BIOETHICS BRIEFING NOTE

NUFFIELD COUNCIL ON BIOETHICS

The search for a treatment for ageing

OVERVIEW

- Geroscience research is exploring interventions that delay biological ageing and reduce the risk of age-related diseases and conditions.
- Strong market demand is driving investment in geroscience research, particularly in the US. Investment in this area has been highlighted as a key opportunity for the UK in the future.
- Animal research has led to the discovery of several potential interventions for ageing and some are already being tested in human clinical trials.
- Many uncertainties remain about the effects that treatments for ageing would have on human health span and lifespan, the economy, models of care, health inequalities, personal identity, and how people work and live later in life.
- There are calls for an ethical framework for geroscience research to help guide researchers, policy makers and consumers.

INTRODUCTION

In most countries, people are living longer and healthier lives than ever, but are still spending a significant number of years in poor health towards the end of their lives.[1] Common conditions experienced by older people include cardiovascular disease, cancer, dementia, arthritis, and general frailty. Given that the number of older people is predicted to increase markedly over the next 25 years,[2] addressing age-related health conditions is a pressing societal challenge. Healthy ageing is a priority policy area for the World Health Organization and governments around the globe.

Geroscience, also called biogerontology, is a field of research that is exploring the biological processes that underlie ageing. Researchers working in this field believe that intervening in these processes could be a more efficient way of increasing health span – the number of years we are healthy – than tackling each condition individually. This briefing note summarises the main scientific developments to date, and the potential ethical and social issues that the discovery of a treatment for ageing might raise.

BIOLOGICAL AGEING

Biological ageing is a progressive decline in bodily function and an increasing susceptibility to disease and death as we get older. There is no consensus about the precise processes that cause biological ageing, although it is clear that no single mechanism is responsible. Cell damage and errors in DNA accumulate over our lives, eventually leading to cellular dysfunction.[3]

Hundreds of genes also have been found to be involved in ageing.[4] Recent advances in the tools of research, such as genome sequencing, computer modelling, data science, and the collection of long-term data from specific groups of people, are likely to accelerate our understanding of ageing processes in the near future.[5]

INVESTMENT IN AGEING RESEARCH

Large amounts of public and private funding are being directed towards research on ageing, driven by strong market demand. The US is the world leader in geroscience, with several government-funded research programmes on ageing, such as the US National Institute on Aging, and a number of biotechnology companies exploring potential ageing interventions, many backed by wealthy entrepreneurs. Google founders Sergey Brin and Larry Page, for example, have launched biotechnology company Calico, which is seeking to "devise interventions that enable people to lead longer and healthier lives".[6] Anti-ageing biotech has been described as: "risky and most likely to fail, but if one company is successful the outcomes would be monumental".[7] Geroscience research groups and companies also exist in almost every other developed country in the world, with particularly active centres in Germany, Spain, Australia, and the UK. However, a recent Government strategy for the life sciences suggests that the UK has been underperforming in the field of ageing research, and investment in this field is highlighted as a key opportunity for the UK in the future.[8]

POTENTIAL AGEING TREATMENTS

Although questions remain about the underlying causes of ageing, animal studies have shown that it is possible to intervene in ageing processes. The main scientific developments in the search for ageing interventions are summarised below.[9]

METFORMIN

Metformin has been used as an effective diabetes drug for over 50 years. It works partly by enhancing the activity of an enzyme involved in metabolic processes essential for health. The responsiveness of this enzyme has been found to decline with ageing, suggesting that metformin may have beneficial effects on the ageing process.[10] The Targeting Aging with Metformin (TAME) clinical trial in the US, expected to start in 2018, will explore the effects of metformin on ageing in 3,000 men and women aged 60 or over who have no existing serious illnesses.[11] This is the first trial to study the effects of a drug on biological ageing, which could pave the way to ageing being recognised by regulators as a disease and to further drug trials in this area.

HORMESIS, DIETARY RESTRICTION AND RAPAMYCIN

Inducing a mild stress response in cells, known as hormesis, can delay ageing in animals. Exercise, heat, and radiation are all hormesis-inducing agents.[12] However, the best studied agent is dietary restriction without malnutrition, which can extend healthy lifespan in a range of animals. In humans, it has been shown to reduce risk factors for diabetes, cardiovascular disease, and cancer, and to slow biological ageing, but dietary restriction is not desirable or realistic for most people.[13] Similar effects are seen when the activity of metabolic pathways that detect nutrients are reduced by gene mutations or drugs.[14] Rapamycin, for example, a drug used to prevent organ transplant rejection, inhibits the pathway involved in nutrient sensitivity and extends lifespan in animals.[15] Despite the risk of serious side-effects, the effects of rapamycin on frailty in people aged 60 and over with heart disease are being explored in a small clinical trial in the US.[16] A similar drug, RAD001, has been shown in a small trial to boost the immune system of healthy people aged 65 years or over.[17]

RESVERATROL AND OTHER SIRTUIN INHIBITORS

A group of enzymes called sirtuins have a role in many cellular processes that affect ageing.[18] Chemicals that interact with sirtuins have strong potential as ageing treatments. Resveratrol, for example, a naturally occurring chemical found in red wine, is known to affect sirtuin activity and the ageing process in animals.[19] The resveratrol anti-ageing supplement market is already big business globally, but only small amounts of resveratrol are absorbed into the body when administered in humans and the long-term health effects are unproven.[20] Synthetically produced sirtuin inhibitors show more promise, and some have been found to improve the health and extend the lifespan of mice.[21] The pharmaceutical industry has invested heavily in the development of synthetic sirtuin inhibitors, but they have not yet been translated into drugs for human use.[22]

STEM CELL THERAPY

Stem cells are unspecialised cells involved in repairing and replenishing other cells and tissues in the body. Stem cell function decreases with age, and injecting stem cells into animals has been shown to enhance the repair of age-related damage in organs such as the brain, and increase lifespan.[23] Until recently, there were significant barriers to the use of stem cells for therapeutic purposes in humans. Stem cells can be derived from donated embryos, but are prone to immune rejection when transplanted. The use of embryos is also ethically controversial. In 2006, it was discovered that stem cells could be generated from adult cells, opening up a range of new possibilities in the field of regenerative medicine. The effects of stem cell therapy on age-related conditions such as frailty and Alzheimer's disease are being explored in early-stage clinical trials in the US.[24] Unproven and unlicensed stem cell treatments for a range of 'rejuvenation' purposes are also being offered by private clinics across the world.[25]

YOUNG BLOOD

Research suggests that blood from young mice can have a rejuvenating effect in older mice. It was recently found that injecting one blood protein in particular called GDF11 can regenerate animal organs including the heart and brain.[26] This was hailed as a major breakthrough in ageing research,[27] but the findings have been disputed by companies developing drugs that inhibit, rather than stimulate, GDF11.[28] Nevertheless, a number of commercial clinical trials are exploring the effects of transfusions of young blood in humans. One US study is recruiting 600 people aged 35 and older who will pay to receive a blood transfusion from a donor aged 25 or younger.[29] Critics suggest the design of the study is dubious, both ethically and scientifically.[30] Another trial, also in the US, is studying the effects of young blood transfusion in a small number of people with Alzheimer's disease.[31]

TELOMERASE AND TA-65

The discovery in the 1980s that telomeres, the tips of chromosomes, are vital for cell division and repair earned the researchers a Nobel prize.[32] Telomere shortening occurs with ageing and is associated with an increased incidence of disease and death.[33] The enzyme telomerase lengthens telomeres and thus has been suggested as a target for anti-ageing interventions. The plant-based supplement

TA-65, said to increase telomerase activity, is available to buy worldwide as an anti-ageing aid. Industry studies suggest TA-65 has beneficial effects on the health span of mice and humans.[34] The US-based manufacturer is now conducting clinical trials on healthy adults.[35] However, the reliability and independence of these studies have been questioned and there are concerns that stimulating telomerase activity could increase the risk of cancer.[36] Another way of activating telomerase – gene therapy – has been shown to increase lifespan and health span in mice without causing cancer.[37] At least one biotechnology company is hoping to develop telomerase gene therapy for use in humans.[38]

SENESCENT CELLS AND SENOLYTICS

Damaged cells either die or they become senescent cells, which remain in the body and emit inflammatory chemicals. Studies in mice have shown that removing senescent cells delays age-related diseases and extends lifespan.[39] Several research groups and companies are now working on developing drugs, collectively called senolytics, that will selectively kill senescent cells. Several senolytics have been found to work in mice and it is likely they will be tested in human trials in the near future.[40,41]

HORMONES AND ANTIOXIDANTS

The anti-ageing effects of hormones have been studied for many years. Human growth hormone has been shown to be beneficial for the health of older people, but it has serious side effects making it unsuitable for widespread use.[42] There is no firm evidence that other hormones, such as melatonin and insulin-like growth factor 1, have beneficial effects on ageing. The anti-ageing properties of antioxidants such as vitamins A, C, and E have also been explored. The theory is that they repair damage caused by toxic molecules called reactive oxygen species (ROS), which accumulate in cells with age. However, there is no clear evidence that antioxidants delay ageing, with some studies even suggesting they can be harmful to health.[43]

ETHICAL AND SOCIAL ISSUES RAISED BY AGEING RESEARCH

The discovery of safe and effective treatments that delay ageing and reduce the risk of ageing-related diseases could have consequences for health, society, and the economy.

EFFECTS ON HEALTH

Compressing the period of poor health experienced by many in old age could have a transformative effect on the lives of older people and is widely considered to be the primary goal of geroscience research. It is not known, however, whether biomedical ageing interventions will simply put off the period of ill health, or if this period will be extended, with people living longer in poor health. Other kinds of medical and social interventions have led to improved health and functioning in older people alongside increases in lifespan, but it is not clear whether this trend will continue.[44] Questions also remain about whether ageing interventions will need to be taken while people are still in good health; whether they will be able to reverse diseases that have already started to develop; how often they will need to be taken; and the seriousness of any side effects.

EXTENDING LIFE SPAN

Biomedical interventions, along with environmental, social and lifestyle modifications, have already contributed to the extension of human lifespan. Depending on other factors that could affect lifespan, ageing interventions could lead to a further delaying of death. Some suggest that a realistic target of geroscience research is to delay all ageing-related disorders by about seven years.[45] Other commentators believe that scientific advances will lead to much more radical effects on ageing and human lifespan in the near future.[46] There are differences of opinion about the value and morality of extending lifespan, even moderately.[47] Some philosophers believe that we think of our lives as having a certain shape, which underpins how long we think people should work and how long it is appropriate to be old. Increased longevity therefore might threaten the shape we envisage for our lives and our sense of personal identity.[48] The benefits of experiencing the pleasures of life over a longer time period are used by some to justify life extension;[49] others argue it is quality not quantity of years that

matters.[50] Some equate extending life with saving lives, and suggest there is a strong moral imperative to pursue treatment for disease, even if the side effect is an increase in lifespan.[51]

POPULATION GROWTH

A common concern of lifespan extension is that it would accelerate population growth, and that this would have a range of adverse consequences, particularly for the environment. However, one study suggests that population changes would be surprisingly slow in response to even a dramatic extension of lifespan and would not necessarily lead to overpopulation.[52] It has also been argued that using finite resources in a non-sustainable manner is a problem that needs to be solved independently of how long people live.[53]

ECONOMIC IMPACT

Estimations of the impact of increasing health span on the economy are generally positive. For example, one analysis suggests increasing human health span would reduce healthcare spending and lead to significant economic savings.[54] Another suggests that delayed ageing could mean increases in social benefit and public healthcare costs, but that these would be far outweighed by economic gains as a result of a healthier workforce who remain employed for longer and are given more time to save for retirement.[55] These effects would depend on the relative increases in health span and lifespan that could be achieved by ageing interventions, which currently are highly uncertain.

SOCIAL CHANGE

The social and cultural impact of increased health and lifespan could be far reaching. Even without the availability of ageing treatments, it is expected that people will have to keep working for longer in future, which could change workplace practices and opportunities. If ageing interventions became available, people's experiences and expectations of old age could change further. Enabling older adults to be more active and live longer could have many benefits for individuals, families, and communities. This might also result in changing demands for old age care, with implications for state-funded care, the role of adult children in caring for their parents, and intergenerational living.

HEALTH INEQUALITIES

Ageing interventions are likely to be available only through the private sector initially. As with any paid for therapy, it is probable that access to ageing interventions will be unequal, leading to an exacerbation of existing health inequalities according to income, socioeconomic status, and geography. In addition, personal choices about uptake of ageing interventions could have implications for entitlement to state care and health insurance.[56] There are calls for government policies to ensure unequal access to ageing interventions is avoided.[57] Global health inequalities present particular challenges in this context, given that the citizens of some countries still have low life expectancies owing to poor sanitation, nutrition, and healthcare provision. The duties of developed countries to put efforts into addressing these problems, in relation to the efforts put into research on ageing interventions, require consideration.

MEDICALISATION OF AGEING

Some argue that the focus on finding medical treatments for ageing is unhelpful, in that it suggests ageing is a problem that requires fixing and reinforces negative views of ageing.[58] There are parallels with how the medical community view frailty. Frailty is commonly regarded as a state of overall poor health, weakness and vulnerability, but diagnosing people with frailty may serve to marginalise them from society and unfairly label people as being destined to decline.[59] There is also concern that other important elements of successful ageing, such as personal relationships, social position, physical environment and independence, are side-lined by geroscientists.[60] The World Health Organization recommends that a holistic policy framework for healthy ageing should include a combination of public health measures, capacity building strategies, and the creation of an age-friendly world.[61]

CONSUMER ISSUES

The fact that there are no proven treatments for delaying or reversing ageing has not curtailed the anti-ageing product market. Despite strict regulations on nutritional supplement health claims, resveratrol and TA-65 are widely touted as having anti-ageing properties. A three month

supply of TA-65 can be purchased for around £400. Unproven and potentially harmful stem cell therapies that promise anti-ageing and rejuvenating effects are offered by clinics around the world at great cost. The US Food and Drug Administration recently announced it will increase regulatory enforcement of unlicensed stem cell therapies and has taken action against a number of clinics in the US.[62] As research in this field progresses, reducing harm to consumers from the use of unscrupulous clinics and retailers will become an increasing challenge.[63] Similar challenges exist within the cosmetic procedures industry, which the Nuffield Council on Bioethics has recommended should be subject to tighter regulation.[64]

RESEARCH ETHICS

An important question for geroscience research is whether potential interventions should be tested in younger people, before biological ageing has started, or in older adults already experiencing symptoms of ageing. In the past, involving older adults in research was thought to be difficult and of no benefit to them. This view has broadly changed.[65] The challenges of research have been found to be much the same whatever the age of the participant,[66] and medical interventions in people aged over 80 can have beneficial effects on their health.[67] In addition, 'older adults' are a diverse group and generalisations about people's ability and willingness to take part in research should be avoided. More tangible barriers exist to testing ageing interventions in healthy people, whatever their age. In the US, the state-funded healthcare system will only cover clinical trial costs for people with diagnosed disease.[68] In addition, measuring the effects of ageing interventions presents major challenges, given humans have a long life span and show great heterogeneity in ageing.[69] Participants at a recent Nuffield Council on Bioethics workshop called for an ethical framework for geroscience research to be developed to help guide researchers, policy makers and consumers.[70]

CONCLUSIONS

The search for an intervention that will delay ageing and reduce the risk of age-related diseases is advancing quickly. Several treatments are already being tested in human clinical trials. The wider effects of being able to extend human health span and possibly life span are uncertain, but this could have far reaching consequences for health, society and the economy.

Acknowledgments: Thank you to Nir Barzilai (Albert Einstein College of Medicine, US), and Terrie Moffitt (Duke University, US) for reviewing a draft of this briefing note.

Published by Nuffield Council on Bioethics, 28 Bedford Square, London WC1B 3JS

bioethics@nuffieldbioethics.org @Nuffbioethics NuffieldBioethics

www.nuffieldbioethics.org

REFERENCES

1 Office for National Statistics (2016) *Healthy life expectancy at birth and age 65 by upper tier local authority and area deprivation: England, 2012 to 2014;* GBD Causes of Death Collaborators (2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016 *The Lancet* **390**: 1211-59.

2 Office for National Statistics (2015) *National population projections: 2014-based statistical bulletin.*

3 See, for example, Kirkwood TBL (2005) Understanding the odd science of aging *Cell* **120**: 437-47; van Deursen JM (2014) The role of senescent cells in ageing *Nature* **509**: 439-46.

4 de Magalhães JP *et al*. (2009) The human ageing genomic resources: online databases and tools for biogerontologists *Aging Cell* **8**: 65-72; Sethe S and de Magalhães JP (2013) Ethical perspectives in biogerontology in *Ethics, health policy and (anti-) aging: mixed blessings*, Schermer M, and Pinxten W, eds.

5 For example, bioinformatics were recently used to study how environmental factors, or epigenetics, influence the genes of mice and biological ageing: Stubbs TM *et al*. (2017) Multi-tissue DNA methylation age predictor in mouse *Genome Biol* **18**: 68.

6 See: www.calicolabs.com.

7 de Magalhães J *et al*. (2017) The business of anti-aging science *Trends Biotechnol* (in press).

8 Bell J (2017) *Life sciences industrial strategy - a report to the Government from the life sciences sector*.

9 The Journals of Gerontology publish research in this field, available at: https://academic.oup.com/biomedgerontology.

10 Salminen A and Kaarniranta K (2012) AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network *Ageing Res Rev* **11**: 230-41.

11 Barzilai N *et al.* (2016) Metformin as a tool to target aging *Cell Metab* **23**: 1060-5.

12 Rattan SI (2012) Biogerontology: from here to where? The Lord Cohen Medal Lecture-2011 *Biogerontology* **13**: 83-91; Rattan SI (2013) Healthy ageing, but what is health? *Biogerontology* **14**: 673-7.

13 Everitt AV and Le Couteur DG (2007) Life extension by calorie restriction in humans *Ann NY Acad Sci* **1114**: 428-33; Fontana L and Klein S (2007) Aging, adiposity, and calorie restriction *JAMA* **297**: 986-94; Belsky DW *et al*. (2017) Change in the rate of biological aging in response to caloric restriction: CALERIE biobank analysis *J Gerontol A Biol Sci Med Sci* **73**: 4-10.

14 Fontana L *et al*. (2010) Extending healthy life span: from yeast to humans *Science* **328**: 321-6; Veech RL *et al*. (2017) Ketone bodies mimic the life span extending properties of caloric restriction *IUBMB Life* **69**: 305-14.

15 Ehninger D *et al*. (2014) Longevity, aging and rapamycin *Cell Mol Life Sci* **71**: 4325-46.

16 ClinicalTrials.gov (2016) *Exercise and low-dose rapamycin in older adults with CAD: cardiac rehabilitationa and rapamycin in elderly trial (CARE)*.

17 Mannick JB *et al*. (2014) mTOR inhibition improves immune function in the elderly *Sci Transl Med* **6**: 268ra179.

18 Bonkowski MS and Sinclair DA (2016) Slowing ageing by design: the rise of NAD+ and sirtuin-activating compounds *Nat Rev Mol Cell Biol* **17**: 679-90; Li J *et al*. (2017) A conserved NAD+binding pocket that regulates protein-protein interactions during aging *Science* **355**: 1312-7.

19 Borra MT *et al*. (2005) Mechanism of human SIRT1 activation by resveratrol: *J Biol Chem* **280**: 17187-95; Kaeberlein M *et al*. (2005) Substrate-specific activation of sirtuins by resveratrol *J Biol Chem* **280**: 17038-45.

20 Walle T (2011) Bioavailability of resveratrol *Ann N Y Acad Sci* **1215**: 9-15.

21 Minor RK *et al*. (2011) SRT1720 improves survival and healthspan of obese mice *Sci Rep* **1**: 70; Mitchell S *et al*. (2014) The SIRT1 activator SRT1720 extends lifespan and improves health of mice fed a standard diet *Cell Rep* **6**: 836-43.

22 Nature News Blog (2013) *GSK absorbs controversial 'longevity' company*.

23 Lavasani M *et al*. (2012) Muscle-derived stem/progenitor cell dysfunction limits healthspan and lifespan in a murine progeria model *Nat Commun* **3**: 608; Zhang Y *et al*. (2017) Hypothalamic stem cells control ageing speed partly through exosomal miRNAs *Nature* **548**: 52-7.

24 ClinicalTrials.gov (2017) *Allogeneic human mesenchymal stem cells (hMSC) in patients with aging frailty via intravenous delivery (CRATUS)*; ClinicalTrials.gov (2017) *Allogeneic human mesenchymal stem cell infusion versus placebo in patients with Alzheimer's disease*.

25 International Society for Stem Cell Research (2017) *ISSCR responds to FDA announcement of enforcement direction for stem cell treatments*.

26 Loffredo FS *et al.* (2013) Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy *Cell* **153**: 828-39.

27 Science News (2014) *Breakthrough of the year: the top 10 scientific achievements of 2014*.

28 Egerman MA *et al*. (2015) GDF11 increases with age and inhibits skeletal muscle regeneration *Cell Metab* **22**: 164-74.

29 ClinicalTrials.gov (2016) *Young donor plasma transfusion and age-related biomarkers*.

30 Science News (2016) *Young blood antiaging trial raises questions*.

31 ClinicalTrials.gov (2016) *The plasma for Alzheimer symptom amelioration study (PLASMA)*.

32 Greider CW and Blackburn EH (1985) Identification of a specific telomere terminal transferase activity in tetrahymena extracts *Cell* **43**: 405-13.

33 Shammas MA (2011) Telomeres, lifestyle, cancer, and aging *Curr Opin in Clin Nutr* **14**: 28-34; Rode L *et al*. (2015) Peripheral blood leukocyte telomere length and mortality among 64,637 individuals from the general population *J Natl Cancer Inst* **107**: djv074.

34 de Jesus B *et al*. (2011) The telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence *Aging Cell* **10**: 604-21; Harley CB *et al*. (2011) A natural product telomerase activator as part of a health maintenance program *Rejuv Res* **14**: 45-56.

35 ClinicalTrials.gov (2016) *Effect of TA-65MD on healthy volunteers (TA-65MD)*.

36 See, for example, Artandi SE *et al.* (2002) Constitutive telomerase expression promotes mammary carcinomas in aging mice *Proc Natl Acad Sci USA* **99**: 8191-6.

37 de Jesus B *et al*. (2012) Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer *EMBO Molecular Medicine* **4**: 691-704.

38 See www.bioviva-science.com.

39 Baker DJ *et al*. (2011) Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders *Nature* **479**: 232-6; Baker DJ *et al*. (2016) Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. *Nature* **530**: 184-9.

40 Chang J *et al*. (2016) Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice *Nat Med* **22**: 78-83; Yosef R *et al*. (2016) Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL *Nat Commun* **7**: 11190.

41 ClinicalTrials.gov (2017) *Senescence in chronic kidney disease*; Kirkland JL *et al*. (2017) The clinical potential of senolytic drugs *J Am Geriatr Soc* **65**: 2297-301.

42 Blackman MR *et al*. (2002) Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial *JAMA* **288**: 2282-92.

43 Bjelakovic G *et al*. (2007) Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis *JAMA* **297**: 842-57; Sayin VI *et al*. (2014) Antioxidants accelerate lung cancer progression in mice *Sci Transl Med* **6**: 221ra15.

44 Baltes PB and Mayer KU (2001) *The Berlin aging study: aging from 70 to 100 ;* Mor V (2005) The compression of morbidity hypothesis: a review of research and prospects for the future *J Am Geriatr Soc* **53**: S308-S9.

45 Olshansky S *et al*. (2006) In pursuit of the longevity dividend *The Scientist*.

46 Financial Times (2017) *Aubrey de Grey: scientist who says humans can live for 1,000 years*.

47 Horrobin S (2006) The value of life and the value of life extension *Annals NY Acad Sci* **1067**: 94-105; see also Williams B (1973) *The Makropulos case: reflections on the tedium of immortality*.

48 Bavidge M (2006) Ageing and human nature in *Dementia: mind, meaning and the person* Hughes JC, Louw SJ, and Sabat SR, eds.; Lesser AH (2006) Dementia and personal identity in *Dementia: mind, meaning and the person* Hughes JC, Louw SJ, and Sabat SR, eds; Wareham C (2016) The transhumanist prospect: developing technology to extend the human lifespan in *The Palgrave handbook of the philosophy of aging* Scarre G, ed.

49 Horrobin S (2006) The value of life and the value of life extension *Ann N Y Acad Sci* **1067**: 94-105; Overall C (2003) *Ageing, death and human longevity. A philosophical inquiry*.

50 van Tongeren P (1990) Longevity and meaning of life. Philosophical-ethical considerations of the theme 'extension of life' *Tijdschr Gerontol Geriatr* **21**: 223-8.

51 Harris J (2007) *Enhancing evolution*; Gems D (2011) Tragedy and delight: the ethics of decelerated ageing *Philos T Roy Soc B* **366**: 108-12.

52 Gavrilov LA and Gavrilova NS (2010) Demographic consequences of defeating aging *Rejuv Res* **13**: 329-34.

53 Sethe S and de Magalhães JP (2013) Ethical perspectives in biogerontology in *Ethics, health policy and (anti-) aging: mixed blessings*, Schermer M, and Pinxten W, eds.

54 US National Intelligence Council (2008) *Disruptive civil technologies: six technologies with potential impacts on US interests out to 2025*.

55 Goldman DP *et al.* (2013) Substantial health and economic returns from delayed aging may warrant a new focus for medical research *Health Aff* **32**: 1698-705.

56 Foresight (2016) *Future of an ageing population*; US National Intelligence Council (2008) *Disruptive civil technologies: six technologies with potential impacts on US Interests out to 2025*.

57 Ehni H-J and Marckmann G (2009) Social justice, health inequities and access to new age-related interventions *Med Stud* **1**: 281-95.

58 See, for example, Vincent JA (2008) The cultural construction old age as a biological phenomenon: science and anti-ageing technologies *J Aging Stud* **22**: 331-9; Hadler NM (2011) *Rethinking aging. Growing old and living well in an overtreated society*.

59 Gilleard C and Higgs P (2010) Frailty, disability and old age: a re-appraisal *Health* **15**: 475–90.

60 Lai WF and Chan ZC (2011) Beyond sole longevity: a social perspective on healthspan extension *Rejuv Res* **14**: 83-8.

61 World Health Organization (2015) *World report on ageing and health*.

62 US Food and Drug Adminstration (2017) *Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA's new policy steps and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine*.

63 Cossu G *et al*. (2017) Lancet Commission: stem cells and regenerative medicine *The Lancet*.

64 Nuffield Council on Bioethics (2017) *Cosmetic procedures: ethical issues*.

65 See, for example, Crome P *et al*. (2014) The PREDICT (increasing the participation of the elderly in clinical trials) study: the charter and beyond *Expert Rev Clin Phar* **7**: 457-68.

66 Fudge N *et al*. (2007) Involving older people in health research *Age Ageing* **36**: 492-500.

67 Beckett NS *et al*. (2008) Treatment of hypertension in patients 80 years of age or older *New Engl J Med* **358**: 1887-98.

68 Medicare policy states: "Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers". See: Medicare (2000) *Medicare coverage clinical trials: final national coverage decision*. See also: Moffitt TE *et al.* (2017) The longitudinal study of aging in human young adults: knowledge gaps and research agenda *J Gerontol A Biol Sci Med Sci* **72**: 210-5.

69 Belsky DW *et al*. (2015) Quantification of biological aging in young adults *Proc Natl Acas Sci USA* **112**: E4104-E10; Belsky DW *et al.* (2017) Impact of early personal-history characteristics on the pace of aging: implications for clinical trials of therapies to slow aging and extend healthspan *Aging Cell* **16**: 644-51; Belsky D *et al*. (2017) Telomere, epigenetic clock, and biomarker-composite quantifications of biological ageing: do they measure the same thing? *Ame J Epidemiol (in print);* Kirkland JL *et al*. (2017) The clinical potential of senolytic drugs J Am Geriatr Soc **65**: 2297-301.

70 Nuffield Council on Bioethics (2016) *The ethics of ageing research: note of workshop held on 30 November 2016*.