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Modelling ageing and age-related disease

Ilaria Bellantuono[1], Paul K. Potter[2,*]

[1]MRC/Arthritis Research—UK Centre for Integrated Research into Musculoskeletal Ageing (CIMA), Academic Unit of Bone Biology, The Mellanby Centre, The University of Shefield, S10 2RX, UK
[2]MRC Harwell Institute, Mammalian Genetics Unit, Medical Research Council, Harwell, Oxfordshire, OX11 0RD, UK

An increased lifespan comes with an associated increase in disease incidence, and is the major risk factor for age-related diseases. To face this societal challenge search for new treatments has intensified requiring good preclinical models, whose complexity and accuracy is increasing. However, the influence of ageing is often overlooked. Furthermore, phenotypic assessment of ageing models is in need of standardisation to enable the accurate evaluation of pre-clinical intervention studies in line with clinical translation.

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Introduction

What has become clear over the last decade or so is that the concept that ageing is simply an accumulation of damage and physiological systems 'wearing out' are simplistic. Ageing processes are major contributors to the development of age-related disease [1–4] and can be modified, by interventions and genetically, across a range of organisms. Ageing can also impact on efficacy of disease treatments through changes in drug pharmacokinetic (PK) and pharmacodynamics (PD), which exerts its effects on therapeutic regimens. Whilst there is no unified 'theory of ageing' we are learning more and more about the physiological processes and the consequences of ageing and it is clear that this is a factor we should incorporate into modelling of disease and in preclinical studies. Within the context of such studies using aged models introduces several challenges including; increased frailty in older animals, limiting the number and types of assessment possible, increased difficulty in interpreting signs of ill health or humane endpoints, variability due to the differential rates of ageing in individual organisms, and the influence of environmental factors. In addition, models may need to be very complex to reproduce aspects of the multiple pathologies associated with frailty and multimorbidity. For this reason the standardisation of phenotypic assessment of animals and standardisation of study design is more critical than ever.

The importance of ``ageing'' in modelling age-related diseases

Mice are used to study ageing itself. For a review of how mice have been used in some studies of the ageing process please refer to Vanhooren and Libert [5]. Many disease studies do routinely incorporate ageing into their design, but many disease areas also use genetically modified organisms that have an early onset and/or acute phenotype when the disease burden is primarily a chronic or age-related condition. Examples of such models are the *Apoe* knockout mice [6,7] for the study of atherosclerosis and the *ob*/*ob* diabetic mouse [8]. While both have advanced our understanding of disease, these are extreme examples of disease with a rapid onset and do not necessarily recapitulate all aspects of human

*Corresponding author: P.K. Potter (p.potter@har.mrc.ac.uk)

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disease. Indeed as we gain a deeper understanding of the processes underlying age-related disease it is clear that we cannot model the complete range of phenotypes observed in patients in a single model, and it would be naïve to expect this to be so. We must therefore ensure there is a clear comprehension of the limitations and drawbacks of individual models as well as their similarities to symptoms observed in patients. Indeed the term model is often applied too freely and it should be acceptable to state that these are genetically modified organisms that aid our understanding of disease rather than labelling everything with moniker of model. This is exemplified by the recently published comment on mouse lines used to study amyotrophic lateral sclerosis (ALS) [9]. Although not an age-related disease it highlights the need for a complete understanding of disease in models and patients. As emphasised in this article, a commonly used 'model' of ALS, TDP-43 mutant mice, were found to die of a bowel obstruction rather than the progressive muscle atrophy seen in patients, thus severely limiting its usefulness in pre-clinical studies [10]. This work drives home the importance of understanding why data does not translate from putative disease models. It is not sufficient to say that mouse lines are not suitable; we must investigate if and why they are not suitable and understand any limitations, which may indeed ultimately aid our understanding of disease pathogenesis.

The rapid nature of the disease reproduced in some of these models also means there is also a limited window of opportunity for testing therapeutic interventions. In addition, because of the lack of an ageing physiology in such models, the influence of age on other aspects of therapy such as PK and PD are missing [11]. Drug toxicity is also a major problem in drug development and a significant proportion of this toxicity can be attributed to mitochondrial toxicity [12,13]. With ageing there is an accumulation of mitochondrial mutations and a concomitant decline in mitochondrial function [14,15], which could therefore sensitise the aged to toxic side-effects of drugs. Without proper pre-clinical testing in age–appropriate disease models this toxicity may go unnoticed. Even then mouse lines *per se* may have limitations as there may be differences between mitochondrial ageing between mice and humans [16]. Effectively, therapies are being tested in a worst case scenario in such models where there is a rapid and aggressive disease in young organisms rather than the chronic progression seen in older patients. As our understanding of disease in models and patients progresses, so we must refine our models accordingly. The cost of using ageing models in preclinical testing may be more than that currently encountered but these are insignificant when compared to the cost of failed clinical trials.

Using mice to study ageing, age-related diseases

As we age the risk of disease increases so surely the best murine model of age-related disease is an old mouse? Whilst some common age-related pathology can be recapitulated in mice simply by ageing mice those such as cataracts, sarcopenia, cancer, and tissue dysfunction is what is mostly observed in ageing mice. Therefore there is still a need for age-appropriate models of individual disease to recapitulate more complex aspect of age-related diseases. This is because age and age-related disease are not overlapping but rather can be seen as two parts of a multistep process [17] whereby ageing is the first step, leading to loss of tissue reserve and homeostasis and increased chances of developing one or more age-related diseases. Accumulation of multiple diseases and age-related loss of functions can result in frailty. Mechanisms of ageing such as chronic inflammation, senescence are interlinked and thought to exacerbate many age-related diseases such as atherosclerosis, neurodegeneration, and osteoarthritis [18]. Chronic inflammation can arise from obesity, with adipose tissue being an active inflammatory tissue [19], and as a result of cellular senescence whereby senescent cells release pro-inflammatory cytokines; the senescence associated secretory profile (SASP). In a model of chronic inflammation Jurk *et al.* demonstrated that persistent inflammation can in turn accelerate ageing via telomere dysfunction and cellular senescence [20]. However, not all patients get the same diseases in the same order. This is because there are other factors such as genetic components associated with specific pathways which contribute to susceptibility to disease. Consequently to push forward with personalised medicine we must understand the specific pathways contributing to disease. Specific models of disease will help our understanding of the specific pathways involved in individual pathologies, how they interact with the ageing process, and will also assist in the identification of disease biomarkers that predict later disease.

Using mice as models to improve age-related health outcomes

A key aim of ageing research is to translate this into beneficial interventions to reduce the burden of age related disease. An increase in longevity has already been shown to result in an improved healthspan [21]. However, longevity is not necessarily the best readout when considering disease parameters; an organism may live longer but still suffer from chronic diseases or disease may simply be delayed. Health span, defined as time free of diseases, is now considered a better measurement of the outcome of interventions and the main goal of ageing research is to contract the period of morbidity before death rather than just simply increase lifespan[22]. A recent study on the effect of rapamycin, a dietary restriction mimetic, demonstrated similar health benefits to dietary restriction but without a concomitant increase in longevity [23]. Whilst beneficial outcomes have been demonstrated from modulating ageing processes, this does not necessarily mean there is a generalised health benefit affecting all age-related diseases. Resveratrol treatment of mice on a high

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