Are Better Animal Models Needed Beyond C57BL/6 Mice to Study Aging-Associated Osteoarthritis?

Authors: Shouan Zhu, Richard F. Loeser, Brian O. Diekman, John Collins, Hirotaka Iijima, Michael J. Jurynec, Matlock A. Jeffries

Response/Recommendation: There really isn't a better or an ideal animal model to study age-associated OA. **Strength of evidence**: Strong

Osteoarthritis (OA) is an age-associated, multifactorial joint disorder characterized by progressive cartilage degradation, subchondral bone remodeling, osteophyte formation, and synovial inflammation that results in pain and loss of function. The contribution of aging to OA pathogenesis involves an intricate interplay between cellular senescence, metabolic reprogramming, and chronic low-grade inflammation ("inflammaging")[1-3]. Animal models remain indispensable for dissecting these mechanisms and testing interventions. However, the widely used C57BL/6 mouse—while genetically tractable and cost-efficient—develops only mild and variable spontaneous OA lesions during natural aging, raising the question of whether other models might better replicate the human aging-OA continuum[4-6]. Notably, aging studies in C57BL/6 mice benefit from relatively well-defined correspondence to human aging; for example, 18–24-month-old mice are often considered analogous to ~56–69-year-old humans based on Jackson Laboratory criteria. Comparable age-to-human mappings are far less standardized for most other species and strains, complicating interpretation of "aging-associated" OA across models.

Limitations of the C57BL/6 Aging Model: C57BL/6 mice at 18–24 months of age exhibit gradual proteoglycan loss, mild cartilage thinning, and limited subchondral sclerosis, often more pronounced in males than females[4,6]. These lesions are relatively modest compared with the severity and heterogeneity seen in human late-life OA. The slow onset and small effect size necessitate large cohorts, increasing study duration and cost. Moreover, the sex bias toward male susceptibility in this strain contrasts with the higher prevalence of OA in aged women. Another issue is that there is no actual C57BL/6 mouse available but rather there are two sub-strains: C57BL/6J and C57BL/6N that arose from the original C57BL/6 mice due to mutations in the colony after breeding at either Jackson labs (6J) or the NIH (6N)[7]. Important to OA research, the 6J mice have a mutation in the nicotinamide nucleotide transhydrogenase (Nnt) gene that affects NADPH levels resulting in metabolic abnormalities including alterations in glucose homeostasis and increased susceptibility to oxidative stress.

Despite these shortcomings, C57BL/6 remains a valuable background for genetic manipulation, behavioral assays, and integration with "omics" analyses. Yet, for mechanistic fidelity to human aging, complementary or alternative strains and species are increasingly considered.

Alternative Murine Models Showing More Robust OA with Aging: Several mouse lines display stronger or earlier spontaneous OA, enabling more efficient exploration of age-related joint degeneration.

- STR/Ort mice develop spontaneous, male-biased OA as early as 5–7 months, with prominent osteophytes and subchondral thickening[8-10]. Although pathology is driven by unique genetics rather than physiologic aging, this model offers consistent penetrance and robust histopathology.
- Senescence-accelerated SAMP8 mice demonstrate cartilage degeneration, meniscal lesions, and systemic frailty by 6–9 months[11]. They provide a bridge between accelerated aging biology and joint pathology, albeit with confounding systemic decline.
- UM-HET3 mice, a four-way cross of inbred strains, develop spontaneous OA by 22–25 months with variability resembling human heterogeneity[12,13]. The model's genetic diversity enhances translational relevance for aging interventions. The variation of disease severity among mice is also often large, which necessitates large N to reach statistical significance.

Together, these models extend beyond the mild phenotype of C57BL/6 and capture key aspects of aging biology—cellular senescence, mitochondrial stress, hormonal imbalance, and altered mechanotransduction. However, they all suffer from caveats ranging from physiological irrelevance to confounding systemic decline to large variability.

Genetically Engineered Models Linking Aging Pathways to OA: Targeted genetic modifications in cartilage structural or signaling pathways yield spontaneous OA, even in younger animals:

- PANX3-deficient mice exhibit severe OA and subchondral remodeling in old age, linking purinergic signaling to cartilage integrity[14,15].

- Growth hormone (bGH) transgenic mice show accelerated OA and chondrocyte hypertrophy by mid-life, offering insights into endocrine drivers of joint aging[16].
- Smurf2-transgenic mice develop progressive cartilage fibrillation due to TGF-β/Smad3 pathway suppression[17].
- Col9a1$^{-/-}$ and Col2a1 mutant mice exhibit cartilage erosion and pain sensitivity with age, modeling matrix instability[18-21].
- Col11a1 haploinsufficient mice display gradual OA and osteophyte formation due to disrupted fibrillar collagen organization[22].
- NFATc1/2 double-deficient mice show accelerated spontaneous OA, highlighting transcriptional control of chondrocyte aging[23].

Although these lines are not strictly "aging models", they emulate cellular mechanisms—matrix senescence, altered signaling, and oxidative stress—integral to age-driven OA.

Non-Murine Species Offering Greater Translational Relevance: Larger species naturally developing OA with age provide advantages in cartilage size, biomechanical loading, and clinical relevance:

- Dunkin-Hartley guinea pigs spontaneously develop bilateral knee OA by 12–18 months, closely paralleling human histopathology[24,25].
- Fischer-344 rats display age-related cartilage changes, though less consistent[26].
- Dogs (particularly companion and Beagle breeds) exhibit naturally occurring hip and knee OA in mid-to-late life, and develop multi-joint OA with a similar prevalence to humans allowing gait and pain studies in "One Medicine" contexts[27-29].
- Horses serve as high-fidelity models for large-joint OA, with cartilage thickness and biomechanics similar to humans[30,31].
- Nonhuman primates, including rhesus macaques and common marmosets, develop spontaneous OA with aging, exhibiting radiographic, histological, and sex-linked features highly analogous to human disease[32-37].

These systems bridge the translational gap between rodent molecular genetics and human pathology, though cost, ethics, and logistical barriers limit their use. Comprehensive comparative evaluations of large-animal OA models have been reviewed elsewhere[38].

Comparative Assessment and Future Directions: Given the mild phenotype of C57BL/6 aging OA, a tiered approach is increasingly advocated[5]:

1. Mechanistic discovery: Use genetically defined mice (C57BL/6J background, Smurf2-TG, PANX3-KO) to probe molecular pathways.
2. Phenotypic robustness: Employ spontaneous or accelerated models (STR/Ort, SAMP8, bGH) to examine structural and functional endpoints.
3. Translational validation: Apply large-species or primate models for interventional testing and biomarker correlation.

Incorporating both sexes, metabolic stressors, and longitudinal imaging will improve fidelity to human aging. The integration of transcriptomic, lipidomic, and single-cell analyses across models will help identify conserved "aging-OA" signatures[1,3].

Conclusion: After reviewing the animal models that currently exist, it becomes apparent that there really isn't a better or an ideal animal model to study age-associated OA. While C57BL/6 mice remain essential for mechanistic studies, their mild spontaneous OA limits translational power. An additional limitation is that C57BL/6 mice poorly model female-predominant, age-associated OA, as spontaneous disease is weaker and less consistent in aged females than in males. Complementary use of genetically predisposed, accelerated aging, and larger natural models better captures the multifactorial nature of aging-associated OA. The future lies in cross-model integration—leveraging murine genetics for discovery, heterogeneous and spontaneous models for validation, and large mammals or primates for preclinical translation—toward a unified framework connecting basic mechanisms of joint aging to human disease.

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Animal models to study aging associated OA

Species	Strain / Model	Typical Onset / Age Window	Relative Severity	Key Features Observed	Pros for OA-Aging Research	Cons / Caveats	Key References
Mouse	C57BL/6 (aging WT)	~17–24 mo	Mild–moderate (variable)	Gradual cartilage thinning, PG loss; subchondral & gait/pain changes (sex-modulated)	Widely available; genetics; tools for longitudinal behavior/pain	Lesions are modest & variable; strong male bias vs human female bias	(Geraghty et al., 2023) (Armstrong et al, 2021)
	STR/Ort (spontaneous)	~5–7 mo (♂ earlier)	Moderate–severe (male more severe than female)	Robust knee OA; osteophytes; subchondral bone thickening; gait changes	Fast, penetrant spontaneous OA; rich literature; genetics emerging	Male-biased; Severe OA at early age due to unique genetic background rather than gradual accumulation of aging processes	(Javaheri et al., 2018; Mason et al., 2001; Poulet et al., 2014; Staines et al., 2017)
	SAMP8 (senescence-accelerated)	~6–9 mo	Moderate	Accelerated aging context; cartilage degeneration; meniscus/subchondral changes	Captures aging biology; earlier onset than C57BL/6	Background systemic frailty; availability vs standard strains	(Sanada et al., 2022)
	bGH overexpression (bovine GH transgenic)	~6 mo (observed)	Moderate–severe	Cartilage structure loss, chondrocyte hypertrophy, synovitis, subchondral plate thinning	Hormone excess and accelerated aging context; strong phenotype; mechanistic insights into GH's role in OA	Not purely "aging spontaneous"—driven by transgene; metabolic/ systemic pleiotropy	(Zhu et al., 2023)
	UM-HET3 (genetically heterogeneous cross)	~22–25 mo (old age)	Mild–moderate → variable	Cartilage lesions (OARSI), osteophytes, synovitis, correlations with subchondral BMD (esp. females), sex variability, inflammation / senescence markers	Captures genetic heterogeneity; more translational relevance; allows detection of inter-individual variability; good for interventions in aging context	Requires aged cohorts (long duration); variability may require larger N; fewer prior OA-specific characterizations	(Poudel et al., 2024) (Ewart et al, 2020)
	PANX3 knockout (global; ± cartilage-specific)	~18–24 mo (aging), earlier with stressors	Moderate–severe (late-stage)	Full-thickness cartilage erosion; severe synovitis; enthesitis; subchondral bone remodeling	Strong spontaneous aging-OA phenotype; robust histopathology; models chondrocyte ATP/ion channel biology	Context-dependent biology (protective in DMM/post-traumatic OA); may vary with background and sex	(Moon et al., 2021; Wakefield et al., 2025)

	Smurf2 transgenic (cartilage overexpression)	~6–12 mo	Moderate	Spontaneous cartilage degeneration, proteoglycan loss, fibrillation	Mechanistic model linking TGF-β/Smad3 suppression to OA catabolism; relatively early onset	Driven by non-physiological transgene levels; not aging-specific	(Wu et al., 2008)
	Col9a1$^{-/-}$ (type IX collagen knockout)	~9–12 mo	Moderate	Cartilage erosion; intervertebral disc degeneration; gait & pain changes	Connects ECM structural deficiency to OA; progressive phenotype	Background-sensitive; Driven by non-physiological systemic knockout; may affects other tissues	(Allen et al., 2009; Costello et al., 2010; Hu et al., 2006)
	Col2a1 mutant / internally deleted transgene	~15 mo	Mild–moderate → progressive	OA-like cartilage degeneration; fibrillation; structural weakening	Mimics type II collagen abnormalities; onset in mid-life	Some lines have skeletal/chondrodysplasia phenotypes confounding pure OA	(Helminen et al., 1993)
	Col11a1 haploinsufficiency (cho/+ background)	Early signs ~3 mo; overt OA ~12–15 mo	Moderate	Cartilage fibrillation, proteoglycan depletion, osteophytes, synovitis	Fibrillar collagen network instability; gradual OA progression	Homozygous lethal; heterozygotes may show skeletal features beyond OA	(Xu et al., 2003)
	NFATc1/ NFATc2 combined deficiency (cartilage)	Accelerated with aging	Moderate–severe	Increased spontaneous OA lesions vs WT; cartilage fibrillation and degeneration	Identifies NFAT transcription factors as repressors of OA development	Requires careful genotyping; background strain dependent; not a pure aging model	(Greenblatt et al., 2013)
Rat	Fischer-344 (aging)	>18 mo	Mild–moderate	Age-associated cartilage degeneration (strain-dependent)	Larger joint than mouse; aging lesions occur without surgery	Spontaneous OA less consistent than guinea pig; rats often used for induced models	(Smale et al., 1995)
Guinea pig	Dunkin-Hartley (DH)	Begins ~3–4 mo; progressive with age	Moderate–severe by 12–18 mo	Bilateral knee OA; osteophytes; PG loss; pain/nociception increases with age	Gold-standard small mammal natural OA; joint size helps imaging; histopath parallels human OA	Outbred variability; husbandry length/cost; fewer genetic tools than mouse	(Jimenez et al., 1997; McDougall et al., 2009)

Dog	Pet/Beagle	Middle-to-late life; breed/size dependent	Variable; often clinically significant	Hip/knee OA as well as multi-joint OA with age; real-world comorbidities; gait/force-plate endpoints	High translational relevance; natural disease course; one-health pipelines	Heterogeneity (breed, lifestyle); cost/ethics; regulatory/logistical complexity	(Meeson et al., 2019; Moreau et al., 2013) (Nelson et al, 2025)
Horse	Naturally occurring	Adult/older; workload- & age-linked	Moderate–severe (often clinical)	Thick cartilage; synovitis; imaging and lameness endpoints	Cartilage thickness & joint scale close to humans; interventional trials feasible	Often post-traumatic/overuse mixed with aging; high cost/logistics	(Mayet et al., 2023; McIlwraith et al., 2012)
NHP	Rhesus / Cynomolgus	Adult→aged; prevalence rises with age ≥10 years	Mild–moderate → severe	Age-related radiographic & histologic OA; sex/parity effects reported	Closest biology to humans; natural history	Cost/ethics; smaller cohorts; specialized facilities	(Chateauvert et al., 1990; Simmons, 2016; Yan et al., 2021) (Carlson et al, 1994, 1996)
	Common marmoset	Adult (~3–5 y) → geriatric (>7–10 y)	Progressive	Age-related knee OA on µCT; subchondral sclerosis; synovitis; sex differences	Shorter lifespan; colony scalability; emerging OA-aging platform	Field still maturing; colony resources needed	(Minton et al., 2024)

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