Written evidence submitted by Dr Andrew Steele

Summary

- Increasing healthy lifespan is the most important challenge facing governments today.
- The Government's aim to provide five additional years of healthy life expectancy by 2035 is likely to happen without significant policy intervention if healthy life expectancy returns to trend for the UK.
- This goal should be supplemented with a series of longer-term, mission-driven projects based on 'hallmarks' of the ageing process identified by scientists.
- Incorporating these challenges into the Government's Industrial Strategy should be accompanied by better auditing of investment in ageing research, together with a full assessment of the economic and social costs of ageing to the UK. This would allow a high-level cost–benefit assessment of this research.

Introduction

1 Increasing healthy lifespan is arguably the most important challenge facing societies and governments across the world. Ageing is the primary risk factor for diseases like cancer, heart disease, stroke and dementia. Global life expectancy is now 72 years, meaning that most of the world's population can expect to live long enough to experience the effects of ageing, and one or more of these diseases. These conditions have a huge impact on quality of life, as do the symptoms of growing older which are typically not labelled as diseases, from frailty and incontinence to forgetfulness. As a result, they are a substantial burden both on wellbeing and the economy. It is therefore vital that governments prioritise extending healthy lifespan.

2 Our rapidly increasing scientific understanding of the ageing process has the potential to play a key role. We now understand that the many diseases and disabilities of old age result from a collection of fundamental processes which we have begun to catalogue, and for which we can envisage treatments. We have multiple, independent ways to slow or even reverse ageing of organisms in the lab, including in mice, and several approaches in or nearing human clinical trials.

3 This presents a historic opportunity. Current biomedical research largely exists in silos, looking at individual diseases in isolation, and treating them when they arise. Treatments for the ageing process itself offer the hope of addressing multiple diseases and dysfunctions simultaneously, and doing so preventatively. The first treatments for ageing will begin a revolution in healthcare as significant as the discovery of antibiotics.

4 However, it is not obvious that the Government's current plans embrace this scientific potential. The aim of providing five more years of healthy life expectancy by 2035 (hereafter referred to as HLE+5) is a short-term target, and one which is likely to happen without the need for significant scientific discoveries.

5 In this submission, I will suggest that we create a series of mission-driven moonshots around ageing biology, aiming to intervene in the hallmarks of the ageing process which scientists

have identified. Though many strands of this research are in their early stages, it is understanding and intervening in the ageing process itself which will yield the greatest biomedical and economic dividends in the long term.

Please note that headings in this submission are numbered according to the questions in the Call for Evidence and do not appear in numerical order.

11. How feasible is the Government's aim to provide five more years of health and independence in old age by 2035?

6 The Government's aim to provide five additional years of healthy life expectancy by 2035 (HLE+5) is highly feasible. Indeed, given a return to trend for healthy life expectancy (HLE), it is quite likely to happen with little or no policy activism.

7 Though improvements in both HLE and life expectancy (LE) overall in the UK have stagnated since 2010, during the period 1995–2010 HLE and LE increased by 4 months per year and 3 months per year respectively[1]. According to the WHO's figures for healthy life expectancy at birth (HALE)[2], similar trends are ongoing in countries like Spain, Norway and Japan which have higher (H)LE than the UK, suggesting that this stagnation is not the result of a fundamental biological limit on healthspan or lifespan, or limits on country-level improvements to healthcare or lifestyle. According to WHO HALE, Singapore was already 4.3 years ahead of the UK, and Japan 2.9 years ahead in 2016—these are both significant fractions of the 5-year target, implying that reaching it is plausible without radical change.

8 The factors underlying the UK's stagnating (H)LE statistics remain to be fully elucidated, but suggestions include the effects of austerity, high recent winter mortality due to unusually bad flu seasons, and statistical fluctuations[3]. Assuming a reversion to trend, the 16 years to 2035 is likely to see a five-year increase in HLE without substantial intervention. Further, this is being quantified using the ONS's 'Disability-Free Life Expectancy' or DFLE time series, with a 2014–16 baseline. This baseline HLE is already one year below 2009–11 levels (the earliest data for DFLE due to a change in methodology), suggesting that one of the five additional years of HLE could be expected simply from a return to levels in the recent past.

9 I therefore believe that we should supplement the current HLE+5 target with longer-term, more ambitious goals based around current scientific understanding of the ageing process.

1. How complete is the scientific understanding of the biological processes of ageing (including the relative roles of genetics, epigenetics, lifestyle, environment, etc.)?

10 The scientific understanding of ageing is far from complete. However, our understanding has been transformed in recent decades, and scientists are now able to outline the biological changes which underlie the diseases, disabilities and dysfunctions of old age.

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[1] Own calculations based on ONS HLE and DFLE data https://docs.google.com/spreadsheets/d/1IL-iRgstODoWa6zjB3dl4Ddm22CQPJM5thOLjfcwVDg/edit#gid=1579648520
[2] https://www.who.int/gho/mortality_burden_disease/life_tables/hale/en/
[3] https://www.kingsfund.org.uk/publications/whats-happening-life-expectancy-uk

11 These changes were dubbed ‘Hallmarks of Aging’ in a 2013 paper of the same name[4], identifying nine biological processes which fulfilled the criteria of changing with age, having a mechanistic association with disease, and whose alteration in the lab could modulate ageing. A prior and more controversial categorisation known as Strategies for Engineered Negligible Senescence (SENS) first published in 2002, argues that fixing seven forms of ageing ‘damage’ could substantially extend human healthspan and lifespan[5]. There is significant overlap in the causes of ageing suggested by these two different taxonomies of biological changes.

12 There are plausible therapies at various stages of development which could intervene in the processes identified. For example, both Hallmarks of Aging and SENS identify the accumulation of aged, ‘senescent’ cells as a primary cause of ageing. It has been demonstrated in mice that both genetic interventions and so-called ‘senolytic’ drugs are able to remove these senescent cells and, in doing so, improve the health and lifespan of old mice[6]. The drugs identified are now in clinical trials for age-related diseases where senescent cells appear to play a pivotal role. However, if they are successful and safe, they could provide early examples of a more radical treatment paradigm: senolytics could be provided to people currently considered ‘healthy’ to slow or reverse the ageing process, and reduce the odds of them developing age-related diseases. Since senescent cells have already been implicated in diseases like cancer, heart disease and Alzheimer’s, and their removal shown to improve function in multiple organ systems in mice, their potential is application is broad.

13 Senescent cells are the ageing hallmark which is by far the best understood and where therapies are closest to clinical application, and the relative importance of these processes and how they interact is yet to be elucidated. However, classifying age-related changes provides the framework for a more ambitious, concrete set of targets for ageing biomedicine.

14 I recommend that the Government, in consultation with scientists, draws up a list of ageing hallmarks and sets a series of mission-driven moonshots to develop treatments to intervene in each of them. This would not only have the benefit of increasing HLE should some of these be successfully translated into treatments, but it would provide vital data as to the relative contributions of and interactions between hallmarks which could guide future basic and translational research. There are already ideas for treatments for each of the hallmarks and attempts to develop them would be valuable basic science projects in themselves, providing a deeper understanding of medically relevant technologies such as gene and stem cell therapy.

15 To briefly examine the examples in the question, genetics is relevant in that which genetic variants you carry can influence the progression of ageing hallmarks. The overall influence of genetics appears to be small, probably accounting for less than 10% of the variation in lifespan between individuals, though it is larger in the handful of individuals who achieve extreme ages (90+ and particularly 100+). This suggests that searching the general population for longevity-promoting genetic variants is unlikely to impact on HLE significantly, though studies based on isolated populations or the extremely long-lived may uncover more unusual variants with greater potential.

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[4] López-Otín *et al.* 2013 https://doi.org/10.1016/j.cell.2013.05.039
[5] Zealley and de Grey 2013 https://doi.org/10.1159/000342197
[6] Baumann 2018 https://doi.org/10.1038/s41580-018-0047-5

16 This further implies that the other 90% of variation is down to lifestyle and environmental factors. However, this is not to suggest that 90% of the potential of ageing research lies in optimising lifestyles and environments: whilst public health measures to improve these would be beneficial and likely highly cost-effective, this figure accounts for current variation in human lifespan, and doesn't account for the potential for future biomedical discoveries to increase HLE. Public health interventions would be sufficient for achieving the HLE+5 target, but to focus solely on these sells the biomedical science of ageing substantially short.

17 Epigenetic changes are a hallmark of ageing and have provided us with 'epigenetic clocks', the most accurate measures of the ageing process (also known as 'biomarkers of ageing') to date. These clocks can predict chronological age to within a few years only by examining chemical modifications to an individual's DNA, and having an 'epigenetic age' greater than your chronological age is indicative of a heightened risk of disease and death. However, in spite of some suggestive evidence, it is not clear whether these epigenetic changes are causal, or merely an accurate read-out of ageing. This is nonetheless a worthwhile target for one of the moonshots I have described: establishing whether epigenetic changes are a cause or an effect, what causes them to happen and what processes they influence, is likely to be central to understanding the ageing process as a whole.

18 Whilst I believe that the best approach in the next decade or so is to tackle each element of a framework of hallmarks independently, the long-term goal of ageing research (in common with many other aspects of biomedicine) has to be an understanding grounded in systems biology. Whilst treatments such as senolytics have the potential to substantially improve HLE, it is inevitable that interventions focused on a single mechanism will have side-effects which affect multiple organ systems around the body. As a result, it is vital that our early efforts are conducted in tandem with detailed gathering of data which will inform systems biology models which can ultimately be used to develop more advanced treatments. Though this is a long-term goal, it is important that the groundwork is laid now. Many basic questions in ageing biology, such as how many senescent cells accrue in which tissues at different ages, lack hard, numerical data, and this will be critical to developing treatments in both the short and long term.

3. Which developments in biomedical science are anticipated in the coming years, in time to contribute to the Government's aim of five more years of healthy and independent life by 2035?

19 The short-term nature of the HLE+5 by 2035 target undermines the ability of biomedical research to contribute towards it. For a medical treatment commissioned as part of this initiative to have an impact on HLE statistics in 2035, it would need to be in widespread use for perhaps five years beforehand. Assuming it would take several years to be rolled out nationwide, this means its development would need to be completed by the mid-2020s. Given typical timescales for pharmaceutical and medical technology, that would in turn require any biomedical treatments for ageing to be ready for translation in the next few years. Whilst there are a few candidates which could conceivably be deployed this quickly, there are large numbers of promising treatments which could emerge in the next five to ten years which are likely to be unable to contribute due to the short timescale.

20 Drug repositioning to slow ageing is one intervention which could contribute to HLE+5. There are several drugs which may slightly slow the ageing process which could be considered for

widespread or even whole-population use if shown to be safe and effective for this. For example, a trial of metformin—a very widely-used, off-patent diabetes drug with an excellent safety profile—has just been approved by US regulators to assess its performance in 'healthy' old volunteers to assess its ability to postpone a number of age-related ailments[7]. If existing drugs were found to be suitable for widespread use, this could provide a quick win perhaps amounting to months or years of additional HLE at low cost.

21 Biomedicine could contribute more effectively to a more ambitious target with a more distant deadline. Even a goal set fifty years from now would benefit a large fraction of people alive today. Though research into many hallmarks of ageing would likely bear fruit substantially before this, it nonetheless illustrates the time available for more ambitious projects.

22 Research into biomarkers is also critical to the ultimate success of ageing biomedicine. The epigenetic clocks mentioned in the previous answer are a strong contender, but there are many other candidates from measuring levels of proteins in blood to using AI to discern biological age from an image of a face. Developing biomarkers will make trials of therapies vastly quicker and cheaper. In a conventional trial of a preventative treatment for ageing, researchers would have to wait for subjects to die, or be diagnosed with an age-related disease, in order to gather data. Even over many years, it is likely that the majority of subjects will remain alive, which weakens statistical power. With a biomarker, by contrast, every patient in the trial can provide data based on how the biomarker changes over time. Thus, trials can be conducted more rapidly and with smaller groups, at much lower cost.

23 It is therefore important that research into biomarkers proceeds alongside missions to alter ageing hallmarks, and integrated with them. Whether altering a particular hallmark alters a related or seemingly unrelated biomarker will provide guidance for those biomarkers' suitability in trials of particular therapies, and insight into how the hallmarks and biomarkers are related which will increase our understanding of the ageing process overall.

9. & 10. Industrial strategy

24 There is relatively little work globally on biomedical interventions to increase lifespan and healthspan. Any country which makes a substantial investment in the basic science and its translation is likely to be able to take a leading position. The UK has a world-leading biomedical science sector and is therefore in a strong position to take the lead.

25 Most of the work towards addressing ageing hallmarks is at the basic science stage, and the key is to establish funding mechanisms which allow us to explore this but with a view to short- and medium-term translation of discoveries. The easiest way to do this is to focus on funding projects which will intervene in these processes, as they will have obvious potential for translation as well as exploratory and descriptive value.

26 It is also important to examine regulation around preventative treatments which slow or reverse aspects of ageing in people who would currently be considered healthy, as this is the area which ultimately has the greatest scope for commercialisation. Such treatments have a vast potential market: eventually, every living human. This is exactly the type of investment which should form part of a publicly funded industrial strategy: early-stage work which could have enormous economic significance over a timescale of decades.

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[7] Targeting Aging with MEtformin (TAME) trial https://www.afar.org/research/TAME/

27 Though the Government has listed healthy ageing as one of its Grand Challenges as part of its Industrial Strategy, the Grand Challenge framework has been criticised for a lack of specificity[8], and a mission-driven approach to defining challenges has been recommended[9]. This is compatible with the approach described in this submission.

28 There are also no centralised data on investment in biomedical research into ageing. This makes it difficult to establish the extent of work being performed in different areas, or the total amount invested. Government should conduct an audit of research funding into ageing to assess the size of these investments both relative to other fields of research, and to the social and economic problems that progress could address. I have made the case for a centralised audit of investment in different areas of research in previous submissions to the Commons Science and Technology Committee[10]. The lack of data is particularly acute for ageing research because, unlike traditional disease-focussed research into dementia or cancer, there are no studies drawing together funding data by charity or academics.

29 It is likely that research into the ageing process in the UK totals low tens of millions of pounds, and mission-driven or translational approaches comprise a small subset of that. This compares to the economic cost of age-related disease to both the NHS and the wider economy measured in tens of billions. There is a strong economic case for additional investment in research, before the enormous human cost of age-related disease and disability is even considered.

13. What would be the implications of a paradigm shift to people leading healthier lives for longer?

30 There is a surprising lack of work considering the economic and social impacts of ageing as a whole on the UK and the world. From the standpoint of both setting policy and advocacy for ageing research, it would be very useful to have an authoritative assessment of the current costs of ageing to the UK. This would involve both direct costs to Government and private individuals for provision of health and social care, and indirect costs to the wider economy. These already exist for specific diseases like dementia and cancer. An initiative called the Longevity Dividend established that the savings to the US from a modestly slowed ageing leading to a 2.2-year improvement in life expectancy would provide $7 trillion of economic value, substantially more than progress against heart disease and cancer in isolation[11]. It would be very valuable to have a similar assessment for the UK to which to compare levels of investment in ageing research.

About this submission

31 This evidence is submitted in a personal capacity. I am a scientist and writer currently writing a book on the biology of ageing, due to be published in 2020. Prior to this I worked as a post-doctoral computational biologist at the Francis Crick Institute. I have campaigned on science funding as Chair of Science is Vital and co-founder of Scienceogram.

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[8] See eg https://revivingeconomicthinking.com/technology-and-innovation/

[9] A Mission-Oriented UK Industrial Strategy, UCL Institute for Innovation and Public Purpose https://www.ucl.ac.uk/bartlett/public-purpose/publications/2019/may/mission-oriented-uk-industrial-strategy

[10] See https://scienceogram.org/blog/2015/08/science-technology-committee-parliament-submission/ and https://scienceogram.org/blog/2013/11/science-technology-committee-research-funding/

[11] Goldman *et al.* 2013 https://doi.org/10.1377/hlthaff.2013.0052