibit the smallest functional *TAS2R* repertoire, likely reflecting the low toxin burden of their blood-based diet (Hong & Zhao, 2014; Lu et al., 2021). Corresponding to changes in diet, bats have also evolved modifications in digestive enzymes. The *TREH* gene, which encodes trehalase for the breakdown of trehalose in insect hemolymph, is conserved in all insectivorous bats but has been independently lost in various non-insectivorous clades (Jiao et al., 2019). Insectivorous bats have also undergone multiple duplications of the chicken-type *LYZ* gene, with derived paralogs showing enhanced activity against glycol chitin—a major component of insect exoskeletons (Liu et al., 2014). Together, these findings demonstrate how molecular changes contribute to dietary shifts in bats, which underpin bats' extraordinary ecological diversity.

Comparative genomic and transcriptomic insights into bat longevity

Unlike most small mammals, many bat species exhibit exceptional longevity, living 3-10 times longer than expected based on body size (Wilkinson & Adams, 2019). Species such as the greater mouse-eared bat (*Myotis myotis*) and Brandt's bat (*M. brandtii*) are known to survive well beyond two decades, with some individuals reaching over 40 years (Austad & Fischer, 1991; Foley et al., 2018; Wilkinson & South, 2002). This extended lifespan suggests the evolution of unique physiological and molecular mechanisms that mitigate the oxidative and metabolic stress associated with flight, confer enhanced viral tolerance, and support resistance to cancer (Foley et al., 2018; Gorbunova et al., 2020; Seluanov et al., 2018). Rather than exhibiting canonical age-related transcriptomic changes, as observed in other mammals, bats display a shift in core aging pathways, with age-associated gene expression enriched for functions related to DNA repair, immune/inflammation regulation, and telomere maintenance.

Flight imposes substantial energetic demands and generates reactive oxygen species (ROS), which increase the risk of DNA damage. Despite this, bats demonstrate a remarkably efficient DNA repair system and robust oxidative stress responses. For instance, they maintain naturally high serum uric acid levels—a potent antioxidant that buffers ROS produced during flight (Brunet-Rossinni, 2004). Genome-wide transcriptomic comparisons across species have revealed that bats up-regulate genes involved in DNA repair, autophagy, immune response, and tumor suppression (Huang et al., 2016, 2019). Bats also exhibit a distinct immunological profile characterized by a dampened immune and inflammatory response, which may contribute to their tolerance of viral infections and delayed onset of age-related pathologies. In long-lived species, this modulation is exemplified by a non-canonical amino acid substitution at a highly conserved serine residue (S358) in the stimulator of interferon gene (STING), a key regulator of cytosolic DNA sensing. This modification attenuates proinflammatory signaling and reduces chronic inflammation associated with aging (Wang et al., 2024; Xie et al., 2018). Another feature distinguishing bat longevity is their capacity to maintain telomere stability. In contrast to humans and most mammals, in which telomerase activity is repressed in somatic tissues, leading to progressive telomere shortening with age, bat species such as *Myotis myotis* maintain telomere length throughout their lifespans. This stability likely results from a finely tuned balance between telomerase expression and alternative telomere-lengthening pathways (Foley et al., 2018). Comparative genomic studies

have further identified recurrent signatures of positive selection in genes involved in DNA damage checkpoints, DNA repair, and NF-κB signaling—pathways essential for maintaining genome integrity under high metabolic stress (Zhang et al., 2013). In addition, long-lived bat species exhibit unique amino acid substitutions in the growth hormone receptor (GHR) and insulin-like growth factor 1 receptor (IGF1R), genes implicated in lifespan regulation by modulating growth, metabolism, and cellular senescence (Seim et al., 2013). Collectively, these findings reveal a coordinated set of molecular adaptations encompassing enhanced DNA repair, redox balance, immune modulation, telomere maintenance, and altered endocrine signaling that underpin the extraordinary longevity of bats.

BIOMEDICAL RELEVANCE OF BATS

Bats are increasingly recognized as valuable models for human biomedical research due to their unique, evolutionarily acquired health-related adaptations. Their sophisticated echolocation system exposes them to repetitive, high-intensity sound stimuli, yet many species demonstrate resistance to noise-induced hearing loss (Liu et al., 2021). Despite their small body size, bats also exhibit remarkable longevity and a notably low incidence of cancer (Hua et al., 2024; Seluanov et al., 2018; Vincze et al., 2022; Zhang et al., 2013). In addition, their ability to harbor diverse viral pathogens without developing severe symptoms underscores the distinctiveness of their antiviral immune strategies (Irving et al., 2021). Elucidating the molecular and physiological bases of these traits offers critical insights into mechanisms of hearing preservation, cancer resistance, and immune tolerance, with broad implications for human health, disease prevention, and pandemic preparedness.

Uncovering the mechanisms of noise resilience in bats

Noise-induced hearing loss (NIHL), driven by multi-factorial damage to cochlear structures following hazardous acoustic exposure, represents a major global health concern (Natarajan et al., 2023). Echolocating bats, however, routinely emit high-intensity vocalizations for navigation and prey detection yet display no evidence of noise-related auditory impairment (Amichai et al., 2015; Jakobsen et al., 2013). Empirical studies have shown that species such as the Japanese house bat (*Pipistrellus abramus*) and the big brown bat (*Eptesicus fuscus*) retain auditory sensitivity even after prolonged exposure to intense sound levels (Simmons et al., 2015, 2016, 2017). While middle ear muscle (MEM) contractions, synchronized with sonar emission, have been proposed to attenuate incoming sound pressure (Suga & Jen, 1975), functional disruption of this reflex in species such as Pratt's roundleaf bat (*Hipposideros pratti*) does not diminish auditory resistance, indicating MEM suppression is not the primary protective mechanism (Cui et al., 2025). In addition, big brown bats exhibit negligible age-related hearing loss (Capshaw et al., 2024), supporting their capacity to withstand both acoustic and age-associated cochlear degeneration. Given the convergence of molecular pathways involved in noise- and age-related auditory decline (Chen et al., 2022), echolocating bats offer a powerful tool for uncovering protective mechanisms that preserve hearing.

Comparative cochlear transcriptomic analyses have begun to shed light on these protective adaptations. Gene expression in echolocating bats is enriched for pathways linked to cochlear protection and sensory maintenance (Liu et al., 2021). Notably, experimental overexpression of ISL1 enhances cochlear hair cell survival in bat models. Cross-species transcriptomic profiling of noise-exposed cochleae has revealed distinct molecular responses: while mice exhibited marked immune and inflammatory activation, eastern bent-winged bats (*Miniopterus fuliginosus*) did not show these deleterious changes (Chen et al., 2025). Mechanistically, increased expression of HRAS in bat hair cells enhances resistance to NIHL, both *in vitro* and *in vivo*, via activation of the PI3K/Akt survival pathway, implicating this pathway as a key component of bat-specific auditory protection.

Collectively, these findings establish echolocating bats as a uniquely resilient mammalian system capable of resisting both noise-induced and age-related cochlear damage. Expanding this work through single-cell-resolved transcriptomic and epigenomic approaches across diverse taxa may uncover conserved protective circuits with translational potential for preserving human hearing.

Cancer resistance in bats

In mammals, longevity is frequently associated with enhanced cancer resistance, as observed in long-lived species such as naked mole-rats and blind mole-rats (Gorbunova et al., 2014; Seluanov et al., 2018). Bats, despite their small body size, exhibit remarkably long lifespans and strikingly low rates of spontaneous malignancies (Gorbunova et al., 2014; Teeling et al., 2018; Vincze et al., 2022). Comparative genomic analyses have revealed recurrent positive selection on tumor suppressor genes and DNA repair pathways in bats, suggesting sustained evolutionary pressure to maintain genome integrity and suppress cancer (Scheben et al., 2023; Zhang et al., 2013). Moving beyond correlative evidence, recent studies integrating high-throughput sequencing and functional validation have begun to elucidate specific molecular mechanisms underlying this phenotype. For instance, *Myotis pilosus* demonstrates enhanced resistance to malignant transformation due to a disrupted enhancer regulating COPS5, a gene implicated in oncogenesis (Hua et al., 2024). Furthermore, *M. pilosus* cells effectively withstand replication stress through coordinated up-regulation of ribosome biogenesis and suppression of canonical p53 pathway activation (Huang et al., 2025). Primary fibroblasts derived from four bat species have also been shown to maintain active telomerase, avoid replicative senescence, and resist stress-induced premature senescence (Athar et al., 2025). These results highlight a refined, context-dependent tumor-suppressive architecture rather than uniformly heightened resistance in bats.

Together, these findings establish bats as powerful natural models for exploring the biology of longevity and cancer resistance. Integrative evidence points to multiple, coordinated adaptations, including efficient mitochondrial function, robust genome maintenance, optimized p53 signaling, non-canonical replication stress responses, and organism-level traits such as torpor and potentially enhanced tumor immunosurveillance. Future work should evaluate the consistency of these mechanisms across taxonomically diverse bat lineages, resolve tissue-specific and species-specific differences, and integrate cell-autonomous responses with immune and environmental influences. Ultimately, unraveling the principles underlying bat cancer resistance may offer valuable insights

for mitigating cancer risk and promoting healthy longevity in other mammals, including humans.

Advancing studies of bat antiviral defenses using organoid models

Bats serve as natural reservoirs for a wide array of pathogenic viruses, yet they frequently remain asymptomatic upon infection (Calisher et al., 2006; Irving et al., 2021). Elucidating the cellular and tissue-level mechanisms that support this tolerance could transform current models of mammalian immunity and viral pathogenesis. However, such investigations have been hampered by the absence of physiologically relevant experimental models. *In vivo* studies in bats are limited by ethical constraints, logistical challenges, high costs, and the restricted genetic diversity of available colonies (Schountz, 2014). *In vitro* models, including primary bat cell cultures, often undergo rapid dedifferentiation and lack the three-dimensional architecture and multi-cellular complexity needed to recapitulate tissue-specific host-pathogen interactions (Banerjee et al., 2020; Hua et al., 2024; Irving et al., 2021). These limitations underscore the urgent need for reproducible, scalable, and biologically representative bat models.

Organoids, which are self-organizing three-dimensional structures derived from stem or progenitor cells, recapitulate key architectural and functional features of native tissues (Lancaster & Knoblich, 2014). Compared with traditional cell cultures, they more closely mimic *in vivo* physiology and are especially well-suited for studying non-traditional model organisms such as bats. Bat-derived organoids offer a tractable platform for investigating tissue tropism, receptor use, antiviral signaling, cell death cascades, and tissue repair. Their compatibility with genetic manipulation and high-throughput screening also facilitates mechanistic studies in virology and immunology.

Recent developments have enabled the generation of bat organoids from multiple tissues and species (Table 2). The first system was established from the intestinal epithelium of the Chinese horseshoe bat (*Rhinolophus sinicus*), which supported productive SARS-CoV-2 replication and revealed robust innate immune responses that rapidly restricted viral spread (Zhou et al., 2020a; Liu et al., 2022a). These results provide a mechanistic explanation for asymptomatic viral carriage in bats. Subsequent studies have developed intestinal, lung, and airway epithelial organoids from multiple bat species, facilitating comparative analyses of epithelial barrier function and antiviral immunity (Chan et al., 2023; Elbadawy et al., 2021, 2025; Hashimi et al., 2023; Kellner et al., 2025; Su et al., 2023). Most recently, multi-tissue organoids, including respiratory, intestinal, and renal types, have been derived from five wild bat species and used for the isolation and characterization of bat-borne orthoreoviruses and paramyxoviruses, as well as antiviral drug testing (Kim et al., 2025), demonstrating the breadth and clinical relevance of organoid-virology pipelines. Bat organoids thus serve as versatile systems for: (i) dissecting innate immune mechanisms such as interferon signaling and inflammasome activation that contribute to viral tolerance; (ii) mapping tissue and cell-type tropism across diverse bat lineages in comparison with human systems; (iii) evaluating the influence of host genetic variation and viral genotypes on replication dynamics and pathogenesis; and (iv) enabling scalable, standardized, and ethically tractable experimentation without reliance on live animal models.

In summary, bat organoid platforms address long-standing experimental barriers by offering physiologically relevant and reproducible systems for studying host-pathogen interactions. Integration of these models with functional genomics, immunology, and virology promises to illuminate the mechanisms underlying viral tolerance in bats and may yield novel strategies for pandemic preparedness and host-directed therapies.

FUTURE DIRECTIONS: EMERGING TECHNOLOGIES TRANSFORMING BAT BIOLOGY

Although molecular and cellular studies of bats are advancing rapidly through innovative methodologies, several unresolved questions persist, particularly regarding resistance to acoustic trauma and cancer. The prevalence of these traits across bat species, the molecular and evolutionary mechanisms that underpin them, and the specific cellular processes involved remain unclear. Progress is further constrained by the limited availability of robust genetic tools. However, recent advances in multi-omics, cell biology, and AI are generating new opportunities to address these challenges. Three emerging technologies in particular—XAI, single-cell multi-omics, and bat organoid models—are poised to transform the field (Figure 4). XAI enables the interpretation of complex genotype-phenotype relationships by integrating heterogeneous datasets; single-cell multi-omics provides high-resolution insights into the cellular and molecular mechanisms that drive development and adaptation; and organoid models offer scalable, physiologically relevant platforms for mechanistic investigation and translational research. Together, these tools establish a multi-scale framework for studying bat biology, with the potential to unravel species-specific adaptations and inform broader research in virology, oncology, and regenerative medicine.

XAI for deciphering genotype-phenotype relationships in bats

Recent advances in sequencing technologies and computational modeling have rapidly expanded the landscape of bat genomics, offering new opportunities and challenges for decoding the genetic basis of complex traits. XAI has emerged as a powerful approach for interpreting complex genotype-phenotype relationships in animals, including bats, while also providing model transparency and interpretability for biomedical use (Mwangi et al., 2023; Sharma & Goel, 2025; Zhang et al., 2023). XAI techniques enable researchers to unravel non-linear and high-order associations between molecular variation—such as single nucleotide polymorphisms (SNPs), indels, and site mutations—and complex traits, including echolocation, viral resistance, and metabolic adaptations (Cao et al., 2025; Novielli et al., 2024). Techniques such as SHapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME) have been applied in bat genomic studies to quantify the contribution of individual genetic features to phenotype predictions (Novielli et al., 2024; Yagin et al., 2023).

Despite these advances, bat genomic resources remain less complete than those of classical model organisms, with many species represented by low-coverage or fragmented assemblies. These limitations restrict the ability to train robust, generalizable models. Additionally, traits such as longevity or immune tolerance are often polygenic and environmentally

Table 2 Established bat organoids

Species	Organoid type	Infected viruses and susceptibility	References
Artibeus jamaicensis	Intestinal	SARS-CoV-2: limited susceptibility	Hashimi et al., 2023
Carollia perspicillata	Airway	Porcine IAV (H1N1/2006 and H3N2/2007): susceptible	Su et al., 2023
Eptesicus serotinus	Tracheal	SARS-CoV-2: insusceptible; MERS-CoV: susceptible; IAV: susceptible; MRV: susceptible	Kim et.al., 2025
	Lung	SARS-CoV-2: insusceptible; MERS-CoV: susceptible; IAV: susceptible	
	Kidney	SEOV: susceptible	
	Small intestinal	SARS-CoV-2: insusceptible	
Hypsugo alaschanicus	Tracheal	SARS-CoV-2: insusceptible; MERS-CoV: insusceptible; MRV: susceptible; IAV: susceptible	Kim et.al., 2025
	Lung	SARS-CoV-2: insusceptible; MERS-CoV: insusceptible; IAV: susceptible	
	Kidney	SEOV: susceptible; MRV: susceptible	
	Small intestinal	MRV: susceptible; SARS-CoV-2: insusceptible	
Myotis aurascens	Tracheal	SARS-CoV-2: insusceptible; MERS-CoV: susceptible; IAV: susceptible; MRV: susceptible	Kim et.al., 2025
	Lung	SARS-CoV-2: insusceptible; MERS-CoV: susceptible; IAV: susceptible	
	Kidney	IAV (Human H1N1, Avian H5N1): susceptible; SEOV: susceptible	
	Small intestinal	IAV (Human H1N1, Avian H5N1): susceptible; SARS-CoV-2: insusceptible	
Pipistrellus abramus	Tracheal	SARS-CoV-2: insusceptible; MERS-CoV: insusceptible; IAV: susceptible; MRV: susceptible	Kim et.al., 2025
	Lung	SARS-CoV-2: insusceptible; MERS-CoV: insusceptible; IAV: insusceptible	
	Kidney	SEOV: susceptible	
	Small intestinal	SARS-CoV-2: insusceptible	
Rousettus aegyptiacus	Intestinal	MARV: susceptible	Kellner et al., 2025
	Respiratory	MARV: susceptible	
Rhinolophus ferrumequinum	Tracheal	SARS-CoV-2: insusceptible; MERS-CoV: susceptible; IAV: susceptible; MRV: susceptible	Kim et.al., 2025
	Lung	MERS-CoV: susceptible; SARS-CoV-2: insusceptible; IAV: susceptible	
	Kidney	SEOV: susceptible	
	Small intestinal	SARS-CoV-2: susceptible	
Rousettus leschenaultii	Intestinal	SARS-CoV-2: insusceptible; PRV: susceptible	Elbadawy et al., 2021
Rhinolophus sinicus	Intestinal	SARS-CoV-2: susceptible	Zhou et.al., 2020a
	Intestinal	SARS-CoV-2: susceptible; EV-71: insusceptible; CoV-HKU4: susceptible	Liu et.al., 2022a

modulated, complicating efforts to isolate causal variants without experimental validation. Integrating genomics with transcriptomic, epigenomic, and environmental data offers a promising strategy to improve resolution, but poses technical and computational challenges (Jaganathan et al., 2025). Studies in other species demonstrate the feasibility of such integration. For example, To et al. (2024) established a multi-omics atlas of human embryonic skeletal development, advancing our understanding of cell-fate determination in human development. Similarly, Xue et al. (2023) combined genomics, transcriptomics, and epigenomics to explore trait evolution in humans and other taxa. Despite these obstacles, XAI serves as a vital bridge between advanced computational modeling and actionable biological discovery. By making AI-derived predictions transparent, XAI facilitates the identification of adaptive mechanisms underlying bat-specific traits with implications for evolutionary biology, disease resistance, and translational medicine (Mathew et al., 2025; Mwangi et al., 2023).

Single-cell multi-omics reveals the regulatory basis of bat development

Single-cell multi-omics technologies have redefined biological research by enabling the dissection of cellular heterogeneity, gene regulatory networks, and tissue development with an unmatched resolution (Wu et al., 2024). These cutting-edge technologies have arrived at a crucial juncture for bat developmental biology, where the molecular mechanisms underlying complex traits remain largely unresolved. Although scRNA-seq has facilitated significant advances, it alone often lacks the depth to fully capture how diverse cell states and regulatory interactions shape bat-specific adaptations. By integrating genomics, transcriptomics, epigenomics (e.g., scATAC-seq, DNA methylation), and proteomics at the single-cell level, multi-omics now permits comprehensive characterization of gene regulation, cellular identity, and developmental trajectories in bats, as demonstrated in other mammalian models (Baysoy et al., 2023; Vandereyken et al., 2023; Ren & Liu, 2024). These integrative approaches also illuminate how evolutionary modifications in gene regulatory architecture contribute to phenotypic divergence between bats and other mammals.

Despite their promise, applying these methods to bats poses significant challenges. Access to high-quality embryonic or neonatal tissues is constrained by ethical considerations, conservation concerns, and logistical barriers in colony management. The absence of high-quality, chromosome-level genomes for most bat species complicates accurate mapping and cross-modal data integration. Computational pipelines established in model systems may not be generalizable to bats, and both experimental implementation and downstream analysis require considerable financial and technical resources. Functional follow-up validation remains limited due

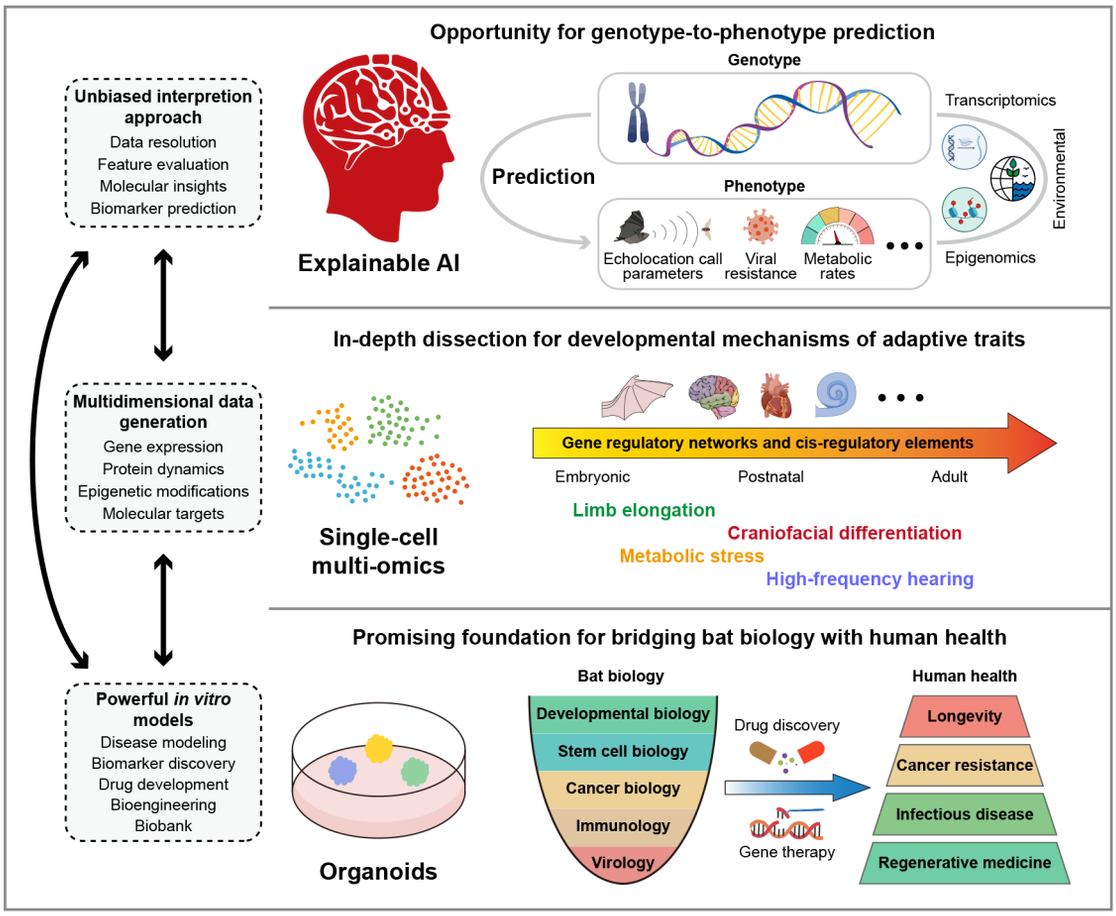

Figure 4 Future directions in bat biology enabled by explainable artificial intelligence (XAI), single-cell multi-omics, and organoid systems

XAI can integrate multi-omics, ecological, and phenotypic datasets to infer gene regulatory networks and prioritize candidate genes, enhancers, and pathways underlying complex traits in bats. Single-cell multi-omics approaches enable resolution of cell types, regulatory states, and lineage relationships across diverse bat lineages and life stages. Standardized bat organoid platforms, including co-cultures with immune and endothelial cells, provide experimental systems to examine host-pathogen interactions, tissue repair processes, and cellular stress responses.

to current gaps in genetic manipulation and *in vitro* culture systems for bats. Nevertheless, single-cell multi-omics offers an unparalleled lens through which to explore bat development at the cellular, molecular, and systems levels. As reference genomes and experimental protocols advance and technical limitations diminish, these technologies will enable high-resolution mapping of the cell types, lineage hierarchies, and regulatory circuits that underlie hallmark adaptations in bats (Badia-i-Mompel et al., 2023; Cui et al., 2024). These capabilities promise to elevate bats as central models in developmental and evolutionary biology, offering transformative insights into the origins of mammalian innovation and phenotypic diversity.

Organoids as emerging frontiers in bat biology

Bat-derived organoids are rapidly becoming a transformative platform for studying antiviral mechanisms, physiological adaptation, and developmental biology (Park et al., 2025; Wang et al., 2025b). These three-dimensional, self-organizing cultures enable detailed assessment of antiviral compounds, immune modulators, and gene therapies in a bat-specific cellular context. Crucially, side-by-side comparisons between bat and human organoids facilitate the assessment of species-specific efficacy and cytotoxicity of candidate interventions, laying the groundwork for more effective preemptive strategies against zoonotic threats and viral emergence (Kellner et al., 2025). Bat organoids also provide a robust platform for functional genomics. Advanced techniques, such as CRISPR-based gene editing, transcriptomic profiling, and high-throughput screening, can be applied to organoid models (Andreatta et al., 2025; Pagliaro et al., 2025), enabling dissection of the regulatory architecture underlying bat-specific traits, including antiviral defense, DNA repair, metabolic regulation, and resistance to stress-induced damage. The ability to engineer isogenic organoids with precise genetic alterations further allows for mechanistic studies and the mapping of genotype-to-phenotype relationships.

Future directions should prioritize expanding the taxonomic and tissue representation of bat organoid cultures, establishing species-specific reagents and genetic tools, and integrating multi-omics and high-throughput functional pipelines. Strategic collaboration across disciplines, including stem cell biology, immunology, virology, and bat ecology, will be essential for fully realizing the fundamental and translational potential of bat organoids. The rationale and objectives of bat organoid research are firmly rooted in the extraordinary biology of bats and their pivotal role in zoonotic transmission. As technical barriers are addressed, bat organoids promise to revolutionize comparative and translational studies in infectious disease, tissue regeneration, cancer biology, and drug discovery—filling a long-standing

methodological gap in bat research and pushing bats to the forefront of biomedical innovation.

CONCLUSIONS: SYNERGISTIC FRAMEWORK FOR MULTI-TECHNOLOGY INTEGRATION

Establishing bats as model organisms presents several challenges, including slow reproductive rates, difficulties in breeding and colony maintenance, and limited tools for genetic manipulation. However, advances in iPSCs and organoid cultures offer promising alternatives. These systems enable *in vitro* modeling of bat tissues and organs, thereby reducing reliance on live animals and complex breeding, accelerating functional studies, and facilitating targeted genetic manipulation in a controlled setting.

The integration of XAI, single-cell multi-omics, and bat organoids provides a synergistic framework for advancing mechanistic studies in bat biology. Single-cell multi-omics enables high-resolution profiling of gene expression, chromatin accessibility, and protein dynamics at the cellular level, generating rich, multi-dimensional datasets that reveal key molecular features. XAI can analyze these complex datasets to uncover interpretable relationships between genetic variation and phenotypic traits. Organoid platforms then allow experimental validation of XAI predictions and mechanistic dissection of bat-specific adaptations under physiologically relevant conditions. Together, these approaches create a closed-loop discovery pipeline (Figure 4) in which hypothesis generation, data analysis, and experimental testing are continuously refined, accelerating the discovery and validation of new biological insights.

Despite the success of XAI, multi-omics, and organoid models in human and murine systems, several barriers hinder their broad application in bats. Unlike the high-quality genomes and comprehensive datasets available for traditional model organisms, most bat genomes remain incomplete or poorly annotated (Jebb et al., 2020), hindering the effectiveness of AI and multi-omics analyses (Li et al., 2025b; Zhang et al., 2023). AI models require high-quality, species-specific training datasets, which are often unavailable for bats (Kraemer et al., 2025). As a result, models based on other species may fail to capture bat-specific features, leading to biased or unreliable results. The remarkable taxonomic and ecological diversity among bats further complicates comparative studies and limits the generalizability of findings. Technical limitations also constrain the development of bat organoids. Unlike human and mouse systems, protocols for bat-derived organoids are still under development, with limited understanding of bat-specific growth factors, signaling pathways, and developmental kinetics. These differences reduce the efficiency and fidelity of bat organoid cultures. Additionally, a shortage of bat-specific reagents—including antibodies, cell lines, and gene-editing tools (e.g., CRISPR/Cas9)—further impedes experimental progress. Ethical and conservation constraints complicate tissue acquisition, particularly for threatened or endangered species, necessitating careful adherence to animal welfare and conservation regulations.

Although these limitations remain significant, they are not insurmountable. Strategic efforts are needed to build foundational infrastructure for bat research. First, single-cell multi-omics can be leveraged to improve genome annotation and inform the development of AI models tailored to bats. Second, integration of transcriptomic and epigenomic data will support the optimization of organoid protocols across diverse species. Third, cross-disciplinary collaboration among virologists, immunologists, geneticists, and conservation biologists will be essential for developing standardized protocols, shared resources, and species-specific experimental systems. Addressing these challenges through coordinated innovation will enable the full potential of emerging technologies to be realized in bat biology, transforming them from understudied mammals into tractable systems for advancing developmental, immunological, and translational research.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Z.L. and C.G.Z. conceived and designed the study. Z.N.Z., Q.L., and R.S.L. drafted the "Recent advances in bat species diversity" section; Z.N.Z., Z.L., and C.G.Z. drafted the "Molecular evolution of adaptive traits in bats" section; and P.C. drafted the "Biomedical relevance of bats" section. R.S.L. compiled Table 1, and Z.L.Z. compiled Table 2. Z.L. drafted the manuscript. All authors read and approved the final version of the manuscript.

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