What inspired you to rise to the challenge of confronting age-related diseases?

Ageing is arguably the most complex biological process, and is thus an enormous intellectual challenge. When I started my research career, colleagues told me: ‘you suffer from ageing, you don’t study it – this is useless’. I found this a challenge. In less than 30 years, this view has been completely overturned. With biological interventions, we can now extend life in many animals – in some species up to five times their normal lifespan. The goal now is to ensure that those extra years are lived in good health.

In humans, progress in hygiene, lifestyle, food and classical medicine causes a continuous increase in life expectancy of up to three months per year. Healthy life expectancy, however, increases much more slowly. If this discrepancy is not dealt with, quality of life for older people will decline and health service costs will soon spiral out of control. Intervening to slow the ageing process as the common underlying cause of all age-related diseases is the only real hope there is.

The strong link between chronic disease and old age has been widely acknowledged, but research on how to combat this issue is lacking. Why is this?

In humans, progress in hygiene, lifestyle, food and classical medicine causes a continuous increase in life expectancy of up to three months per year. Healthy life expectancy, however, increases much more slowly. If this discrepancy is not dealt with, quality of life for older people will decline and health service costs will soon spiral out of control. Intervening to slow the ageing process as the common underlying cause of all age-related diseases is the only real hope there is.

What is cellular senescence? How does this mechanism lead to chronic disease, frailty and other age-related health problems?

Cellular senescence is a response to irreparable DNA damage that causes a permanent block in cell division. As long as this block works, a cell with damaged DNA cannot proliferate to generate a tumour. However, cells cannot just stop dividing, so the senescence response also triggers many other changes in the way cells behave. Importantly, they generate free radicals and many other potent signalling molecules, including those that induce inflammation. These signals change the behaviour of surrounding cells, making some of them senescent as well and redirecting the functions of others. Thus, senescence limits tissue regenerative capacity, causes chronic systemic inflammation and changes function in both senescent and non-senescent cells.

Is there potential for your research to lead to the development of chronic inflammation prevention strategies?

Having shown chronic inflammation to be a causal mechanism for accelerated ageing, we are, of course, thinking about the possibility of anti-inflammatory interventions in fast-ageing humans. It is well established that some of us age more slowly than others. Could anti-inflammatory drugs help those on the ‘fast track’? The problem is that all anti-inflammatories in use have very serious side effects if taken long term. New, safer drugs are needed.
THE SOCIETAL AND

Economic burdens that come with an ageing global community are some of the most challenging issues we are confronted with today. People may be living longer than ever before but, as age-related illnesses cause individuals to lose their independence, available resources are spread ever more thinly. To ease this burden, biomedical researchers are investigating ways to ensure that ageing individuals stay healthy for longer.

Unfortunately, effective treatments against many age-associated conditions have proven difficult to develop, due in part to the complex nature of the processes underlying neurodegeneration and cellular ageing. In fact, treating co-morbid diseases individually has been shown to have little positive impact on overall health. Taking a different approach, biomedical scientists are now setting their sights on understanding the underlying biological mechanism of cellular ageing itself. As scientists begin to reveal mechanistic insights, the reality of effective interventions against age-related conditions as a collective is getting tantalisingly nearer.

At Newcastle University, UK, Professor Thomas von Zglinicki’s lab has been at the forefront of several major breakthroughs that have profoundly affected how ageing is understood. His research points toward long-suspected chronic, non-microbial inflammation as the prime candidate behind a broad range of age-related disorders such as heart disease, stroke, cancers and arthritis. However, it is the underlying cause of this chronic inflammation that is of real concern.

TRIMMING TELOMERES

Over time, evidence has emerged pointing toward cellular senescence – a permanent arrest of cell division when a normally replicating cell encounters DNA damage – as a main driver of numerous age-related pathologies. Telomeres are lengths of non-coding DNA found at the end of each chromosome that act as a buffer to protect the integrity of the genetic code during replication. It was originally thought that telomeres are shortened step by step within each cell division by a constant molecular mechanism. When telomeres get too short, they are recognised as damaged DNA by the cell and trigger a signal that induces cell senescence or, in some cases, cell death. It appeared from existing evidence that telomere loss had similar characteristics to a regular clock ticking down to the end of a cell’s ability to replicate.

The results of Zglinicki’s research conflict with this longstanding picture, showing for the first time that DNA replication is not the only determinant of telomere loss. His team assumed, based on current knowledge, that using oxidative stress to induce cellular senescence would cause cell division to stop before telomeres were significantly sheared off.

Although cell division was soon halted, the rate of telomere loss actually increased, thereby indicating that telomere shortening is affected by oxidative damage. In short, DNA repair is less efficient in telomeres than elsewhere in the genome such that oxidative damage speeds up telomere shortening. Rather than a countdown to the end of cell proliferation as previously thought, telomere loss could be viewed as a measuring stick to assess the risk of DNA damage.

Zglinicki’s lab was the first to propose and test the hypothesis that the extent of telomere shortening could be used as a biomarker for ageing and the risk of developing age-related disease. The researchers measured telomere length in people with various age-related conditions, such as cerebrovascular disease and strokes, and compared the results to the lengths of telomeres in healthy individuals. While the results in large cohorts supported the theory, the prognostic power was not significant enough to be used accurately in individuals to define biological age or foretell the outlook of health for the future.

CIRCULUS VITIOSUS

Though telomere shortening may not be the accurate biomarker one might hope for, it provides a key to unlocking the pathology of accelerated ageing. Zglinicki’s lab has found the first evidence of a dynamic feedback loop characterising the relationship between cellular senescence and chronic inflammation.

This circulus vitiosus, or vicious circle, starts when telomeres become too short, triggering a DNA damage response that causes cellular senescence. As a result, a gene known as CDKN1A is activated causing mitochondrial dysfunction and the production of reactive oxygen species and of signalling peptides like IL-1 and IL-6 that cause inflammation. Reactive oxygen species cause more DNA damage which spurs on the damage response, and so the circle continues.

Recently, Zglinicki’s lab investigated the effects of this feedback loop in mice to determine whether chronic low-grade inflammation accelerates the accumulation of senescent cells.
cells, and if these cells in turn aggravate chronic inflammation. Genetically engineered to produce enhanced inflammatory signals, Zglinicki’s team found that the mice aged faster than their normal counterparts, who lived twice as long. The researchers showed that the inflammation signals trigger the production of oxygen free radicals to induce DNA damage that generated senescence signalling. This signalling led to more inflammatory signals and the increased release of oxygen free radicals.

INTERVENTION ON THE HORIZON

Although ageing and age-related conditions in humans have long been associated with chronic inflammation, the research carried out by Zglinicki’s team provides the first mechanistic explanation of this relationship, and has even provided a starting point from which to explore potential interventions. Anti-inflammatories may have had no beneficial effects for healthy mice but, for those with enhanced inflammation, the cellular signs of accelerated ageing came to a halt. Although long-term use of existing anti-inflammatories has serious side effects, they at least provide a crucial platform for the development of interventions for individuals ageing faster than normal. Ageing is an extraordinarily complex process but as biomedical research continues to unravel its mysteries, the reality of prolonging lifespans and maintaining quality of life becomes ever nearer.