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Health-Extending Medicine in an Aging Society

Prospects for Medical Research and Practice

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Executive summary

By 2035, almost a third of the adult population in Germany will be over 65 years of age. Every second person in that age group suffers from multiple chronic age-related diseases. Multimorbidity in such a large proportion of the population poses unprecedented threats to economic and societal integrity, exacerbating inequality and poverty in the aging society. Research on the biology of aging has shown that health can be extended and the risk for age-related diseases can be reduced. In this paper we advocate gaining a better understanding of the science of aging and implementation of evidence-based health maintenance interventions to address the challenges of a multimorbid, aged society. We propose that the scientific research excellence in the field of aging biology in Germany provides a strong foundation for developing geroprotective medicines, i.e. medicine that treats the aging process rather than individual diseases, to maintain lifelong health and prevent disease, thus fostering an inclusive, healthy aging society.

Specifically, we propose:

1. Supporting basic research to expand the mechanistic understanding of the biology of aging as a foundation for effective interventions promoting healthy aging.
2. Accelerating the translation of biological knowledge into geroprotective pharmaceutical interventions aimed at disease prevention.
3. Geroscience-driven clinical trials and accessible national biobanks that provide multi-omics datasets to enable evidence-based strategies for health maintenance and disease prevention.
4. The implementation of geromedicine, which aims to prevent disease by treating aging, as a way to tackle the health crisis that is inevitable given the rapid increase in the elderly population over the coming decade.

Contents

1 Introduction

The demographic transformation of German society, with a steeply increasing proportion of people above 65 years of age, has made aging-associated diseases a major socioeconomic challenge. The majority of people in this age category suffer from multiple chronic diseases [(1)]. Half of healthcare expenditure today is already devoted to people above 65. This discussion paper sets out a forward-thinking approach to address this imminent challenge. Research on aging biology has revealed key mechanisms that underlie aging and the common causes of age-related diseases [(2)]. In various model organisms, lifespan and healthy lifespan (or "healthspan") can be extended by genetic, dietary, or even pharmacological interventions. Biomedical research is currently addressing how such interventions could be implemented to extend human health during aging and effectively prevent age-related diseases. It is a central medical goal to prevent disease rather than treat the multitude of diseases. In this discussion paper, we summarize the results of a workshop of the National Academy of Sciences Leopoldina, which took place from November 14–15, 2024, in Halle (Saale) with national and international experts in the field of geriatric medicine, and under the scientific leadership of Professor Dr Björn Schumacher.

We dissect the current state of the implementation of insights from the biology of aging research into medical practice. We address how the understanding of these mechanisms of aging could be deepened and how they could become the target of preventative therapies and interventions. We assess how geroprotective medicine could shift medical practice from disease treatment to disease prevention. Moreover, we propose how evidence-based public health advice could remove faith in evidence-free claims on longevity lifestyle supplements, which are flooding the public sphere. We discuss which opportunities are at hand and which challenges – scientific, educational, and regulatory – must be overcome to achieve these goals.

2 Mechanisms of aging

Die Aging research has demonstrated that the biological mechanisms of aging are likely causative for virtually all chronic age-associated diseases and, therefore, delaying the aging process could protect people from such diseases. To maintain health and prevent morbidity upon aging, it is essential to understand the underlying mechanisms of aging. Research on these mechanisms will lead to new concepts that enable novel preventive interventional approaches in healthcare.

The cellular aging process that causes vulnerability and reduces resilience to chronic diseases

Aging is a biological process that exponentially increases the risk of chronic diseases and mortality. The biology of aging is complex as a multitude of cellular processes are affected [(2)]. The mechanisms that repair and regenerate cells and tissues function well during youth, but are not sufficient to maintain the function of cells and organs at higher ages. Cells and their building blocks (organelles and the biomolecules: nucleic acids, proteins, and lipids) are frequently damaged as a result of normal metabolism and environmental insults and must be repaired or replaced. Quality control and repair mechanisms for DNA, RNA, proteins, mitochondria and other organelles are essential for maintaining cell function.

The genetic material that contains all information for the building of cells is critically dependent on continuous monitoring and repair because of its vulnerability to decay. Unrepaired DNA damage causes cancer when mutations change the function of cells and it promotes aging when present in a chronic form [(3)]. Mutations accumulate with age, thereby explaining why age is the single greatest risk factor for cancer [(4)]. DNA damage can trigger programmed cell death, thus eliminating damaged cells, or trigger senescence, which prevents damaged cells from proliferating and mutating. Too much cell death and senescence in the aging

organism compromises tissue regeneration. Moreover, damaged and senescent cells induce chronic, sterile inflammation that makes tissues vulnerable to disease [5].

Changes in cellular metabolism that occur with aging contribute to increasing amounts of damage that overwhelms the quality control and repair systems and compromises the molecular mechanisms of cells. The maintenance of functional proteins, e.g. enzymes or structural components, requires energy-costly production, folding, and turnover of proteins [6]. The molecular mechanisms that fold and replace proteins, or the proper function of systems that organize the protein or the epigenetic infrastructure of cells, are impaired with aging, rendering almost all types of cells less functional – particularly long-lived ones such as neurons, but also stem cells.

The cellular response to chronic stress is impacted by its tissue microenvironment and cell-to-cell communication. For example, cell morphology and protein expression on the cell surface are altered by senescence, affecting cell-to-cell communication and their clearance by immune cells. Further, senescent cells secrete enzymes that modify their local environment and inflammatory signaling molecules, disrupting tissue architecture and homeostasis [7]. These are all important determinants of age-related chronic inflammation, tissue damage, and regenerative potential.

During aging, the dysfunction of cells, their declining capacity to renew and repair tissues, and chronic inflammation leave the body increasingly vulnerable to diseases. Consequently, aging is often characterized by the clustering of chronic diseases in an individual, known as multimorbidity. Aging is indeed the primary risk factor for cancer, dementia, and cardiovascular disease, by orders of magnitude more than common risk factors that are currently treated, such as hypertension or smoking [8]. This fact, plus Germany's inevitable change in demographics, will lead to an ever-increasing portion of the population that suffers from multimorbidity, underscoring the looming impact on the health economy system.

Interventions at the level of mechanisms of aging could protect from disease

Basic research on the mechanisms of aging has already delivered therapeutic concepts for delaying chronic age-related diseases. Targeting mechanisms of aging, for example by eliminating senescent cells with so-called senotherapeutic drugs, yields an extension of healthy aging (healthspan) in mice [9, 10]. Such healthspan extending interventions provide the proof of concept that by targeting a mechanism of aging, healthspan could be extended [11]. The study of aging biology is bound to yield new targets for geroprotectors. To achieve this, it is particularly important to gain a better understanding of how the maintenance and repair mechanisms, and the cellular stress responses operate in the context of the aging organism. The gradual deterioration of cells, the influence of chronic inflammation and altered hormonal circuits, and the resulting loss of resilience to disease can only be understood in the context of a living organism. Hence, it is important to study aging via observations and experiments in a range of animals that are valid models for processes relevant to human aging and disease. Such model organisms include simple metazoans such as nematodes and fruit flies, highly regenerative animal models such as planaria or salamander, exceptional long-living mammals such as bats and naked-mole rats, and well-established genetic models of chronic diseases, such as mice and rats.

Approaches need to combine mechanistic investigation on the biology of aging with systems approaches to understand how a specific mechanism affects complex signaling networks in cells and tissues. It is also important for investigations to consider the effects of sex, in utero conditioning, exposure to psychosocial stress, nutritional stress, and environmental exposures that are emerging as important determinants of human aging trajectories and susceptibility to disease [12]. Such factors have complex effects on the mechanisms of aging and are often challenging to model in a laboratory setting.

Organizing research networks for integrating the complexity of aging biology

Aging affects every aspect of physiology and requires integration of data from the whole organism. The distinct mechanisms of aging do not operate in isolation, but are intimately interconnected [3]. Each of those pro-

cesses represents complex biology in and of itself and are often technically challenging to detect and quantify, creating silos of expertise. The integration of data from experts in different aspects of aging biology needs to be done at the systems level. For this, a systems aging infrastructure could integrate multiple data types obtained from model organisms as well as humans and their electronic health record. A model for such a network is the NIH-funded SenNet Consortium, which was established in order to create an atlas of senescent cells in 18 human and mouse organs [13]. SenNet integrates researchers across the USA and uses preexisting intellectual and technological strengths in the different research centers, thus enabling a rapid implementation of the project. An essential component of such an investment is to make data accessible for discovery science from model organisms and humans. Open science is essential to drive progress as it allows new ideas and hypotheses to be tested rapidly and economically, accelerating discovery science. SenNet data are released continuously and immediately upon quality assurance and includes single cell and spatial data acquired from healthy humans and mice across their lifespans. This has tremendous value to the research community beyond the primary goal and capacity of SenNet.

Geroprotective outcomes, i.e., reducing the risk of multiple chronic age-associated diseases, have been realized in the use of metabolic drugs developed for a single indication, such as glucagon-like peptide-1 receptor (GLP-1R) agonists (e.g., semaglutide) and sodium-glucose transporter-2 (SGLT2) inhibitors (e.g., glifozines). It is very timely to investigate how geroprotective effects of such metabolic drugs affect the underlying mechanisms of aging. New tools to measure metabolism, genome stability, and functional data such as repair capacity in situ and at the single cell level are needed [14]. Such efforts are likely to provide new concepts of how geroprotective interventions work and could be improved.

The combination of systems aging approaches with mechanistic studies of aging will provide new insights and perspectives for effective geroprotective treatments that could be developed into the medicine of the future that is required to maintain a healthy aging society.

3 Drug discovery approaches

Human life expectancy has doubled in the past 150 years without any change in the human genetic makeup, i.e., non-genetic factors were sufficient to prolong lifespan and also healthspan. Multimorbidity, which is very common in persons over 65 years old, likely results from the progressive and collective impact of the mechanisms driving aging biology leading to reduced resilience. The study of resilience to various stressors is thus integral to understanding how health could be maintained during aging [15, 16]. The first intervention to reduce multimorbidity was described a century ago when calorie restriction (CR) in rats was demonstrated to extend their lifespan. CR has subsequently been shown to reduce multimorbidity in all species tested, including primates [17]. It is thought that CR elicits some of its effects through increasing resilience. However, CR is very difficult to implement in humans as adherence to dietary interventions tends to be low and the optimal calorie intake might be very individual depending on a person's genetic and epigenetic make-up and age. An alternative approach to CR is the development of pharmaceuticals that mimic CR or target central causative processes in aging. The first example establishing the feasibility of this approach is rapamycin, a natural product that inhibits the growth regulator and nutrient sensor mTOR, which increases the lifespan of multiple species and attenuates certain morbidities [18]. However, rapamycin has side effects and is registered as an immunosuppressant. First and foremost, interventions aimed at disease prevention, such as geroprotectors, must be safe and side effects minimized.

Metabolic drugs show geroprotective effects

The concept of geroprotective drugs has been substantially expanded in recent years. Drugs that are used to treat hypertension or type 2 diabetes are increasingly shown to act as geroprotectors by effectively treating their disease indication but concomitantly delaying heart disease, cognitive decline, and cancer [19]. The repurposing of such drugs will play

a major role in geroprotective treatment strategies. Currently, the most prominent candidates are GLP-1R agonists, and SGLT2 inhibitors, which were developed to treat type 2 diabetes mellitus and are now applied to obesity, heart failure, and kidney disease [20–22]. Clinical studies revealed a wide range of health benefits. For instance, patients taking a GLP-1R agonist show lower risk of chronic kidney disease, heart disease, and other age-associated morbidities. It will be particularly important to determine whether such drugs could also promote the long-term health of people not yet affected by any age-related chronic disease.

With geroprotective approaches, it is particularly important to focus on extending healthspan and compression of morbidity and not just an extension of lifespan. If the gain in healthspan fails to outpace the gain in lifespan, sickspan will be delayed rather than reduced. Sickspan is currently estimated to comprise >10 years at the end of life [23]. Thus, it is imperative to monitor organ function and susceptibility to disease in long-term studies on the effects of geroprotective interventions. Preclinical studies in mice with geroprotective drugs such as rapamycin or senotherapeutics indeed indicate successful compression of sickspan [18, 24], validating the geroscience concept of healthspan extension.

New therapeutic targets in aging biology

Targeting causal mechanisms of aging is illustrated by the emergence of senotherapeutic drugs, which target senescent cells, a hallmark of aging [10]. When the cellular response to DNA damage drives cells into senescence, the cells assume an inflammatory state that contributes to age-associated diseases including cancer [5]. Senescent cells, however, are vulnerable to inhibitors of prosurvival pathways and can thus be pushed into programmed cell death [9]. Senotherapeutics extend median lifespan in mice and are being pursued in clinical trials. Notably, the senotherapeutic trials are largely designed around specific age-associated diseases such as Alzheimer's disease [25], due to the challenges of designing human studies on healthspan extension. The complexity of senescence phenotypes and their physiological role in development and tissue regeneration will require further basic research on senescent cells in a variety of health and disease contexts to fully deploy senotherapeutics safely and efficaciously.

Another example is targeting genome instability. For the first time, it appears possible to not only target the cellular response to DNA damage, but also boost its repair, thus keeping the genetic information in cells intact for longer. In this regard, the pharmacological targeting of a recently uncovered master regulator of the cellular DNA repair capacities, the DREAM complex, offers a new route for enhancing genome stability [26].

A major leap forward in reversing aging has been the discovery of cellular reprogramming that turns a differentiated cell such as a skin cell into a pluripotent stem cell, which has the capacity to generate many types of cells that could be used to replace old cells and restore tissue function. Partial cellular reprogramming offers a potential approach for regenerating tissues from one's own cells, even in older adults. Mounting evidence indicates that partial reprogramming through the Yamanaka factors resets the biological age of the cells. These factors were named after Dr Shinya Yamanaka, who was awarded the Nobel Prize for his discovery that a combination of four transcription factors can revert a fully differentiated cell into a stem cell capable of producing multiple specialized cell types such as neurons [27]. Reprogramming technologies have already entered clinical trials, for instance, to replace dopaminergic neurons in Parkinson's disease patients [28]. The Yamanaka factors normally act early during embryonic development, where they likely take part in the resetting of the biological age at the beginning of a new life. This therapeutic approach, while promising, will require extensive testing not only of efficacy but also of long-term safety.

Clinical implementation

Geroprotective drug development can be advanced expeditiously by tackling four challenges. First, identifying the geroprotective effects of established medicines that have already passed safety studies and have extensive clinical data associated with them. The proof of concept is provided by the aforementioned drugs used to treat diabetes and obesity. Second, developing aging biomarkers that reveal a person's biological age, which can be very distinct from chronological age, and perhaps predict healthspan. Such biomarkers are critical for proving the efficacy of geroprotectors and enriching the target population of patients most in need of an intervention. Aging clocks, outlined below, are a poten-

tial example of this. Third, the discovery of novel ways of targeting the causal mechanisms of aging. Here, the pipeline of mechanistic studies as outlined in the first section needs to be expanded from aging biology to target discovery, drug development, and testing. Fourth, prospective and controlled clinical trials need to be designed and performed to clearly establish evidence of geroprotection, first in persons with an already compromised healthspan to prevent multimorbidity, then in increasingly healthier persons to prevent disease altogether.

4 Translation into medical practice for lifelong health and disease prevention

In the coming decade, nearly 30 % of the German population will be over 65 years of age. In an era of an aged society, in which a large proportion of elderly persons will suffer from multimorbidity, treating individual diseases is simply not economically sustainable [29]. Therefore, medicine must aim at a paradigm shift that replaces disease intervention with disease prevention and boosting resilience processes [15, 16]. Disease prevention has already provided far-reaching health benefits, such as vaccines, help quitting smoking, or treatment of hypertension. Lifestyle interventions such as diet and exercise have long-term beneficial health-promoting effects [12]. An obstacle to successful preventative medicine is the lack of quantifiable evidence of an intervention's efficacy in reducing disease susceptibility and mortality. Even some cancer screening programs have failed to show such effects across a broad population. Measuring physiological parameters such as blood pressure or body weight provide only very rough and limited indices of the efficacy of approaches to disease prevention. A broader assessment of preventive efficacy may arise from the combination of physiological and clinical markers as suggested in approaches like the Healthy Aging Index (HAI), Multi-dimensional Prognostic Index (MPI), or the Vitality Capacity [30].

Recently, biomarkers of aging have emerged with the promise to provide an accurate prediction of biological age. Biological age is distinct from chronological age as it aims to predict the relative age, i.e., the risk of age-related diseases and remaining lifespan. Currently, aging clocks, based on changes in CpG methylation in DNA, are the most advanced types of such age predictors [30]. Transcriptomic, proteomic and metabolomic clocks are currently being developed, which could provide additional layers of information. Aging clocks can identify age acceleration and deceleration, for example in smokers or upon CR, respectively. The stratification of the impact of such interventions is a major leap forward in the assessment of geroprotectors as well as of disease risk

factors. Moreover, aging clocks typically indicate disease stages, which could add to their usefulness. Current limitations of aging clocks are their reproducibility and restricted value as diagnostic markers at the level of individuals, which would be required in order to introduce aging clocks into clinical practice. Further development of aging clocks is essential to reliably quantify biological age and the effectiveness of geroprotective interventions on an individual.

Evidence-based geroprotective medicine, paired with meaningful diagnostics, will be crucial to effectively promote healthy aging and prevent disease. A plethora of supplements and lifestyle interventions are currently touted as anti-aging without any scientific evidence of effectiveness in humans. To deploy geroprotectors, it will be important that medical practitioners are able to provide evidence-based advice. Such evidence-based aging medicine should become an integral part of modern medicine at multiple levels ranging from general practitioners to emergency care physicians, and hospital wards that are increasingly treating older adults with multimorbidities. This will reduce the costs associated with visiting multiple specialists and the risk of polypharmacy.

Data integration and national biobanking is required to assess geroprotective effects

Geroprotective medicine requires the integration of large datasets on multiple organs and disease risks as well as of personal biological parameters such as genetic background and epigenetic status. Large biobanks such as the UK Biobank [31] and the NIH GTeX consortium [32] have in recent years provided a plethora of new insights into human disease, particularly chronic diseases of aging. The advent of omics in medicine has allowed the generation of multi-molecular datasets in readily accessible biofluids, in particular blood samples. Omics methods such as genomics, transcriptomics, epigenomics, proteomics, and metabolomics can provide an unprecedented comprehensive assessment of human health. It is, however, essential that other data types, such as anamneses, are included. Such data integration will help unveil target conditions for candidate geroprotective drugs, supplements, and lifestyle factors that are already in common use. The analysis of pre-existing data is valuable for avoiding unnecessary trials on drugs that

were established for other indications but which could be repurposed for geroprotection. Finally, robust evidence of geroprotective efficacy requires controlled and ultimately randomized, double-blinded clinical trials.

The combination of new omics data types and the clinical evaluation of existing and novel geroprotectors could open a new era of medicine for disease prevention. This is essential to target, as early as possible, common denominators of aging and age-related pathologies to mitigate or even prevent their progression to full-blown disease, and subsequent multimorbidity, in order to extend the healthspan of our aging population.

5 Specific recommendations

In order to reduce the impact of disease in the later phase of life, several critical goals need to be accomplished:

1. Expanding the mechanistic understanding of the biology of aging. Its complexity requires the implementation of state-of-the-art technologies in whole organism studies. Currently, the regulatory landscape of animal experiments is an obstacle to such studies and needs to be revised to allow Germany to play a role in this fundamental discovery work. Germany has a suitable research landscape with several internationally renowned research institutes that provide a solid foundation for building a leading research hub on geroscience. Systems Aging approaches allow the integration of the multiple layers of molecular, cellular and physiological data types including environmental, transgenerational and sex-specific influences on an organism's aging trajectory. Data from animal models must be integrated with human data. This will require a systems aging consortium comprising expertise in aging biology and computational biology. A systems aging consortium could be rapidly implemented, and effective integration of existing multiomics data between sites could already provide a more complete understanding of human aging and how geroprotectors operate.

2. Translation of biological knowledge into pharmaceutical interventions, including the discovery and further development of novel drugs, needs to be accelerated. Drug repurposing currently plays a major role, particularly in the recognition of drugs' geroprotective properties based on large human datasets. However, repurposing tends to be neglected by the pharmaceutical industry given the limited commercial revenue. In this regard, public funding could promote the implementation of known drugs with apparent geroprotective properties into health-promoting treatments accessible to a wide

population at limited cost. Importantly, a better understanding of the mechanisms of aging increasingly allows pharmacological targeting of the causal factors of aging. However, given the large number of people affected by multimorbidity, the current timeline for drug discovery to translation must be accelerated. Investments need to be made in potentially high-risk innovations in gerosciences. Such investments will enable Germany to become a leader in this field.

3. Geroscience-driven clinical trials and the building up of biobanks need to be organized at a national level to allow systematic data generation and open science analysis. Humans each have a unique set of genetic and epigenetic variations, the impact of which on healthy aging can only be deciphered by performing large cohort studies. The identification of human geroprotectors requires the discovery and implementation of aging biomarkers, e.g., aging clocks and physiological markers, in clinical studies. Implementing such biomarkers as a standard part of clinical trials could accelerate the identification of long-term effects on healthy aging and the identification of treatments' geroprotective potential. Aging biology is complex, and thus the clocks that report biological age are highly likely to be complex and comprised of multiomic data types. Increasingly, such biomarkers will become surrogate markers for preventive therapies that maintain health and lower mortality. Scandinavian countries have implemented well-organized repositories for clinical data on a large population basis. The UK Biobank is being used for a plethora of discovery science data that drives progress in medical sciences. The current regulatory landscape in Germany is an impediment to the systematic generation and integration of human health data. A major initiative to develop a national German biobank that includes human health data and that is accessible to scientific research is required.

4. Geromedicine, which prevents aging-associated diseases by treating aging biology, is essential to address the health challenges posed by the ongoing demographic change. Germany can build upon its significant strength in basic geroscience but requires investment in the translation to clinical research. This could be facilitated by the

development of preventive biomedical research clinics linked to academic centers. Awareness of geromedicine should be spread across the numerous medical disciplines, stakeholders, and also patient and public involvement (PPI) to integrate the general population in geroscience. The diagnostics indicating a healthy aging trajectory and assessing the risk of age-related diseases will rely on biomarkers of aging (see above). Germany is technically in an ideal position but needs to introduce a geromedicine educational component into clinical training. The development of geroprotective therapies can benefit from the country's strong pharmaceutical industry. The combination of geroscience (biomedical research centers) and very strong pharma (drug development) could provide the basis for solutions to Germany's aging society.

The doubling of life expectancy in the past one-and-a-half centuries is a major achievement of human civilization. The ensuing demographic change has brought new challenges that must be addressed. In fact, demographic change poses one of the key societal challenges of modern times and has already led to a shift in economic resource allocations. A major challenge of an aging society is multimorbidity, leading to a large portion of the population suffering from chronic diseases. Aging biology research has provided groundbreaking new insights into the mechanisms underlying aging and age-associated diseases. Geroprotective interventions that lower age-associated disease risks and extend healthspan have started to emerge. The systematic development of the field based on molecular understanding and evidence-based approaches will provide strategies for healthy aging and a more inclusive society.

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