Intervening in ageing to prevent the diseases of ageing

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Increases in human lifespan worldwide have revealed that advancing age is the predominant risk factor for major life-threatening diseases. Recent work has shown that ageing in diverse animals, including humans, is malleable to specific types of genetic mutation, diet, and drugs that can extend lifespan and improve health during ageing. These findings point to the prospect of broad-spectrum preventive medicine for the diseases of ageing based on intervention in relevant aspects of the ageing process itself.

Rising life expectancy

Human populations in developed countries, and in many developing ones, are getting older. Human life expectancy at birth has been increasing by about 2.5 years per decade since the middle of the 19th century, with no demographic hint so far of an intrinsic limit to human lifespan [1]. This sustained trend has been brought about by successive contributions from lifestyle and medical care, including improvements in water and food quality and the prevention of many infectious diseases, which is particularly important for increased survival in children. Recently, improvements in medical care have played an important role, with increasing survival now occurring almost entirely in older age groups, although there is growing evidence that these health benefits are not evenly distributed across different sections of the population [2].

Although increases in health and lifespan are to be celebrated, they come with several downsides. Some of these are economic. In many countries increased lifespan is accompanied by falling birth rates and hence a rapid increase in the proportion of the population that does not participate in the labour force. There is also debate about the extent to which increasing lifespan is also increasing health span [3]. However, the main problem of longer lives is that increasing age is proving to be the major risk factor for all of the common chronic and killer conditions of the developed world: metabolic, cardiovascular, and neurodegenerative disease and cancer [4]. The major burden of ill health is hence now falling on the older section of the population and their carers and there is an urgent need to find ways of keeping people healthy for longer.

Ageing is a malleable process

Because ageing is the major risk factor for all of these diseases, one obvious approach to maintaining the health of older people would be to intervene in the underlying ageing process itself. The intrinsic rate of ageing can be drastically altered by (presumably complex) genetic change, because there is great diversity in the natural lifespans of animals, even when they are brought into environments where they are largely protected from extrinsic hazards. For instance, among mammals, bats, primates, and whales are notably long lived [5]. Scientific discoveries from research into ageing in recent years have also suggested that intervening in human ageing is more plausible than it once seemed. Although ageing is complicated and variable, with diverse kinds of damage and pathology accumulating in a way that varies between both different body tissues and individual organisms, the process has nonetheless proved to be malleable. Both genetic mutations and environmental interventions such as altered diet and drugs can increase lifespan and health during ageing in laboratory organisms (yeast, nematodes, fruit flies, and mice). Furthermore, despite the very different lifespans and lifestyles of these creatures, similar interventions have proved capable of extending health span in all, implying some commonalities in the underlying mechanisms of ageing. Simpler organisms with shorter lifespans can thus contribute to an understanding of the mechanisms of mammalian, including human, ageing, and to the discovery of interventions that could ameliorate it [6–8].

What makes us age?

The ageing process remains a considerable biological mystery. Virtual immortality of cell lines is clearly possible because all current life on earth originated from a common ancestor, as evidenced by the use of a common genetic code. Germlines, therefore, do not have to die. Also, some multicellular organisms, such as Hydra and some sea anemones, do not become less able to reproduce or more likely to die over time [9]. Organisms are generally maintained in a youthful state during their development and it is only with the onset of reproduction that the effects of ageing start to become apparent [8]. However, it is not clear in any organism how the ageing process starts and which of the many phenotypes of ageing are causal in the different aspects of functional decline and risk of ageing-related diseases. Many features may be bystander effects with little functional significance, such as the greying of hair. Homeostatic responses of the organism to ageing-related damage and loss of function also occur. Some hallmarks of...
ageing across different organisms have recently been as-
sembled [10]. Common features of ageing include genomic
instability, telomere attrition, epigenetic alterations, loss of
proteostasis, deregulated nutrient-sensing, mitochon-
drial dysfunction, cellular senescence, stem cell exhaust-
ion, and altered intercellular communication. These hallmarks vary in prominence between different tissues
and are present to differing degrees in different organisms.
Their functional significance and the causal nexus between
them are the subject of intense study. In multicellular
organisms the picture is further complicated by systemic
effects, with one tissue affecting the ageing of others.

**Slowing down ageing**

Interventions that improve health during ageing and in-
crease lifespan across multiple organisms, including mam-
mals, are of particular interest. They indicate that the
normal ageing process has been targeted and can therefore
reveal both fundamental mechanisms of ageing and poten-
tial drug targets for the prevention of ageing-related dis-
ease. Dietary restriction (DR), a reduction of food intake
short of malnutrition, increases health during ageing in
nearly all organisms so far investigated, including pri-
mates and possibly humans [8]. DR is not a practical
intervention for most humans because compliance with
this rigorous dietary regimen is low. However, recent work
in both animals and humans has suggested that reduced
intake of certain nutrients, particularly specific amino
acids, may be more important than reduced calorie intake
in conferring the health benefits of DR [11]. Furthermore,
altered activity of the key metabolic and endocrine signal-
ling networks that sense nutrients can also improve health
during ageing. Mutations that reduce the activity of insu-
lin/insulin-like growth factor signalling (IIS) and the con-
nected target of rapamycin (TOR) network can extend
lifespan in organisms ranging from yeast to mammals.
There is also a broad-spectrum improvement in the health
of these animals during ageing [7–9]. For instance, mu-
tant-IIS mice show improvements in glucose handling,
immune profile, and motor performance and are protected
against osteoporosis, cataract, and skin problems. Impor-
tantly, there are many potential drug targets in this sig-
nalling network, including several kinases, and
rapamycin, a specific inhibitor of TOR, can extend lifespan
in mice [12].

The IIS/TOR network senses the status of nutrients,
growth factors, and various forms of stress and adjusts
growth, metabolism, and reproduction accordingly. Ex-
treme alterations of its activity can therefore be harmful.
For instance, reduced insulin signalling can cause dia-
betes. However, it is clear that specific reductions in IIS and
TOR activity (which one being determined possibly by the
magnitude of the reduction or the exact part of the network
affected) can improve overall health during ageing. For
these and other interventions, such as diet and drugs, the
key challenge is to understand exactly how they do it, to
triate away beneficial effects on health from undesirable
side effects. The hallmarks of ageing provide candidate
processes for further detailed analysis [10]. For instance,
experimental work has addressed the potential role of
cellular quality-control processes including autophagy
and proteosomal degradation of damaged proteins and the
maintenance of telomeres in maintaining the health
of the whole organism during ageing.

**Mechanistic connections between ageing and ageing-
related disease**

The improvements in health during ageing seen in animal
models of slowed ageing provide an excellent context in
which to understand the mechanistic connections between
ageing and ageing-related disease. For instance, in the
fruit fly Drosophila, rapamycin administered to old flies
was recently shown to lower dopamine activity and hence
reverse their natural, age-related fragmentation of night
sleep, a common problem in older humans [13]. The inter-
action between interventions that slow ageing and genetic
models of disease has also proved informative. For in-
stance, in the nematode Caenorhabditis elegans, genetical-
ly reduced IIS protected against the pathology associated
with a worm model of cancer by altering the expression of
genes that were highly enriched with the worm equivalents
of human oncogenes and tumour suppressors, including a
worm orthologue of lysosome-associated transmembrane
protein 4B (LAPTM4B), which stimulates cell proliferation
and inhibits cell death in mammalian cancer [14]. Dement-
ia in humans is proving a particularly intractable feature
of ageing, with the incidence projected to increase to un-
manageable levels in many countries. Mouse genetic mod-
els of this condition have shown that reduced IIS and
rapamycin can ameliorate the associated pathology, and
understanding the detailed mechanisms at work may help
to solve this major medical problem.

**Targeting ageing to treat diseases of ageing**

Economic analysis has shown that amelioration of
ageing would have enormous health benefits [15]. Specific

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**Figure 1.** Current and potential future strategies for understanding and preventing ageing-related diseases. Left: Current strategy tends to research and treat individual ageing-related diseases separately. Right: Recent research points to the prospect of research to understand and intervene in the underlying ageing process as a means for simultaneously preventing multiple diseases of ageing.
interventions for specific problems of ageing are important and will continue to be so. What the animal models of slowed ageing have shown us is that there is also the prospect of a broad-spectrum preventive medicine for the diseases of ageing (Figure 1). Rapamycin is an early example of a licensed drug proving to have a wider therapeutic range than previously suspected and others such as metformin and aspirin are starting to show similar features.

Acknowledgements
The author thanks the Max Planck Society and the Wellcome Trust for funding her research.

References
2 Olshansky, S.J. et al. (2012) Differences in life expectancy due to race and educational differences are widening, and many may not catch up. Health Aff. (Millwood) 31, 1803–1813
15 Goldman, D.P. et al. (2013) Substantial health and economic returns from delayed aging may warrant a new focus for medical research. Health Aff. (Millwood) 32, 1698–1705