

Ageing and ageing-related disease

Ageing is a natural process whereby the molecules, cells and tissues in a body accumulate damage, leading to loss of function and increased risk of death. Ageing occurs at many levels of organization, including modifications and damage to macromolecules, changes in gene expression, alterations in cellular biochemistry and the metabolome, damage to tissues and the systemic environment, and alterations to the behaviour of the whole system. In developed countries today, ageing is the major

has been that certain single-gene mutations can extend the healthy lifespan of laboratory animals. Outside of the laboratory, research has also benefitted from comparative work on the rate of ageing in different organisms and from population-based genetic-association studies. Experimental work in humans has looked, for instance, at the effects of diet and exercise⁵. Clinical work on ageing in itself is less common, largely owing to practical considerations of the time involved.

One of the main messages coming out

to identify downstream factors in the signalling cascade and retain the benefits without the negative side effects.

QUESTIONS AND OPPORTUNITIES

Although it is known that ageing is an accumulation of damage, less is known about the nature of the damage, the processes that generate it and the systems that can protect against it. There are many systemic changes within an organism as it ages, and it is a major challenge to differentiate between them. Interventions that have been discovered to improve health during ageing and to extend lifespan can provide some clues to these processes. Such studies have, for example, called into question the supposition that oxidative damage causes ageing, pointing instead to other factors such as endobiotics and xenobiotics, cellular detoxification and proteotoxicity.

Another major challenge will be to understand the connection between the ageing process and the aetiology of ageing-related diseases. This will require work that encompasses both ageing processes and animal models of disease. Translating this work into humans will require cooperation with clinicians. In fact, research on ageing frequently has to draw on expertise from other fields. For instance, molecular chaperones and their role in prevention of proteotoxicity are of great relevance to both ageing-related damage and neurodegeneration. Epigenetic mechanisms are also important in ageing, as are stem cells, tissue regeneration and biomaterials research. As with other areas of biological science, bioinformatics is vital to help gather, store, analyse and process data. Overall, coordinating different types of research across different levels of life sciences and health care will be an important undertaking.



» If I'd known I was gonna live this long, I'd have taken better care of myself.

Eubie Blake (1883–1983), ragtime composer and pianist, on his one-hundredth birthday, 5 days before his death.

risk factor for predominant killer diseases such as cancer, and neurodegenerative and cardiovascular disorders. By understanding the mechanisms of ageing it should be possible to help relieve this disease burden, and to work towards developing interventions to prevent the complications of ageing and ageing-related disease.

THE ERA OF AGEING RESEARCH

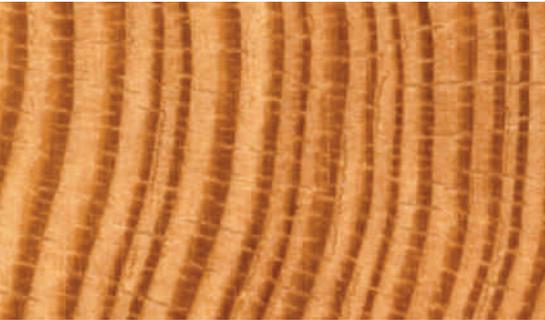
Given the importance of ageing in disease processes, understanding its mechanisms might provide the opportunity to identify interventions — genetic and environmental — that can improve health and prevent or delay ageing-related diseases^{1,2}. Animal models, such as nematode worms, fruit flies and mice, are often used in laboratory research because many biochemical pathways are conserved across the evolutionary tree^{3,4}. Ageing research has accelerated in recent years: perhaps the most exciting discovery

of this work is that ageing is the primary risk factor for diseases later in life^{6–10}. Interventions that protect against the effects of the ageing process and extend lifespan in laboratory model organisms also delay or reduce the impact of diverse, ageing-related disability. This implies that it might be possible to develop a broad-spectrum, preventative medicine for the diseases of ageing, in sharp contrast with current medical practice, which tackles each disease separately.

For a drug target identified in animals to have human therapeutic potential, its pathway must be conserved across species. This is not always straightforward; for example, a key biomolecular signalling pathway of ageing in mice involves insulin and target of rapamycin (TOR) proteins. Reducing the activity of this pathway can extend lifespan and improve health in mice, but it can also cause diabetes and cell death. A more thorough investigation is necessary

Recent experiments at the Max Planck Institute for Biology of Ageing in Cologne have elucidated how rapamycin, which is a drug approved for human use, extends lifespan in fruit flies and mice. In fruit flies, both an increase in the cellular clean-up mechanism,

autophagy, and reduced activity of the S6 kinase are involved, pointing to new drug targets for improving health during ageing (Bjedov, I. *et al.* *Cell Metab.* 11, 35–46, 2010).



- Ageing is a complex process of accumulation of damage, and is the major risk factor for the predominant killer diseases in developed countries.
- A recent breakthrough is the discovery that mutations in single genes can produce a broad-spectrum improvement in healthy ageing in animals models.
- These findings could lead to development of a new, broad-spectrum, preventative medicine for the diseases of ageing.

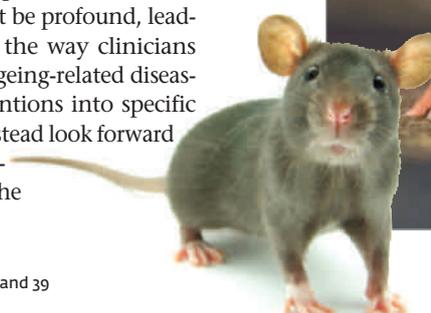
There are other challenges, both practical and economic. Working with mammals in ageing research is particularly expensive — a long-lived mouse can survive for more than 4 years — and many animals are required for demographic analysis, which need major animal facilities. Moreover, development of a broad spectrum, preventative medicine for the diseases of ageing is both a major promise and a major challenge. Any drug would require years of testing in clinical trials and would have to be given to people who were not yet ill. This is unlikely to be practicable in the foreseeable future.

These are early days for ageing research, it is a younger field compared with research into the individual diseases of ageing — such as Parkinson’s or Alzheimer’s disease. However, despite the comparatively longer duration of research and the larger international research community, there are still no preventative and limited palliative treatments for these conditions. Hence there is an opportunity for ageing research to make a major contribution, as signified by a rise in the number of institutions and international meetings devoted to ageing research.

Ageing not only reduces quality of life, it also appears to underlie diverse ageing-related diseases. Basic research in this area has already identified many single-gene mutations and environmental interventions that increase healthy lifespan as well as signalling mechanisms at work within cells. Further research will refine our understanding of these mechanisms and hopefully identify areas of intervention. The promise is that this work will, in turn, lead to the identification of drugs to improve human health and protect against diverse ageing-related conditions. The impact of this research on human health might be profound, leading to a revolution in the way clinicians think about and treat ageing-related diseases. Rather than interventions into specific conditions, we could instead look forward to broad spectrum, preventative medicine for the diseases of ageing.



- above Four generations of one family. Ageing is a complex process of accumulation of damage. Studying ageing in humans is a long-term process.
- below Many people remain healthy and active into their later years; the goal is to determine why some do while others do not.
- bottom Mice are the mainstay of laboratory research. A long-lived mouse can survive for more than 4 years.



Top image: Bluestone, Science Photo Library / Far right image: David McLain, Getty Images