NEW ANIMAL MODELS OF AGEING

23rd September 2022

Royal Veterinary College
University of London

Royal Veterinary College

Hawkshead Lane

Hatfield

Hertfordshire

AL9 7TA

Conference Rooms 1 & 2

Organisers:

Royal Veterinary College - Jay Dudhia, Chavaunne Thorpe, Roger K Smith

University of Brighton - Richard Faragher

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Abstracts

Richard Faragher

What are we modelling and why? Perspective and challenges in the comparative biology of ageing

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Since at least the mid-1930s a wide range of animal models have been used to study ageing. The conceptual thrust of these efforts has been two-fold. To understand why most, but not all, species in the biosphere show ageing and to determine which process 'control' ageing and how they operate. The sheer volume of model system work elides several strands of study. These are as follows:

1. Common laboratory models, such as mice or *Lymnea*, in which ageing is studied because the system combines pre-existing data with the availability of genetic tools, ex-vivo techniques and potential human relevance.
2. Common laboratory models, such as flies and worms, where low cost and genetic tractability render them especially suited to the study of the evolution of ageing or the identification of mutants.
3. Uncommon models, such as *Arctica islandica* (the quahog) or *Nothobranchius furzeri*, (turquoise killifish) selected because they show traits of interest to gerontologists (negligible or rapid senescence). These models often lack genomic information or common tools.
4. Domesticated mammals such as canines or equids with many fundamental physiological similarities to humans and the added advantage that understanding ageing in these species is of innate economic and societal importance.

There is now an urgent need to identify the research gaps within this diverse collection of model systems which can maximise their combined value as well as the fundamental gerontological questions that may require the development of new models. One example which will be discussed is the unusual nature of the evolution of human ageing for which domesticated mammals may provide valuable and previously unrecognised parallels.

Lynne Cox

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Research into the biology of ageing has undergone a dramatic transformation over the past decade, leading to identification of key hallmarks of ageing together with the demonstration that age-related multimorbidities are underpinned by a small number of tractable biological ageing processes. In particular, removal of senescent cells through drugs known as senolytics, and/or targeting fundamental biological pathways such as nutrient signalling, have been shown to improve health across multiple organs and systems, with noted lifespan increases in experimental organisms. These drugs and other therapeutic modalities that address underlying ageing mechanisms have shown significant promise in preclinical models and companion animals, with a growing number of human clinical trials taking place, for example in idiopathic pulmonary fibrosis and diabetic retinopathy.

While this geroscience revolution is remarkable in both speed and scope, there is still little awareness of the progress and its potential outside the field of ageing biology. Historically, research efforts have often been focused on individual disease areas or research models, isolating researchers and hindering cooperation and innovation. However under a new initiative, the UK government (through BBSRC and MRC), has provided £2m in funding to establish the UK Ageing Research Networks (www.ukanet.org.uk)[1], comprising 11 research networks covering diverse areas including socio-economic determinants of health, cell metabolism, diet and nutrient sensing, exercise and muscle resilience, cognitive frailty, and immune ageing. The BLAST research network (Building Links in Ageing Science and Translation) aims to increase our mechanistic understanding of biological ageing processes, identify actionable ageing biomarkers and move such findings through translation into policy and practice, including clinical trials. In addition to running formal and informal meetings and workshops and providing skills training, we announce here the launch of a pump priming fund to support early-stage research activity and staff exchanges to grow the UK's ageing research capacity.

UKANet, BLAST and partner networks represent a new model for national cooperation in an important and growing field, and we welcome interaction with ageing researchers and those new to the ageing field to improve later life health for all.

[1] Lynne S Cox and Richard G A Faragher (2022) **Linking interdisciplinary and multiscale approaches to improve healthspan—a new UK model for collaborative research networks in ageing biology and clinical translation.** The Lancet Healthy Longevity, Volume 3, Issue 5, e318 - e320

David Gems

Interventions that increase the organismal lifespan: a cross species perspective

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The process of ageing (senescence) is the main cause of disease and death in the world today, and yet its biology remains poorly understood. Given the high degree of conservation in the basic biology of metazoan organisms, the study of simple animal models such as the nematode worm *Caenorhabditis elegans* and the fruit fly Drosophila should yield an understanding of the fundamentals of ageing. Yet although ageing has been studied in such models for decades, this understanding still remains out of reach. Why? Are the wrong models being studied? Have we exhausted what they have to teach us? Do we need other models? Or is are the methodologies and theories that have been used inadequate?

C. elegans shows amazing plasticity in ageing. Recent studies of The Worm have contributed to a new, emerging understanding of the fundamental causes of ageing. According to a recent prototype paradigm, the process of ageing, including development of its constituent diseases, can be understood in terms of a relatively small number of general principles of senescent pathophysiology. Most important among its causes are programmatic mechanisms specified by the normal (wild-type) genome (*1*). The pathogenic effects of normal processes in late life are an evolutionary consequence of an age decline in the force of natural selection, combined with biological constraint. New work also suggests that The Worm's ageing plasticity is, unfortunately, not typical of higher animals. Instead, it may reflect the presence of semelparous reproductive death, as seen in Pacific salmon (*2-4*), and also of altruistic adaptive death, as seen in some colonial microbes (*5-7*).

1. *Ageing Res. Rev.* **74**, 101557 (2022). 2. *Front. Genet.* **13**, 880343 (2022). 3. *Front. Cell Dev. Biol.* **9**, 688788 (2021). 4. *Nat. Commun.* **12**, 5801 (2021). 5. *Aging Cell* **19**, e13141 (2020). 6. *Philos. Trans. R. Soc. B* **376**, 20190730 (2021). 7. *Ageing Res. Rev.* **50**, 58-71 (2019).

Paul Potter

Modelling age-related disease

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Ageing is a factor that is often overlooked in models of disease, particularly in mice, with the majority of models being early onset and with a rapid progression. Given the effect of ageing on disease risk it is important to incorporate ageing into our studies. Furthermore, because of a lack of an ageing component, many models are not necessarily an accurate representation of many of the clinical conditions we are faced with, but also that the opportunities to study pathogenesis and trial interventions are limited by the short timeline of disease. To address this, and develop novel models of age-related and chronic disease, we employed a phenotype-driven screen approach in ageing mutant mice to identify novel models of late-onset and age-related disease. Mutant mice were aged and phenotyped using a wide-range of assessments to identify mice that specifically developed late-onset phenotypes. I will describe some of the initial findings of this study and also discuss the challenges we face in modelling not only single diseases in the context of ageing but also in developing models of ageing per se with the associated development of multimorbidity and frailty. I will also discuss factors involved in developing mouse studies to study ageing and age-related disease.

Julie Thornton

The naked mole rat: an age-defying supermodel

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The naked mole rat (*Heterocephalus glaber*) is a long-lived mammal that maintains a healthy life span, does not exhibit an age-related decline in physiological capacity and has a natural resistance to cancer and other age-related pathologies. With most mammals, including humans, risk of death increases with age, so the naked mole rat is of significant interest to understanding longevity and age-related disease. Mice in captivity rarely live beyond 4 years, so based on size, it could be assumed the life span of the naked mole rat would not exceed 6 years. However, most live beyond 30 years, and even then, breeding females remain fertile. Despite this "old" age, classical signs of ageing e.g., muscle atrophy, bone loss, decreased fertility, metabolic changes are absent, as well as common age-related diseases including metabolic disorders, cardiovascular and neurodegenerative disease, and cancer. Naked mole rats are unusual in that they live in large colonies consisting of only one breeding female, "the queen," with 1-3 breeding males, together with a substantial number of adult non-reproductive subordinates, all socially suppressed in a pre-pubertal state. These subordinates, which can reach significant numbers, are responsible for maintenance of the colony, defence, and care of the queen's litter. The queen has multiple litters throughout her life and does not exhibit reproductive ageing as reflected by the programmed menopause in women. Their age-defying secrets indicate very active DNA repair mechanisms and high levels of chaperone proteins involved in protein folding, which reduce the accumulative damage associated with ageing. Therefore, this slow-aging mammal is emerging as a highly attractive model for the study of ageing.

Eithne Comerford

Companion Animal models of ageing with a musculoskeletal perspective

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We are living in an ageing world with human life expectancy having doubled in the last 100 years. Ageing is a major risk factor for conditions such as cardiovascular disease, osteoarthritis, and cancer.

Many experimental models, namely yeast, nematodes worms, fruit fly and rodents, have been used to determine the hallmarks of ageing such genetic instability, epigenetic alterations and cellular senescence in order to further understand ageing in humans. These models are ideal for well controlled ageing studies as they have short lifespans, well profiled genomes and there is the ability to create mutant strains. However, some are non-mammalian and rodents are kept under laboratory conditions not allowing for full variation of environmental exposures encountered by humans.

The use of companion animals, such as dogs and cats, are increasingly being considered as valuable models to examine the hallmarks of ageing and conservators of longevity. They are genetically diverse, demonstrate spontaneous occurrence of similar chronic diseases to humans, have a shorter lifespan than humans and closely share environment with their human carers. In terms of chronic musculoskeletal disease, degenerative anterior cruciate ligament injury and hip dysplasia/osteoarthritic have many similarities between humans and dogs and should be considered as parallel models for the further study of these conditions.

Increased interest and funding in this area has led to major projects such as the Dog Ageing Project, Generation Pup (Dogs Trust), Dogs Life, Golden retriever lifetime study and Bristol Cats and CatPAWS which will provide data to inform future comparative mammalian ageing.

Roger Smith

Tendon ageing in horses: a veterinary challenge with human applications

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Tendinopathy is common in humans and it is generally accepted that the pathogenesis involves preceding age-related degenerative changes to the tendon that predispose it to injury during exercise. Unfortunately there has a lack of a universally agreed animal model of human tendinopathy because traditional small animal tendons do not have the same structure and function and do not exhibit a similar ageing phenotype to humans. Investigations by a number of groups in the UK, however, have shown remarkable similarities between human and equine tendons in many areas. Equine tendon injuries occur naturally in the tensional extra-synovial superficial digital flexor tendon (resembling human Achilles tendinopathy) as well as in the compressed intra-synovial deep digital flexor tendon (resembling human rotator cuff tearing), although the correlation is best matched with tendon function than anatomically because of the differences between bipedal and quadrupedal locomotion. Equine and human weight-bearing tendons are organised with greater amounts of interfascicular tissue which allows tendon fascicles to slide with respect to one another, thereby achieving greater extension and an ability to store energy for efficient locomotion. Exercise and ageing has been shown to induce degenerative changes within the most injury prone equine tendons and this ageing change appears to be most evident within the interfascicular tissue, where we believe senescence may also play an important role. Even genetic polymorphisms in specific matrix proteins that have been identified as risk factors for Achilles tendinopathy in man appear to have the same influence in equine superficial digital flexor tendinopathy. Finally, recent investigations on the importance of inflammation and its failure to resolve with ageing (so-called 'inflamm-aging') in producing dysfunctional healing in horses have been matched and extended in human tendinopathy. In conclusion, therefore, we hypothesise that the horse represents an under-utilised yet highly relevant model for human tendinopathies.

Ruby Chang

The Turing Network and AI applications in ageing research

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From the first omics technology, genomics, appeared in the literature in 1987, we have seen rapid evolution of omics technologies in the last 20 years. The development of bioinformatics has been driven by the need to store, annotate, analyse, and integrate these omics data into database, biological networks, and systems. With the advance in computational power and predictive modelling techniques, the approaches used by researchers to synthesize information from the data generated have also evolved. Given the complexity of the ageing process and the generation of different high-throughput omics data and large scale of non-omics data (imaging, clinic-pathological, epidemiological, and environmental data), systematic and integrated approaches are needed to tackle the challenges in linking these heterogenous and interdependent information. Machine learning approaches have been utilised in all areas of science in the last 20 years and will doubtless be valuable for comparative ageing research, aging biomarker discovery and personalized medicine investigations against chronic diseases. A summary of recent advances of AI applications in ageing research are provided.

Danielle Sagar

BBSRC survey on the use of models in research

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The complexities of research across disciplines in animal and human biology necessitate a variety of approaches. Often a very large number of different experimental systems (e.g. cell culture, computational approaches and tissue slices) and species are used to investigate biological processes. The use of these model systems has been a vital part of both fundamental and translational scientific research. BBSRC recently conducted a survey on the use of models in research to gain insight into how researchers currently use their experimental systems and models and how they expect to use them in the future, in order to better understand the area and ensure that the health of the disciplines is maintained and opportunities for improvements found. By improving our understanding of the current and future use of models in research, BBSRC is better placed to ensure that the health of the discipline is maintained and that opportunities for further improvement are identified and implemented.

General information

Scientific confidentiality
BLAST network aims to encourage the discussion of new and unpublished work, so please treat all communications within the conference as confidential. Do not photograph slides without the express permission of the presenting author, and please do not post any data from others on any social media or other platform.

Conference rooms
The talks will be in Conference Rooms 1 & 2 which are situated in Building H75 to the left of the Campus Entrance (see map on the next page).

Sponsors
The BLAST New Animal Models of Ageing workshop is only possible because of the generosity of the BBSRC and MRC, through their funding of the UK ageing networks (UKANet) of which BLAST is one of 11 member networks.

Refreshments and Meals
Coffee/tea, lunch and drinks reception will be held Conference Rooms 5 & 6 which are adjacent to Conference Rooms 1 & 2.

Wifi
Eduroam is available through high-speed wifi. For those without an Eduroam account, we will provide internet access through guest wifi access. Please ask during Registration.

Mobile phones
Please ensure you turn your phone to silent for all the scientific sessions.

Fire safety
Please familiarise yourself with the fire safety notices and know the nearest fire exit and meeting point. Please note the "Assembly Point" on the map. **DO NOT** ignore any fire alarms; the policy is to evacuate immediately on hearing an alarm. Please keep fire doors closed.

Smoking
The RVC is strictly no-smoking (including e-cigarettes) on premises; however smoking in designated areas, where provided and in the open, away from buildings, is permitted. To safeguard health, smoking is NOT permitted within 5 meters of doors or opening windows to any College owned building.

Transport
The Hawkshead Campus of the RVC is served by a **free shuttle bus service** from Potters Bar railway station (https://www.rvc.ac.uk/Media/Default/About/Campus/hawkshead-buses-timetable.pdf). There are frequent trains into Potters Bar from London Kings Cross and from station on the Cambridge line. **Taxi/Minicab:** a minicab service is available from beside the Potters Bar railway station forecourt (telephone 01707 650077). The journey to the Campus takes about 10 minutes.

Detailed information on travel can be found at https://www.rvc.ac.uk/about/our-campuses/hawkshead/find-us

Parking

Please note that there is **very limited parking** at the Hawkshead Campus. Parking cannot be reserved. Delegates arriving by road are urged to approach the Main Campus from the East along Hawkshead Road and Hawkshead Lane from the A1000. Satellite Navigation Systems may instruct you to arrive via the western end of Hawkshead Lane. This route is not recommended, especially for larger vehicles, because of the narrow, twisting roads and very narrow bridge.

Hawkshead Campus Plan