Fighting the aging process at a cellular level

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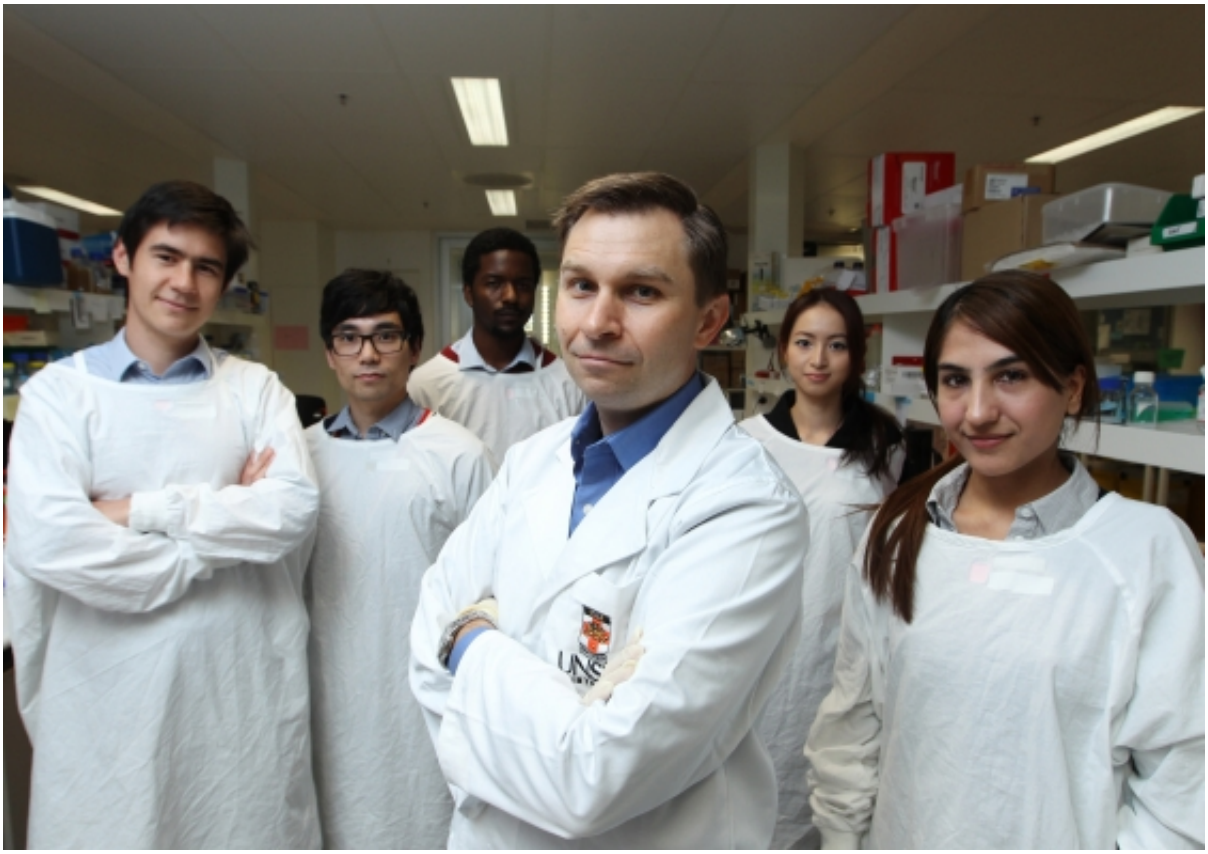

UNSW's Labratory for Ageing Research. Left to right, Lindsay Wu, Myung-Jin Kang, Frank Stoddart, David Sinclair, Ashley Wong, Hassina Massudi. Credit: Britta Campion

It was about 400 BC when Hippocrates astutely observed that gluttony and early death seemed to go hand in hand. Too much food appeared to 'extinguish' life in much the same way as putting too much wood on a

fire smothers its flames. If obesity led to disease and death, he thought, then perhaps restraint was the secret to a longer life?

It would be a couple of millennia before science confirmed, in 1935, a link between reducing calorie intake and living longer. This discovery was just the beginning. In the 21st century, further advances have led to an extraordinary leap in life expectancy; a child born in Australia today can expect to live at least 25 years longer than a child born a century ago. Yet longer life has also unleashed a cocktail of diseases and chronic conditions, attacking us in tandem, to blight our final years.

Scientists are now increasingly focusing on the biology of ageing itself as the key to warding off this multitude of illnesses. "We currently study diseases in isolation, so we look, for example, at cardiovascular disease, cancer, diabetes, heart disease and Alzheimer's separately," said Dr Lindsay Wu, organiser of the recent inaugural Australian Biology of Ageing Conference, hosted by UNSW. "But they all have an underlying process of cellular ageing – so if we are able to treat the biological process of ageing, then we can have a huge impact on all sorts of diseases."

Significant progress is being made on several frontiers. In New York, a human drug study is for the first time targeting ageing rather than a specific disease. US researchers have also recently managed to kill off age-damaged cells in mice to restore vitality, body function and extend life by up to 35%.

And at UNSW's Laboratory for Ageing Research, and its sister lab at Harvard Medical School, scientists have identified and isolated a compound found in red wine that has prolonged life and improved health in animals as varied as worms, fruit flies and mice. Lead researcher, David Sinclair – who splits his time between his roles as head of the UNSW Lab and as Professor of Genetics at Harvard – has long been

taking the compound himself.

Targeting ageing cells

Australian and international researchers are focusing on two key processes. One promising approach is to target naturally occurring 'senescent' cells, the label given to any type of cell as it acquires age-related damage or loss of function. Our immune systems should clear out these cells, but as we age this housekeeping function becomes less and less effective. This means senescent cells accumulate rather than divide, and in turn, they secrete inflammatory agents that can damage adjacent cells, causing the kind of chronic inflammation associated with age-related diseases.

Dr Darren Baker, of the US Mayo Clinic, who was in Australia for the Biology of Ageing conference, and colleagues, recently published their breakthrough results in *Nature*. Their study demonstrated the elimination of senescent cells in mice not only extended their lives but improved their general health, curiosity and energy levels, with no apparent ill effects.

"What we are thinking about is extending healthy life, not just extending life, per se ... we don't want to increase people's time in care," says Baker.

His Mayo Clinic group is now trying to develop components or compounds that can selectively kill senescent cells, without relying on the genetic manipulation used in the mouse study. "If you had asked me five years ago, I would have said we are decades away from human interventions, but we are now moving much faster than we anticipated."

The loosening of DNA

A second prominent research area focuses on the anti-ageing molecules known as sirtuins, particularly the 'SIRT1' enzyme. "When we are young, our DNA is very tightly wound and it's the SIRT1 molecules that keep this structure intact," says Wu. "As we age, DNA structure naturally loosens and can turn on the wrong genes, causing dysfunction that can lead to diseases like cancer." Researchers at UNSW are working on ways to energise the enzyme SIRT1, which Sinclair and his team have been working on for close to two decades, so it works more effectively.

"We think the loosening of DNA is driving whole-of-body ageing, so if we can boost the levels of fuel in our SIRT1 molecules to maintain our DNA in a youthful state, we can slow down ageing," Wu says.

SIRT1 is also the key to Sinclair's landmark discoveries about resveratrol, a naturally occurring compound found in red wine. In 2003, Sinclair first demonstrated that resveratrol made SIRT1 run faster and could extend the life of single organisms. In 2013, the prestigious *Science* journal published his work, proving this single anti-ageing enzyme could be effectively targeted, paving the way for the development of a new class of anti-ageing drug that could potentially prevent some 20 diseases ranging from cancer, to type 2 diabetes and Alzheimer's disease.

The science of diet and exercise

It has also been uncovered that sirtuins (SIRT3 and 4) are behind the link between longevity and dietary restraint that has fascinated so many thinkers since Hippocrates. In the 1500s, the Venetian nobleman, Alvise Cornaro, famously refined Hippocrates' theory and experimented on himself, limiting his daily intake of food to 12 oz (340 g) and 14 oz (397 g) of wine. He reportedly lived until 100, attributing his health, vigour and contentment to this regime.

Calorie restriction and exercise are now both known to activate sirtuins,

explaining in part the protective nature of a good diet and regular physical activity. However, scientists have also greatly refined the link between diet and longevity. Professor David Le Couteur, from the University of Sydney, told the recent conference that a low-protein, high-carbohydrate diet is associated with a longer life, with nutrients ideally balanced in a ratio of about 1:10. This ratio, he said, correlates with the traditional diet of the people of the Japanese island of Okinawa, famous for its high number of centenarians.

Sinclair is confident human life spans of 150 years are likely in the foreseeable future; other researchers suggest 100 will be more commonly attainable. Although Sinclair's resveratrol is on the market as a supplement, it has not yet been formulated as an anti-ageing drug. However, the first human trials of a potential anti-ageing drug, metformin, are taking place in the US. Metformin is actually a common anti-diabetes drug that has been in use for some 60 years.

Research has consistently shown many diabetics taking metformin live longer than non-diabetics, even if they have additional risk factors, like being overweight. This association is so pronounced metformin is now being tested as an anti-ageing drug.

There are, however, simple steps everyone can take right now if they want to live longer, healthier lives, says Baker. "If you exercise a lot you have fewer senescent cells, and if you have a decent diet you also see fewer of these cells, so just by modifying your behaviour you can influence your rate of accumulation of these kinds of cells."

"It is always better to look after yourself ... than to just wait for an anti-ageing pill."

More information: Darren J. Baker et al. Naturally occurring p16Ink4a-positive cells shorten healthy lifespan, *Nature* (2016). DOI:

10.1038/nature16932