Risk of Living Longer

Session 2: biology of aging

Outstanding Q&A

This document accompanies the webinar recording and slides from the Club Vita and Nationwide event on 7 May 2024, titled *The Risk of Living Longer Series, Session 2: The biology of aging.* It provides some high-level responses to questions put to the panel that we did not have time for during the event. Responses in green labelled RH are from Prof Richard Faragher, responses in blue labelled ND are from Dr Niharika Duggal.

1. How old is old?

   RH: That is a more interesting question than it at first appears. There is a clear need to distinguish between the old (65+), the very old (85+) and centenarians. For centenarians it is possible that highly distinctive biology is in play or alternatively there may be survivorship bias. I tend to the former based on rodent data but I stress that I 'tend'.

2. What would happen if senolytics were provided and then stopped? Would the mouse (or individual) begin to shows signs of aging and how quickly? Do senescent cells accumulate more quickly in older mice/individuals.

   RH That experiment has not been performed to my knowledge. Since senescent cells are generated through routine physiological processes they would begin to accumulate again. Cytokinetically rates of generation are higher in cells which have undergone many divisions compared to those which have not but accumulation is a function both of rates of generation and rates of clearance. The latter is a function of the immune system so positive effects on the immune system might produce long lasting effects on accumulation rates.

   NH: Also each person's body responds differently and we can expect individual variability in the rate at which senescent cells return after stopping senolytics. Factors such as underlying health conditions and lifestyle habits can influence the variations

3. Would we expect anti-aging technologies in the next 20 years to increase longevity broadly, or to widen the gap between the affluent and the less affluent?

   RH: My own view is that the first generation of these compounds will not be particularly expensive especially if set against the savings on health care systems so I would not expect a gap to widen. That being said other approaches (e.g. lifestyle) aimed at improving healthy life expectancy do risk increasing (and I believe in some European contexts have increased) the gap because of the resource implications (poor people can't afford gym memberships; also healthy foods are more expensive) and the way in which they are 'sold'.

4. If one or a few senescence cell removal clinical trials passes, how expensive/available will these treatments be to the larger population?

   RH: I expect initial treatments to be cheap and doubly so compared to the costs of illness. From memory NICE uses a standard of £30k per life year as the cut off. They will be much cheaper than that and mass production will lower costs.

5. Do senescent cells have a role in maintaining homeostasis within the body?

   RH: Yes- for example they play a role in wound healing. Formally it is the balance between the number of senescent and growing cells that is the issue. Accumulation and non clearance disrupt this.

6. How can we defer the senescence process?

   NH: It might be possible to delay buildup of senescent cells by addressing potential contributors such as damage accumulation, cellular dysfunction. Maintaining a healthy lifestyle, including exercise, balanced nutrition, adequate sleep and stress management and avoiding harmful habits such as excessive alcohol consumption and smoking. To give an example: consumption of an antioxidant-rich diet (containing polyphenols) can help mitigate oxidative stress and reduce cellular damage.

7. To what extent if any is AI being utilised in this research?

   RH: It is beginning to show promise in identifying links between hallmark mechanisms and pathologies and identifying clinical trial candidates. There is also the potential for its use in the early stages of drug discovery.

   NH: There is also potential for using AI to analyse large-scale omics data (genomics, transcriptomics, proteomics, metabolomics) to identify molecular signatures of individuals' ageing trajectory and identify individuals at risks of developing age-related diseases, such as Alzheimer's, allowing for early intervention and treatment.

8. Given the points made today are we basically saying that even with cures in diseases (e.g. cancer, dementia etc) you think people would still live to similar ages as they do now (as ageing would still make them susceptible to a disease eventually) but it would take senolytics to get people to live longer?

   RH: Modelling indicates that the gains in healthy lifespan made by targeting ageing mechanisms potentially exceed those made by curing individual diseases. I would expect to see significant healthy lifespan extension with senolytics but we have to be mindful not to treat individuals as genetically homogenous. We know that there are healthy life expectancy genetic variants within the population, and I would not be surprised to identify both individuals who are (relative) hyper- and non-responders.

9. Thanks very much.

   Club Vita: Glad you appreciated the session. Don't forget to sign up to the rest of the series here. You can access the recordings for previous sessions in the series here.