



# Banking on a new understanding: translational opportunities from veterinary biobanks

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**Abstract** Current advances in geroscience are due in part to the discovery of biomarkers with high predictive ability in short-lived laboratory animals such as flies and mice. These model species, however, do not always adequately reflect human physiology and disease, highlighting the need for a more comprehensive and relevant model of human aging. Domestic dogs offer a solution to this obstacle, as they share many aspects not only of the physiological and pathological trajectories of their human counterpart, but also of their environment. Furthermore, they age at a

considerably faster rate. Studying aging in the companion dog provides an opportunity to better understand the biological and environmental determinants of healthy lifespan in our pets, and to translate those findings to human aging. Biobanking, the systematic collection, processing, storage, and distribution of biological material and associated data has contributed to basic, clinical, and translational research by streamlining the management of high-quality biospecimens for biomarker discovery and validation. In this review, we discuss how veterinary biobanks can support research on aging, particularly when integrated into large-scale longitudinal studies. As an example of this concept, we introduce the Dog Aging Project Biobank.

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## Introduction

With a growing global life expectancy and increased incidence of chronic disease [1], caring for an expanding geriatric population has revealed a need for a deeper understanding surrounding the biology of aging. Decades of studies that relied on laboratory organisms, including yeast, nematode worms, fruit flies, and mice, have taught us a great deal about the underlying molecular mechanisms of aging, and the

pathways that appear to show deep evolutionary conservation [2, 3].

However, these discoveries have been made mostly under highly controlled experimental settings, with model systems that typically display little to no genetic or environmental variation. As a result, numerous drug candidates that demonstrated efficacy and safety in model organisms have failed in human clinical trials [4–8]. It remains therefore unclear to what extent these laboratory-based discoveries can apply to variation in aging-related traits in natural populations [9, 10].

To investigate more accurately the mechanisms of human aging, the scientific community has started to shift away from traditional laboratory models towards more evolutionarily and ecologically relevant spontaneous model organisms such as the companion dog [11]. Dogs display a highly similar physiological and pathological aging trajectory to their human counterparts, and are exposed to the same environmental factors [9]. Moreover, canines age more rapidly, making them a promising model for studies on aging [9]. The use of canine biomarkers as a minimally invasive way to connect genetic, environmental, and lifestyle factors to morbidity, mortality, and health in dogs could help us better understand the causes and consequences of aging in human populations [12–15]. The success of these endeavors relies heavily on reliable access to high-quality canine biospecimens, and veterinary biobanks can provide invaluable support to scientists in this context.

Modern biobanks are able to support proteomics-, metabolomics-, and epigenomics-based translational research by specializing in the standardization of the processes that create high-quality biospecimens and associated data [16–19]. As the largest proportions of errors in laboratory activities occur during the preanalytical phase, utilizing the standardized procedures and quality management systems implemented by biobanks can reduce the technical variability of an experiment and improve scientific rigor and reproducibility [20–23]. Population- and disease-driven biobanks, and particularly those accredited to an international standard that ensures the quality of their biospecimens and associated data [24], have already proven to be longstanding and valuable partners in precision medicine [25]. Recently, veterinary biobanks have emerged as a key resource not only for studies of domestic animals, but also for

the improvement of public health in human populations [26], through the translational potential of the research they enable. State-of-the-art veterinary biobanking facilities can further contribute to accurate, reproducible research results by adopting best practices and/or international standards [27] and following standard operating procedures, as well as international and governmental regulations to ethically collect samples from domestic dogs [20–24]. By integrating veterinary biobanking into large-scale studies on aging, we can better bridge the longstanding gap between translational research and clinical practice in geroscience [28]. We propose that veterinary biobanks can enhance translational research of aging by improving access to high-quality, clinically annotated biospecimens.

In this review, we will illustrate this concept using the official biobank of the Dog Aging Project, a long-term longitudinal study of companion dogs designed to discover the biological and environmental determinants of healthy aging [28, 29].

## Research models of aging

Aging is a multi-faceted process that depends on interconnecting factors. The complexity of the aging process poses challenges to the pursuit of novel interventions and drug therapies. Human epidemiologic studies looking to extend healthspan focus primarily on aspects of lifestyle and are not able to sufficiently address all aspects of aging-related diseases [30]. While a person's genetics, environment, and socioeconomic status can reveal insight into the susceptibility for disease and the potential for healthy aging, further model-based research is needed to better understand the underlying mechanisms of aging in natural populations [28, 31]. Whereas *in vivo* studies in humans have limitations, animal models offer a practical alternative to studying aging at the molecular, cellular, tissue, and organism level.

Animal models have been useful in helping us to better understand aging and age-related disorders. Studies in model organisms such as yeast, nematodes, fruit flies, and mice have successfully established that lifespan can be increased substantially by mutating specific genes [2, 32–37]. Lifespan and the causes of mortality vary greatly among species, making no one animal the perfect model to study aging [38–41].

Despite that variation, classic vertebrate and invertebrate animal models have led to the identification of several interventions that appear to work across diverse species, and which may ultimately lead to treatments that delay human aging, prevent disease onset and/or progression, and allow humans to maintain functional capacity in the later stages of life [2, 30, 42–44]. Invertebrate models have played a critical role in geroscience, including as models of specific age-related organ pathologies (e.g., heart and brain); yet, their anatomical and physiological differences compared to mammals somewhat limit their translational use as a model species for humans [45, 46]. Evolutionarily, vertebrate animal models have proven to have a closer proximity to humans in regards to their physiology and cellular function [47, 48], and in some cases, species-specific mechanisms for lifespan might inform our understanding of means of increasing human healthspan [49, 50].

Vertebrate animals have a longstanding place in biomedical research and provide promising insight to better understand the fundamentals of disease for the development of diagnostic and therapeutic innovations [51–53]. Over 95% of all studies of animals use mice as the research model [51], as they are relatively easy to maintain, economical, and genetically standardized. Mice have also proven a powerful model for aging research, including recent efforts to develop a “geropathology” for mice, but laboratory mice do not reflect the genetic and environmental variation that characterizes human populations [54]. Moreover, we generally lack the tools to determine ultimate causes of mortality in mice—tools that we have available not only in humans, but also in companion animals. The murine model also faces a number of challenges in the translation to safe and efficacious treatment options for humans [55–58]. While non-human primates may represent the most biologically similar model of human aging, the expense associated with husbandry in combination with their long lifespan makes them more logistically challenging for longitudinal studies of age-related changes [38, 59–61].

Despite the widely accepted practice of using traditional animal models in research, there is a fundamental gap in our ability to translate findings from studies in highly controlled laboratory settings to genetically diverse humans living in a complex environment. Aging as an intricate process demands a more realistic and reliable animal model to predict

clinical outcomes [62, 63]. In this review, we discuss the potential for unlocking the underlying mechanism of aging and disease by exploring the mutualistic relationship humans share with the domestic dog (*Canis familiaris*).

### The companion dog as a research model

Canines and humans share numerous similarities that make dogs a promising translational model for identifying risk factors that influence longevity [11, 64, 65]. Companion dogs experience patterns of actuarial aging and age-trajectories analogous to humans, and share the same environment, including exposure to the same food, water, and air as their human owners, which often impart similar risks for disease in both species [11, 28, 66]. Like humans, they are highly genetically variable, and have access to a health care system almost as sophisticated as human medical care. As a result of living in close proximity for the past tens of thousands of years, we even see examples where dogs and humans have undergone convergent evolution as seen in genes related to environmental adaptation and diet [67, 68].

Many chronic illnesses and spontaneous diseases manifest with similar clinical presentation, molecular, and immunophenotypic composition in humans and dogs, covering a wide range of physiological systems [69]: cardiovascular diseases including congestive heart failure [70] and pulmonary hypertension [71]; renal diseases including chronic kidney disease [72]; gastrointestinal diseases including inflammatory bowel disease [73], idiopathic chronic hepatitis [74], and pancreatitis [75]; endocrine disorders including type 1 diabetes [76], Addison’s disease [77], and Cushing’s syndrome [78]; and cancers including lymphoma [79], melanoma [80], and osteosarcoma [81]. Furthermore, the dog can serve as a translational model for human neurological disorders, such as polyneuropathy [82], epilepsy [83], and Alzheimer’s disease [84], and future plans for research in canine cognitive dysfunction will continue to expand the dog’s translational potential [85].

The “One Health” initiative centers on the detection, treatment, and prevention of disease through the connectivity of humans, animals, and the environment. The historical use of the domestic dog as a model for human diseases highlights the way aging research can benefit from the application of the “One

Health” principles. Connecting the shared characteristics of companion dogs and humans increases the predictability of preclinical study outcomes in ways not possible with laboratory animals [86].

Approximately 80 million households in the USA own at least one companion dog, representing a large population that has a vested interest in maintaining their health [38]. Studies in companion animals have value not only for what they can teach us about human disease, but also for their direct benefits to veterinary medicine, dogs, and their owners. Incorporating translational findings in veterinary clinical practice will amplify our current abilities to identify early signs and enhance our screening procedures for age-related disease, allowing the adoption of various early interventions in the companion dog [38, 87]. The use of the companion dog as a translational research model for health, longevity, and aging in humans also provides an opportunity to gain knowledge that potentially could extend the life and health-span of dogs, increasing the quality time they spend with their owners in their aging years. Pet owners genuinely value the bond that they share with their pet, and veterinarians strive to enhance the physical and mental health of older dogs [88]; involvement from both owners and veterinarians could result in beneficial contributions to translational research.

Voluntary owner participation, including the collection of biospecimens with a robust informed consent process, safeguards the dogs’ best interests and enables geroscientists to use the companion dog as a model for both observational and interventional studies of aging. By utilizing domestic dogs in translational research for aging and age-related diseases, they can contribute towards improving public health as part of the “One Health” initiative. High-quality specimens from donor dogs are critical to the success of translational research, making them a valuable addition to the translational research model landscape.

### **Biobanking in support of research**

Biobanks are entities that receive, process, store, and distribute biospecimens and associated data from a population or subset of a population [89]. Many hold specimens of great value to research, precision medicine, and the advancement of

biotechnology [90]. Biobanks can be classified either as “population-based” or “disease-oriented” [91], or according to the type of research they intend to support (e.g., population study, basic research, translational study, clinical trial, or pathology archive biobanks) [92]. Formal biobanks differ from other types of research collections by having established governance mechanisms in place for their operations and distribution to external users [93]. By providing standardized, high-quality services for the collection, acquisition, transport, processing, storage, and distribution of biological materials, biobanks can improve the traceability, authenticity, and fitness-for-purpose of specimens used for rigorous and reproducible research [94].

It is generally accepted that the more accurate and comprehensive the annotation of specimens, the more valuable and effective the research utilizing them will be. In addition to storing high-quality biospecimens, biobanks also collect and store vast amounts of data, which can be broadly grouped into three categories [95]. The first category pertains to descriptive data regarding the donor and the specimens; it includes demographic, phenotypic, and clinical data of the donor, and categorization of the specimen types and collection sites. Through the anonymization and de-identification of records, this information can be passed on to researchers while maintaining the privacy of the donors. The second category consists of preanalytical data, which includes the procedures and conditions for the collection, processing, transportation, and storage of biospecimens. As preanalytical processes can have a critical impact on the fitness and integrity of specimens, it is critical to capture as much information as possible to make informed decisions about the use of the specimens and to correctly interpret results derived from the downstream analysis of these specimens [96, 97]. The third category is made up of data resulting from the analysis of the biospecimens, including genomic, metabolomic, proteomic, and other “-omics” data, as well as digital bioimaging and other data generated during research. Making the data available to researchers to use for retrospective analysis increases the value of the specimens and decreases sample collection and analysis redundancies. By capturing, storing, and distributing all the data associated with banked specimens, biobanks are uniquely positioned to add value to clinical and translational research [98] while reducing experimental bias and duplication of study efforts.

Since the emergence of translational research as a field in the 1990s, biobanks have evolved as a research resource for human specimens and data [99]. A 2010 review noted that, at that time, biobanks had been involved in approximately 40% of all cancer research papers [100]. In the last decade, there has been increasing recognition of the important role of biobanks in translational medicine and, in particular, for developing novel therapeutics [16]. Biobanks are impactful resources and the cornerstone of future investigations into biomarker discovery, given their critical role in standardizing high-quality biospecimens [101]. For example, the detection of cerebrospinal fluid and blood biomarkers for Alzheimer's disease [102], serum biomarkers for prostate, lung, colorectal, and ovarian cancers [103], and plasma markers for heart failure [104] was made possible by the use of biobank materials. In turn, effective biomarker identification is critical for improved diagnosis and prognosis of disease [91]. A mutual relationship has been formed between biobanks and precision medicine initiatives through the development of patient-derived xenografts and patient-derived organoids [105, 106], providing relevant preclinical models for confirming therapeutic efficacy or testing new treatments [107]. Through a systematic approach to sample/data acquisition, analysis, technical validation, and transparent sharing of biological and clinical data, new pathways are being forged in biomedical research [91].

### Veterinary biobanking and translational research

Non-human animal biobanks can be found associated with veterinary hospitals, zoos, museums, genetic resource gene banks, and research institutions. Though they make up a small fraction of the biobanking sector [26], they play a critical role in clinical research, environmental conservation efforts, and food production [108–110]. While veterinary biobanks have the potential to supply the research community with valuable biological specimens from a variety of species, they remain a relatively untapped resource [111].

Similarly to how human biospecimens are collected through hospitals and clinical settings, veterinary clinical facilities play an important role in the collection of biospecimens from animals. The

healthcare infrastructure of veterinary medicine, which consists of general practitioners and specialists, closely mirrors human medicine, and the principles of biobanking are applicable to both sectors. Ethical principles and values, particularly informed consent and patient confidentiality, play a vital role in all domains of biobanking [112]. However, less rigid laws and guidelines in veterinary biobanking allow for more sampling opportunities to build a collection capable of accelerating the development of novel therapies. Furthermore, owners are more likely to permit collection of samples from their companion animals than they are from themselves, giving them an alternative opportunity to contribute to translational research [113].

The enrollment of a large cohort of specimen donors with frequent collection opportunities has the potential of accelerating the speed at which novel research could be translated into clinical practice. As a result, veterinary biobanks have emerged as a network of resources to study health and longevity [26]. For example, the Australian Veterinary Cancer Biobank obtains its samples from a network of 47 veterinary clinics through the use of a specialized tumor collection kit, increasing the likelihood that these specimens are used for research by providing investigators large collections of fit-for-purpose specimens [114]. These networks can also operate on an international scale, as demonstrated by the LUPA project, a European Commission-funded collaboration of 22 veterinary research institutions from 12 countries aiming to collect canine biospecimens of relevance to human health [115].

Veterinary biobanks support research not only for non-human animals, but also for translational efforts that can advance human medicine in alignment with the “One Health” initiative [116]. One such example, the Munich MIDY-PIG Biobank in Germany, is a pioneer in veterinary translational research, banking porcine tissue specimens for human diabetes research [17]. Similarly, canine biobanks have supported the development of a new high-density single nucleotide polymorphism array, leading to identification of variants relevant to monogenic diseases in humans [115], further supporting the idea that the domestic dog is an excellent model for gene mapping of simple and complex diseases in humans [84, 117–119]. Furthermore, animal registries, such as the Swiss Canine Cancer Registry, can also contribute to translational research

by compiling and providing vast quantities of curated data of a target population which can be used as references for veterinary and human medicine [120].

As the dog develops into a promising model for human aging, veterinary biobanks solidify themselves as an essential component of the future of translational research [121]. By combining the serial collection of high-quality specimens from canine participants over the course of their lifespan, with the utilization of internationally accredited veterinary biobanks, canine population-based and disease-specific studies are uniquely positioned to shift current research and clinical paradigms in geroscience.

### The Dog Aging Project

The Dog Aging Project (DAP) is the first large-scale longitudinal study to follow a diverse cohort of companion dogs, including mixed breed and purebred dogs, throughout their lifespan. This unique National Institute on Aging-funded study is designed to collect molecular, environmental, and lifestyle information from a large, diverse population of dogs across the USA, with the goals of understanding the biological and environmental determinants of healthy aging in companion dogs, and investigating potential treatments for increasing their healthspan [29]. In addition to being an interdisciplinary collaboration involving over 20 academic institutions, the DAP is a community science project that relies heavily on the participation of dog owners and their primary care veterinarians to collect biospecimens and associated data. Furthermore, all data collected and generated by the DAP is made available as a public resource, allowing external researchers to perform ancillary studies.

Over the duration of this study, tens of thousands of companion dogs and their owners participate by answering annual health and life experience surveys that collect comprehensive information regarding the dog's behavior, diet, use of medication and preventatives, physical activity, environment, and health history [29]. At least 10,000 of these dogs also provide a cheek swab as a source of DNA for low-pass coverage, whole genome sequencing. A subset of these dogs additionally provides biospecimens, including blood products, feces, urine, and hair, for analysis of the plasma metabolome, fecal microbiome, and peripheral blood mononuclear cell epigenome,

flow cytometric profiles, and inflammaging assays. Residual samples are stored at the DAP Biobank, housed at the Cornell Veterinary Biobank (CVB), and made available with the associated data to researchers through a DAP ancillary study request. These biospecimens are expected to play a vital role in the discovery and validation of biomarkers in aging, and have the potential to solidify the companion dog as the ideal translational model for age-related conditions.

The CVB, a core resource of the Cornell University College of Veterinary Medicine, was the first biobank to be accredited to the International Organization for Standardization (ISO) normative reference ISO 20387:2018 General Requirements for Biobanking, having implemented a quality management system and standardized procedures for the collection, acquisition, quality testing, processing, storage, and distribution of biological materials and associated data from non-human animals [24]. Since its inception in 2006, the CVB has supported research in canine genomics [122, 123], orthopedics [124, 125], and oncology [126, 127], including translational research using domestic dogs as models for human diseases [128]. By using the CVB to host the DAP Biobank, the DAP ensures that its biospecimens will be quality tested, authenticated, traceable, stored at appropriate temperatures, and distributed out to a wide range of researchers, both veterinary and translational, thereby amplifying the impact of the project.

### Conclusion

Though we have witnessed tremendous progress in unraveling the complex biological process of aging using traditional model species, future scientific discovery and novel drug therapy will depend on a more predictive non-human animal model. Shared age-related changes and a communal living environment make the companion dog a highly promising translational model for geroscience. Together with large-scale longitudinal studies such as the Dog Aging Project, veterinary biobanks have the translational potential to accelerate our understanding of aging, identify treatments that can extend the healthspan of dogs and humans, and improve public health. The success of these endeavors rests primarily on the collection, analysis, storage, and distribution of

high-quality canine biological specimens, which can be achieved by collaborating with accredited veterinary biobanks such as the CVB. Looking towards the future, expanding ways to incorporate standardized biobanking operations into longitudinal studies will have a positive impact on the reliability and reproducibility of translational research and, in turn, have a positive impact on animal and human health.

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**Data Availability** The Dog Aging Project is an open data project. These data are available to the general public at [dogagingproject.org/open\\_data\\_access](https://dogagingproject.org/open_data_access).

## Declarations

**Conflict of interest** The authors declare no competing interests.

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