Living long and well: prospects for a personalized approach to the medicine of ageing

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Abstract

Research into ageing and its underlying molecular basis enables us to develop and implement targeted interventions to ameliorate or cure its consequences. However, the efficacy of interventions often differs widely between individuals, suggesting that populations should be stratified or even individualized. Large-scale cohort studies in humans, similar systematic studies in model organisms, and detailed investigations into the biology of ageing can provide individual validated biomarkers and mechanisms, leading to recommendations for targeted interventions. Human cohort studies are already ongoing, and can be supplemented by *in silico* simulations. Systematic studies in animal models are made possible by the use of inbred strains, or genetic reference populations of mice. Combining both, the comprehensive picture of the various determinants of ageing and healthspan can be studied in detail, and an appreciation of the relevance of results from model organisms to humans emerges. The interactions between genotype and environment, particularly the psychosocial environment, are poorly studied in both humans and model organisms, presenting serious challenges to any approach to a personalized medicine of ageing. To increase success of preventive interventions, we argue that there is a pressing need for an individualized evaluation of interventions such as physical exercise, nutrition, nutraceuticals and calorie restriction mimetics as well as psychosocial and environmental factors, separately and in combination. The expected extension of healthspan enables us to refocus healthcare spending on individual prevention starting in late adulthood, and on the brief period of morbidity at very old age.

Introduction

The need for *ageing research* is growing rapidly. Trends predicted from the EUROPOP survey suggest that the share of the population aged 65 years and over will rise from 17% in 2010 to 30% in 2060, with those aged over 80 increasing from 5% to 12% over the same period [http://futurage.group.shef.ac.uk/road-map.html]. The economic and social consequences of the ageing population therefore cannot be overestimated. Slowing down the deleterious processes of ageing itself would enable significant benefits, going beyond the benefits of eradicating specific diseases, which amount to lifespan extension by just a few years in case of, e.g., cancer and stroke [1]. The diseases of age, whether cardiovascular, neoplastic, pulmonary or cognitive, are increasing in frequency and will be the top four causes of death worldwide by 2020. 75% of all deaths from these diseases occur in people aged 60 and over and their incidence rises with age. In other words, for a host of non-communicable diseases, there is a clear link between the underlying processes of ageing and the age-dependent accumulation of risk, so that eradication of one disease merely makes way for the occurrence of another disease slightly later [2], [3], [4]. Slowing down ageing itself, and addressing its root mechanisms, is expected to *increase healthspan and to compress the period of age-related morbidity*, thus tackling goals considered much more worthwhile than simply extending chronological lifespan [3], [4]. Moreover, for any interventions, the effect of genotype and environment (biological and psychosocial), and of the interaction between underlying mechanisms are most important, and their combinatorial application should be considered (Figure 1).

Therefore, based on the recent convergence of personalized medicine and ageing research in human and model organisms, we suggest in this Viewpoint that a successful research agenda for the next decade should be based on three pillars (Figure 2): (1) extending, complementing and integrating the knowledgebase assembled in existing human cohort studies, (2) running closely similar studies in animal models, and (3) understanding the biology of ageing through detailed investigation of findings in human and animals, to gain a mechanistic understanding of biomarkers and interventions.

Our agenda rests on the biomarker concept. Baker and Sprott [5] defined a biomarker of ageing as ‘a biological parameter of an organism that either alone or in some multivariate composite will, in the absence of disease, better predict functional capability at some late age, than will chronological age’, and the American Federation for Aging Research has proposed more detailed criteria for biomarkers of ageing aimed at estimating biological, not chronological age [6], essentially adding their close relation to processes that underlie ageing, not disease, their ease of measurement and their cross-species relevance. However, while many biomarkers of ageing were described in animal or cross-sectional human studies, most of them failed in the few long-term human studies available [7]. One problem is technical limitation: human marker measurements are rarely comparable across decades. Also, selecting blood as the most easily assayable biological fluid ignores other organs affected by age. Moreover, there are major variations during the day or the year, as e.g. the amount of daylight will have an impact on many markers. Also, some markers such as low body mass index or blood pressure may indicate lesser biological age for younger people only, and the opposite for the very old [9], [10]. Finally, while biomarkers should describe biological age, there is no true "gold standard", which would need to be based on a comprehensive longitudinal study in humans running for almost a century. Studies of populations at an advanced age, such as the Leiden or Newcastle 85-plus studies [11], [12], necessarily focus more on old-age multimorbidity than on the full spectrum of ageing processes over a

human lifecourse. Nevertheless, listings of biomarkers validated for humans in longitudinal studies were compiled and include interleukin 6 (IL-6) and some hormones [7], [8], and, more recently, galactosylated N-glycans [13], plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) [14] and epigenetic markers [15], [16].

'Personalized' approaches to medicine are gaining ground in mainstream medical research. The most well-known of these involve cancer therapeutic agents with a companion diagnostic gene test, such as Herceptin™ and Gleevec™ [17]. More comprehensive, 'omics'-based attempts at personalizing diagnostics and therapy are being tested [18]. Moreover, molecular markers and interventions have to be integrated with biographical ones [19]. Assembling sufficiently large human datasets, in order to enable differentiation and classification of patients within the cohorts, is the key to personalized medicine. Longitudinal cohort studies, such as the Framingham [20], and Study of Health in Pommerania (SHIP) [21] studies, or the upcoming German *National Cohort* [22], therefore attempt to identify disease mechanisms, risk factors, prevention strategies and early markers in the general population; systematic integration of such data is also being attempted [http://www.chancesfp7.eu/].

While the *mechanisms of ageing* are complex [4], [23], [24], evidence is accumulating that ageing is a *potentially modifiable risk factor* [25] for its associated morbidities. Moreover, longitudinal cohort studies for humans (see above) and primates [26], [27], human genome-wide association studies [28], as well as longitudinal studies, genetic manipulation and intervention testing programs for rodents [29], [30], [31] have revealed many insights in recent years. Some of them converge on exercise and diet, and associated pathways. In particular, a recurring theme is that of pathways related to energy and nutrient sensing and production [32] and dietary restriction has emerged as the most robust means of extending lifespan and healthspan alike [26]. Dietary restriction may be the best path towards this goal, even though its long-term effects in humans are ultimately unknown. Pragmatically, its downside is that it requires behavioral modification and great willpower, triggering the search for calorie-restriction mimetics, small molecules that produce comparable effects, with some promising early results [33]. Importantly, the effects of dietary restriction are not uniform: in the case of mice and primates, dietary restriction results vary by genotype (or strain or subspecies), diet and/or environment, and dietary restriction was sometimes found detrimental [34], just as the effects of its mimetics vary [35]. The effects of dietary components vary as well, e.g. whole-grain bread tends to have positive effects mostly in Northern European populations and less in Mediterranean people [36]. Similarly, the effects of fish oil in mouse and human depends on *APOE* genotype [37]. Thus, we may expect to find a high degree of heterogeneity in the informativity of biomarkers, or the efficacy of interventions, for humans and in outbred animals alike. Moreover, studies of the underlying molecular mechanisms in terms of pathways may also wish to take into account individual variability.

Personalized medicine and ageing research are now starting to come together, aided by the explorative and confirmatory power of high-throughput datasets.

The most visible sign of this convergence is the recent startup of Human Longevity Inc [http://www.humanlongevity.com/] by Craig Venter, aiming at finding genomic, metabolomic, microbiomic and other determinants of health in 100,000s of volunteers. Along similar lines, the Institute for Systems Biology in Seattle is now pursuing the 100k project [http://research.systemsbiology.net/100k/]. As time goes by, longitudinal cohort studies are by necessity developing into studies of ageing,

and a few are explicitly gathering data with the aim of fostering a better understanding of ageing processes [38], [39]. Longitudinal studies in model organisms enable the systematic dissection of the molecular architecture of ageing. For example, around 30 strains of mice have recently been studied by the Nathan Shock Center at the Jackson laboratory [29], and phenotypic and/or genetic data are now being analyzed together with lifespan data [40], [9], [41]. Efforts such as the Collaborative Cross [42] enable Genome Wide Association Study (GWAS)-like studies in mice, and the subsequent detailed study of mechanistic insights, and more generally the modeling of approaches to personalized medicine in animals. Here, we can investigate the individual differences in the biology of ageing seen on the cell, tissue and organ level, in great detail. On each of these levels, the speed of ageing can vary substantially, and this is reflected, e.g., epigenetically [15], [16]. More generally, as described in the introduction, biomarkers of ageing are usually found by investigating subpopulations (such as people aged 85 years and older), and these biomarkers also allow the stratification of large populations according to the biology of ageing.

Whilst association studies may provide information on personal risks for specific morbidities, their severity and timing, many of these risks are turning out to be modified by the psychosocial environment and individual history, which in themselves need to be included not only as part of the risk analysis but also as a guide to potential therapies [43]. Many associations with ageing and age-related disease such as Alzheimer's are complex, often with low effect sizes of individual variants, and it is highly likely that at least some of the missing heritability is due to environmental interactions [44]. For example, in a mouse model, disease risk in predisposed strains was shown to be attenuated by environmental factors when Alzheimer-prone mice were placed in a rich and naturalistic environment, showing reduced behavioral effects despite increased plaque density [45]. Moreover, the induction of a neuroinflammatory response was related to chronic unpredictable stress [46]. Conversely, dopamine D4 receptor (*DRD4*) knockout mice do not show the increased longevity seen when background strain mice are brought up in a rich environment, showing them to be refractory to the positive effects of a rich environment. This study found consistency with a parallel human cohort, presenting an excellent paradigm for future work [47]. Individual environmental impact may be reflected epigenetically [15]. Such epigenetic individuality is influenced in part by biographical parameters, reflecting psychosocial environment, social participation and education, and the way this allostatic load was handled by the individual as part of her or his stress response. In turn, targeted interventions may be used to ameliorate the environment [19].

Apart from 'omics' data processing and analysis, *computational studies* enable the well-founded comparison of human and animal data, as well as simulation studies, particularly on the molecular level. At its simplest, the parallelogram approach, originally developed in toxicology [48], suggests use of data of diseased animal tissue to extrapolate to the often inaccessible human diseased tissue, aided by e.g. blood data available for diseased and healthy individuals. Moreover, controlled vocabularies and ontologies, describing the formal relationships between concepts and entities, are developed to enable the systematic comparison of human and animal data [49]. For example, on the (cell) anatomical and physiological level, we can then integrate data and analyze the relationship between phenotypes of humans and model species, yielding estimates for the extrapolation of data and insights from model organisms to humans. Formal data semantics is also useful to systematically mine electronic health record data, to describe phenotypes and diseases [50]. Furthermore, recent promising developments in systems biology and systems medicine include simulation studies of ageing-related pathways and the multi-level

modeling of the large number of interacting processes [51]. Such studies help to disentangle the network of interdependent biological processes that underlie ageing, and distinguish correlation and causality, following the example of cancer research, where computational studies help to distinguish 'passenger' and 'driver' mutations [52]. However, many cancers are characterized by gross modifications of cell and organ physiology, e.g. due to chromosomal aberrations. In contrast, ageing processes are subtler, triggering weaker patterns and signals in terms of phenotype and molecular mechanisms, on a longer time scale. Therefore, the sound integration of data using techniques from data semantics and ontologies is important in ageing research [53], [54], [55], [56], to maximize our chances of detecting meaningful patterns and signals.

The implementation of any recommendations for healthspan extension must be easy and safe.

Many people show high adherence to moderate modifications of exercise and dietary patterns, motivated by their personal instinct or subjective feelings of benefit. Correct use and long-term adherence to changes in dietary composition, nutraceuticals and food supplements is more difficult, though[1]. Healthy and health-conscious individuals consuming high amounts of fruit and vegetables (> 400 g/day) display a more robust organismal antioxidant defense system [57] and a better cognitive performance [58], independent of age and gender, compared to subjects consuming < 100 g/day, although a good plasma micronutrient status can be achieved through targeted counselling [59]. However, as the correct use of nutraceuticals and food supplements is complicated [60], most of the supplementation trials with single compounds and/or single lifestyle preventive strategies against age-related diseases have largely been unsuccessful so far [61]. Furthermore, an immediate subjective feeling of benefit with nutraceuticals is not usually attained, while the possible physiological impact may be significant (on the positive as well as on the negative side). This also applies to long-term small-molecule interventions such as calorie-restriction mimetics. Additionally, quality and safety of nutraceuticals and food supplements are not as strictly controlled as are drugs. Here, subjective feeling has to be supplemented or substituted by sound scientific evidence of benefit, subject to a personalized approach. The *polypill* concept [62] is often criticized, exactly because it does not consider the specifics on the individual. It consists of intensively tested drugs at low dosage, the benefits of which have been shown in large-scale studies. Specifically, it aims to reduce the risk of heart attack and stroke, employing one statin and three blood pressure reducing agents at around half the standard dose, and in a personalized instantiation, it can be considered a model for active interventions to stay healthy for longer.

Sound scientific evidence for healthspan effects of interventions in humans is becoming available.

Conclusive evidence of therapeutic or prophylactic effects of interventions on human healthspan is going to be difficult to establish, because longitudinal intervention studies (starting in mid-life) would take around half a century to complete. Moreover, interventions designed for presumably healthy people need specific justification, and

[1] For example, a six-year study on prevention of dementia failed to show positive effects, possibly due to increasing non-adherence (Jerant A, Chapman B, Duberstein P, Robbins J, Franks P: Personality and medication non-adherence among older adults enrolled in a six-year trial. Br J Health Psychol 2011;16:151-169. (Figure 2 therein)).

no discernible negative side effects. However, a significant delay of ageing-associated disease and morbidity is a distinct positive effect that should not be abandoned without due consideration. Fortunately, there are a couple of convincing arguments that indicate the high likelihood of success of finding valid means towards healthspan extension [25], with people in their late adulthood as the target group. First, very 'mild' forms of healthspan-extending interventions have been practiced for a long time already; their systematic and personalized improvement is already (winning) half the battle. These include exercise, diet and nutraceuticals, as well as indication-based interventions such as drug-based blood pressure reduction, cholesterol modulation and osteoporosis prevention. Also, for many individuals, a significant further extension of healthspan can be expected from improvements in their psychosocial environment, social participation and education. While consistent good parental care in the early years is a good foundation, psychosocial lifestyle interventions can still be effective in adulthood [19]. Second, as a proof of concept, dietary restriction has already been demonstrated to extend healthspan in numerous animal species including mammals, for example benefitting rhesus monkeys (see above), and has been shown to improve biomarkers of ageing in humans in late adulthood as well [63]. Moreover, as described above, pharmacological mimetics of dietary restriction have shown promising results at least in mouse studies [33]. Combination of interventions is important, though, as most of the supplementation trials with single compounds and/or single lifestyle preventive strategies were largely not successful so far [61]. Third, centenarians frequently feature very late onset of age-related diseases and disabilities [64], demonstrating that the goal of healthspan extension can indeed be accomplished at very old age.

Conclusions and prospects

We propose a realistic research agenda with distinctive positive advances within one decade:

- We need to augment ongoing and future clinical studies, measuring as many ageing-related parameters as possible, and to couple them with closely similar animal studies, which feature far shorter execution times and more possibilities for experimental intervention and detailed study. Here, one main aim is to discover and validate new markers of ageing which may assist in stratification of populations with regard to the efficacy of therapeutic and prophylactic intervention. Critical is the recording of environmental parameters, stress, activity and personal history for human studies and detailed analysis of the effects of the environment for model organism studies.

- We need to systematically validate the evidence gained from model animal studies in humans and vice versa. Here, we need an in-depth understanding of the molecular processes that are supposed to be the targets of intervention. Mechanistic studies in mice are essential, and studies in humanized mice, (human) cell lines and other model organisms should be undertaken as well, always selecting the most informative approach.

- Finally, given the range of interventions likely to become validated and available, we should aim for a combinatorial approach through the establishment of a modular system, from which the most appropriate combination of interventions (Fig. 1) can be selected by the individual.

Such an agenda can be expected to yield validated personalized prescriptions for many people within a decade, enabling them to extend their healthspan and to shorten the period of their life that is spent in ill health.

Box 1: Economic implications.
Slowing ageing and extending healthspan has profound economic implications. Importantly, maintaining health and fitness for a longer time period enables later retirement, and more senior-level contribution to society [http://www.healthyageing.eu/]. Furthermore, with the growing lack of young employees there is a great need of people working until the age of 70 or older, in order to avoid staff shortage, especially in service industries such as medicine. Most importantly, however, healthspan increases are one of the few contributors to lowering health care costs in a predictable way, by postponing most of the demand until very old age [65]. Current repair-oriented approaches in cancer, cardiovascular, neuro-degeneration and other areas can then slowly but steadily refocus to serving a population of increasingly advanced age, who stay healthy well beyond their 90s. In summary, the social, economic, and health benefits that would result from advancing healthspan are "longevity dividends" [66].

Conflict of Interest

Herewith the authors declare that we have no conflicts of interest.

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Fig. 1: Healthspan extension includes activity, diet and other interventions, each of which expected to be most effective if personalized, alone and in combination. For the "MediterrAsian" diet, see [67].

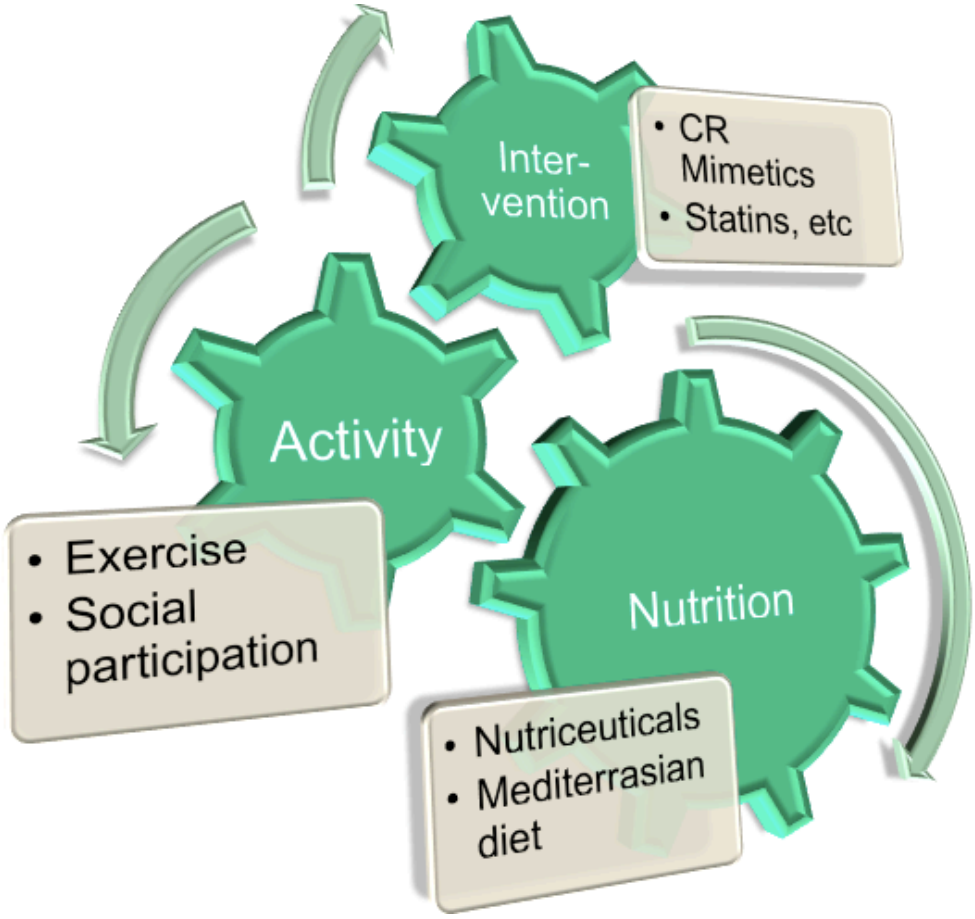

Fig. 2: Robust research on healthspan extension requires a solid base of systematic studies in humans and animals, and an understanding of the biology of ageing, that is, of the mechanisms underlying molecular ageing processes.