View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by ZENODO

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

Georg Fuellen*[1], Paul N. Schofield[2], Thomas Flatt[3], Ralf-Joachim Schulz[4], Fritz Boege[5], Karin Kraft[6], Gerald Rimbach[7], Saleh Ibrahim[8], Alexander Tietz[9], Christian Schmidt[10], Rüdiger Köhling[11], Andreas Simm[12]

[1] Institute for Biostatistics and Informatics in Medicine und Ageing Research, Rostock University Medical Center, Rostock, Germany

[2] Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK, and The Jackson Laboratory, Bar Harbor, ME, USA

[3] Department for Ecology and Evolution, University of Lausanne, Lausanne, Switzerland

[4] Department of Geriatric Medicine, St. Marien-Hospital, Cologne, Germany

[5] Institute of Clinical Chemistry and Laboratory Diagnostics, Heinrich Heine University, Med. Faculty, Düsseldorf, Germany

[6] Chair of Complementary Medicine, Rostock University Medical Center, Rostock, Germany

[7] Institute of Human Nutrition and Food Science, Christian-Albrechts-University Kiel, Kiel, Germany

[8] Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany

[9] Gesellschaft für Gesundes Altern und Prävention, Cologne, Germany

[10] Office of the Medical director, Rostock University Medical Center, Rostock, Germany

[11] Oscar-Langendorff-Institute of Physiology, Rostock University Medical Center, Rostock, Germany

[12] Clinic for Cardiothoracic Surgery, University Hospital Halle, Halle (Saale), Germany

*Corresponding Author.
Institute for Biostatistics and Informatics in Medicine and Ageing Research -- IBIMA
Rostock University Medical Center
Ernst-Heydemann-Str. 8
18057 Rostock, Germany
Phone + 49 381 494-7360
Fax + 49 381 494-7203
http://www.ibima.med.uni-rostock.de/
fuellen@alum.mit.edu

Keywords: healthspan, healthy ageing, cohort study, model organism, bioinformatics
Short title: A personalized approach to the medicine of ageing

This is the peer-reviewed but unedited manuscript version of the following article: Fuellen G, Schofield PN, Flatt T, Schulz RJ, Boege F, Kraft K, Rimbach G, Ibrahim S, Tietz A, Schmidt C, Köhling R, Simm S. Living long and well: prospects for a personalized approach to the medicine of ageing. Gerontology. The final, published version is available at https://www.karger.com/Article/FullText/442746.

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.

Acknowledgements

This paper was derived from a discussion at the 'Hauptstadtkongress 2014', http://www.hauptstadtkongress.de/index.php?id=76&id_programm=103, on "Regeneration and Slowing Down Ageing in the World of Tomorrow". G.F. was supported in part by the BMBF Verbundprojekt ROSAge, FKZ 0315892A and the EU's Horizon 2020 research and innovation program under grant agreement No. 633589; A.S. was supported in part by the state of Saxony-Anhalt.

References

1 Olshansky SJ, Carnes BA, Cassel C: In search of methuselah: Estimating the upper limits to human longevity. Science 1990;250:634-640.
2 Niccoli T, Partridge L: Ageing as a risk factor for disease. Curr Biol 2012;22:R741-752.
3 Partridge L: Intervening in ageing to prevent the diseases of ageing. Trends Endocrinol Metab 2014;25:555-557.
4 Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G: The hallmarks of aging. Cell 2013;153:1194-1217.
5 Baker GT, 3rd, Sprott RL: Biomarkers of aging. Exp Gerontol 1988;23:223-239.
6 Johnson TE: Recent results: Biomarkers of aging. Exp Gerontol 2006;41:1243-1246.
7 Simm A, Nass N, Bartling B, Hofmann B, Silber RE, Navarrete Santos A: Potential biomarkers of ageing. Biol Chem 2008;389:257-265.
8 Lara J, Cooper R, Nissan J, Ginty AT, Khaw KT, Deary IJ, Lord JM, Kuh D, Mathers JC: A proposed panel of biomarkers of healthy ageing. BMC Med 2015;13:222.
9 Moeller M, Hirose M, Mueller S, Roolf C, Baltrusch S, Ibrahim S, Junghanss C, Wolkenhauer O, Jaster R, Kohling R, Kunz M, Tiedge M, Schofield PN, Fuellen G:

394 Inbred mouse strains reveal biomarkers that are pro-longevity, antilongevity or
395 role switching. Aging Cell 2014;13:729-738.
396 10 Martin-Ruiz C, von Zglinicki T: Biomarkers of healthy ageing:
397 Expectations and validation. Proc Nutr Soc 2014;73:422-429.
398 11 Lagaay AM, van Asperen IA, Hijmans W: The prevalence of morbidity in
399 the oldest old, aged 85 and over: A population-based survey in leiden, the
400 netherlands. Arch Gerontol Geriatr 1992;15:115-131.
401 12 Collerton J, Barrass K, Bond J, Eccles M, Jagger C, James O, Martin-Ruiz C,
402 Robinson L, von Zglinicki T, Kirkwood T: The newcastle 85+ study: Biological,
403 clinical and psychosocial factors associated with healthy ageing: Study protocol.
404 BMC Geriatr 2007;7:14.
405 13 Dall'Olio F, Vanhooren V, Chen CC, Slagboom PE, Wuhrer M, Franceschi C:
406 N-glycomic biomarkers of biological aging and longevity: A link with
407 inflammaging. Ageing Res Rev 2013;12:685-698.
408 14 van Peet PG, de Craen AJ, Gussekloo J, de Ruijter W: Plasma nt-probnp as
409 predictor of change in functional status, cardiovascular morbidity and mortality
410 in the oldest old: The leiden 85-plus study. Age (Dordr) 2014;36:9660.
411 15 Horvath S: DNA methylation age of human tissues and cell types. Genome
412 Biol 2013;14:R115.
413 16 Weidner CI, Lin Q, Koch CM, Eisele L, Beier F, Ziegler P, Bauerschlag DO,
414 Jockel KH, Erbel R, Muhleisen TW, Zenke M, Brummendorf TH, Wagner W: Aging
415 of blood can be tracked by DNA methylation changes at just three cpg sites.
416 Genome Biol 2014;15:R24.
417 17 Hamburg MA, Collins FS: The path to personalized medicine. N Engl J Med
418 2010;363:301-304.
419 18 Snyder M: Ipop and its role in participatory medicine. Genome Med
420 2014;6:6.
421 19 McEwen BS, Getz L: Lifetime experiences, the brain and personalized
422 medicine: An integrative perspective. Metabolism 2013;62 Suppl 1:S20-26.
423 20 Mahmood SS, Levy D, Vasan RS, Wang TJ: The framingham heart study
424 and the epidemiology of cardiovascular disease: A historical perspective. Lancet
425 2014;383:999-1008.
426 21 Volzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, Aumann N,
427 Lau K, Piontek M, Born G, Havemann C, Ittermann T, Schipf S, Haring R,
428 Baumeister SE, Wallaschofski H, Nauck M, Frick S, Arnold A, Junger M, Mayerle J,
429 Kraft M, Lerch MM, Dorr M, Reffelmann T, Empen K, Felix SB, Obst A, Koch B,
430 Glaser S, Ewert R, Fietze I, Penzel T, Doren M, Rathmann W, Haerting J,
431 Hannemann M, Ropcke J, Schminke U, Jurgens C, Tost F, Rettig R, Kors JA,
432 Ungerer S, Hegenscheid K, Kuhn JP, Kuhn J, Hosten N, Puls R, Henke J, Gloger O,
433 Teumer A, Homuth G, Volker U, Schwahn C, Holtfreter B, Polzer I, Kohlmann T,
434 Grabe HJ, Rosskopf D, Kroemer HK, Kocher T, Biffar R, John U, Hoffmann W:
435 Cohort profile: The study of health in pomerania. Int J Epidemiol 2011;40:294-
436 307.
437 22 Wichmann HE, Kaaks R, Hoffmann W, Jockel KH, Greiser KH, Linseisen J:
438 [the german national cohort]. Bundesgesundheitsblatt Gesundheitsforschung
439 Gesundheitsschutz 2012;55:781-787.
440 23 Gems D, Partridge L: Genetics of longevity in model organisms: Debates
441 and paradigm shifts. Annu Rev Physiol 2013;75:621-644.

442 24 Behrens A, van Deursen JM, Rudolph KL, Schumacher B: Impact of
443 genomic damage and ageing on stem cell function. Nat Cell Biol 2014;16:201-
444 207.
445 25 Kirkland JL: Translating advances from the basic biology of aging into
446 clinical application. Exp Gerontol 2013;48:1-5.
447 26 Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley
448 TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW, Weindruch R: Caloric
449 restriction delays disease onset and mortality in rhesus monkeys. Science
450 2009;325:201-204.
451 27 Mattison JA, Roth GS, Beasley TM, Tilmont EM, Handy AM, Herbert RL,
452 Longo DL, Allison DB, Young JE, Bryant M, Barnard D, Ward WF, Qi W, Ingram
453 DK, de Cabo R: Impact of caloric restriction on health and survival in rhesus
454 monkeys from the nia study. Nature 2012;489:318-321.
455 28 Nebel A, Kleindorp R, Caliebe A, Nothnagel M, Blanche H, Junge O, Wittig
456 M, Ellinghaus D, Flachsbart F, Wichmann HE, Meitinger T, Nikolaus S, Franke A,
457 Krawczak M, Lathrop M, Schreiber S: A genome-wide association study confirms
458 apoe as the major gene influencing survival in long-lived individuals. Mech
459 Ageing Dev 2011;132:324-330.
460 29 Yuan R, Peters LL, Paigen B: Mice as a mammalian model for research on
461 the genetics of aging. Ilar J 2011;52:4-15.
462 30 Bartke A: Single-gene mutations and healthy ageing in mammals. Philos
463 Trans R Soc Lond B Biol Sci 2011;366:28-34.
464 31 Miller RA, Harrison DE, Astle CM, Floyd RA, Flurkey K, Hensley KL, Javors
465 MA, Leeuwenburgh C, Nelson JF, Ongini E, Nadon NL, Warner HR, Strong R: An
466 aging interventions testing program: Study design and interim report. Aging Cell
467 2007;6:565-575.
468 32 Johnson SC, Rabinovitch PS, Kaeberlein M: Mtor is a key modulator of
469 ageing and age-related disease. Nature 2013;493:338-345.
470 33 Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL,
471 Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin MJ, Schwab M,
472 Pollak M, Zhang Y, Yu Y, Becker KG, Bohr VA, Ingram DK, Sinclair DA, Wolf NS,
473 Spindler SR, Bernier M, de Cabo R: Metformin improves healthspan and lifespan
474 in mice. Nat Commun 2013;4:2192.
475 34 Liao CY, Johnson TE, Nelson JF: Genetic variation in responses to dietary
476 restriction--an unbiased tool for hypothesis testing. Exp Gerontol 2013;48:1025-
477 1029.
478 35 Miller RA, Harrison DE, Astle CM, Baur JA, Boyd AR, de Cabo R, Fernandez
479 E, Flurkey K, Javors MA, Nelson JF, Orihuela CJ, Pletcher S, Sharp ZD, Sinclair D,
480 Starnes JW, Wilkinson JE, Nadon NL, Strong R: Rapamycin, but not resveratrol or
481 simvastatin, extends life span of genetically heterogeneous mice. J Gerontol A
482 Biol Sci Med Sci 2011;66:191-201.
483 36 Kyro C, Olsen A, Landberg R, Skeie G, Loft S, Aman P, Leenders M, Dik VK,
484 Siersema PD, Pischon T, Christensen J, Overvad K, Boutron-Ruault MC,
485 Fagherazzi G, Cottet V, Kuhn T, Chang-Claude J, Boeing H, Trichopoulou A, Bamia
486 C, Trichopoulos D, Palli D, Krogh V, Tumino R, Vineis P, Panico S, Peeters PH,
487 Weiderpass E, Bakken T, Asli LA, Arguelles M, Jakszyn P, Sanchez MJ, Amiano P,
488 Huerta JM, Barricarte A, Ljuslinder I, Palmqvist R, Khaw KT, Wareham N, Key TJ,
489 Travis RC, Ferrari P, Freisling H, Jenab M, Gunter MJ, Murphy N, Riboli E,
490 Tjonneland A, Bueno-de-Mesquita HB: Plasma alkylresorcinols, biomarkers of

491 whole-grain wheat and rye intake, and incidence of colorectal cancer. J Natl
492 Cancer Inst 2014;106:djt352.
493 37 Gardener SL, Rainey-Smith SR, Barnes MB, Sohrabi HR, Weinborn M, Lim
494 YY, Harrington K, Taddei K, Gu Y, Rembach A, Szoeke C, Ellis KA, Masters CL,
495 Macaulay SL, Rowe CC, Ames D, Keogh JB, Scarmeas N, Martins RN: Dietary
496 patterns and cognitive decline in an australian study of ageing. Mol Psychiatry
497 2014
498 38 Collerton J, Martin-Ruiz C, Kenny A, Barrass K, von Zglinicki T, Kirkwood
499 T, Keavney B: Telomere length is associated with left ventricular function in the
500 oldest old: The newcastle 85+ study. Eur Heart J 2007;28:172-176.
501 39 Bertram L, Bockenhoff A, Demuth I, Duzel S, Eckardt R, Li SC,
502 Lindenberger U, Pawelec G, Siedler T, Wagner GG, Steinhagen-Thiessen E: Cohort
503 profile: The berlin aging study ii (base-ii). Int J Epidemiol 2013
504 40 Yuan R, Meng Q, Nautiyal J, Flurkey K, Tsaih SW, Krier R, Parker MG,
505 Harrison DE, Paigen B: Genetic coregulation of age of female sexual maturation
506 and lifespan through circulating igf1 among inbred mouse strains. Proc Natl Acad
507 Sci U S A 2012;109:8224-8229.
508 41 Bogue MA, Peters LL, Paigen B, Korstanje R, Yuan R, Ackert-Bicknell C,
509 Grubb SC, Churchill GA, Chesler EJ: Accessing data resources in the mouse
510 phenome database for genetic analysis of murine life span and health span. J
511 Gerontol A Biol Sci Med Sci 2014
512 42 Threadgill DW, Churchill GA: Ten years of the collaborative cross. G3
513 (Bethesda) 2012;2:153-156.
514 43 Nithianantharajah J, Hannan AJ: The neurobiology of brain and cognitive
515 reserve: Mental and physical activity as modulators of brain disorders. Prog
516 Neurobiol 2009;89:369-382.
517 44 Tosto G, Reitz C: Genome-wide association studies in alzheimer's disease:
518 A review. Curr Neurol Neurosci Rep 2013;13:381.
519 45 Lewejohann L, Reefmann N, Widmann P, Ambree O, Herring A, Keyvani K,
520 Paulus W, Sachser N: Transgenic alzheimer mice in a semi-naturalistic
521 environment: More plaques, yet not compromised in daily life. Behav Brain Res
522 2009;201:99-102.
523 46 Barnum CJ, Pace TW, Hu F, Neigh GN, Tansey MG: Psychological stress in
524 adolescent and adult mice increases neuroinflammation and attenuates the
525 response to lps challenge. J Neuroinflammation 2012;9:9.
526 47 Grady DL, Thanos PK, Corrada MM, Barnett JC, Jr., Ciobanu V, Shustarovich
527 D, Napoli A, Moyzis AG, Grandy D, Rubinstein M, Wang GJ, Kawas CH, Chen C,
528 Dong Q, Wang E, Volkow ND, Moyzis RK: Drd4 genotype predicts longevity in
529 mouse and human. J Neurosci 2013;33:286-291.
530 48 Kienhuis AS, van de Poll MC, Wortelboer H, van Herwijnen M, Gottschalk
531 R, Dejong CH, Boorsma A, Paules RS, Kleinjans JC, Stierum RH, van Delft JH:
532 Parallelogram approach using rat-human in vitro and rat in vivo toxicogenomics
533 predicts acetaminophen-induced hepatotoxicity in humans. Toxicol Sci
534 2009;107:544-552.
535 49 Hoehndorf R, Hiebert T, Hardy NW, Schofield PN, Gkoutos GV, Dumontier
536 M: Mouse model phenotypes provide information about human drug targets.
537 Bioinformatics 2014;30:719-725.

538 50 Machado CM, Rebholz-Schuhmann D, Freitas AT, Couto FM: The semantic
539 web in translational medicine: Current applications and future directions. Brief
540 Bioinform 2013
541 51 Kriete A, Lechner M, Clearfield D, Bohmann D: Computational systems
542 biology of aging. Wiley Interdiscip Rev Syst Biol Med 2011;3:414-428.
543 52 Pon JR, Marra MA: Driver and passenger mutations in cancer. Annu Rev
544 Pathol 2015;10:25-50.
545 53 Sundberg JP, Berndt A, Sundberg BA, Silva KA, Kennedy V, Bronson R,
546 Yuan R, Paigen B, Harrison D, Schofield PN: The mouse as a model for
547 understanding chronic diseases of aging: The histopathologic basis of aging in
548 inbred mice. Pathobiol Aging Age Relat Dis 2011;1
549 54 Johnson SC, Dong X, Vijg J, Suh Y: Genetic evidence for common pathways
550 in human age-related diseases. Aging Cell 2015;14:809-817.
551 55 Cen W, Freitas AA, de Magalhaes JP: Predicting the pro-longevity or anti-
552 longevity effect of model organism genes with new hierarchical feature selection
553 methods. IEEE/ACM Trans Comput Biol Bioinform 2015;12:262-275.
554 56 Callahan A, Cifuentes JJ, Dumontier M: An evidence-based approach to
555 identify aging-related genes in caenorhabditis elegans. BMC Bioinformatics
556 2015;16:40.
557 57 Anlasik T, Sies H, Griffiths HR, Mecocci P, Stahl W, Polidori MC: Dietary
558 habits are major determinants of the plasma antioxidant status in healthy elderly
559 subjects. Br J Nutr 2005;94:639-642.
560 58 Polidori MC, Praticó D, Mangialasche F, Mariani E, Aust O, Anlasik T, Mang
561 N, Pientka L, Stahl W, Sies H, Mecocci P, Nelles G: High fruit and vegetable intake
562 is positively correlated with antioxidant status and cognitive performance in
563 healthy subjects. J Alzheimers Dis 2009;17:921-927.
564 59 Polidori MC, Carrillo JC, Verde PE, Sies H, Siegrist J, Stahl W: Plasma
565 micronutrient status is improved after a 3-month dietary intervention with 5
566 daily portions of fruits and vegetables: Implications for optimal antioxidant
567 levels. Nutr J 2009;8:10.
568 60 Mecocci P, Tinarelli C, Schulz RJ, Polidori MC: Nutraceuticals in cognitive
569 impairment and alzheimer's disease. Frontiers Pharmacol 2014;in Press
570 61 Polidori MC, Schulz RJ: Nutritional contributions to dementia prevention:
571 Main issues on antioxidant micronutrients. Genes Nutr 2014;92:382.
572 62 Wald DS, Morris JK, Wald NJ: Randomized polypill crossover trial in
573 people aged 50 and over. PLoS One 2012;7:e41297.
574 63 Rickman AD, Williamson DA, Martin CK, Gilhooly CH, Stein RI, Bales CW,
575 Roberts S, Das SK: The calerie study: Design and methods of an innovative 25%
576 caloric restriction intervention. Contemp Clin Trials 2011;32:874-881.
577 64 Andersen SL, Sebastiani P, Dworkis DA, Feldman L, Perls TT: Health span
578 approximates life span among many supercentenarians: Compression of
579 morbidity at the approximate limit of life span. J Gerontol A Biol Sci Med Sci
580 2012;67:395-405.
581 65 Goldman DP, Cutler D, Rowe JW, Michaud PC, Sullivan J, Peneva D,
582 Olshansky SJ: Substantial health and economic returns from delayed aging may
583 warrant a new focus for medical research. Health Aff (Millwood) 2013;32:1698-
584 1705.
585 66 Olshansky SJ, Perry D, Miller RA, Butler RN: Pursuing the longevity
586 dividend: Scientific goals for an aging world. Ann N Y Acad Sci 2007;1114:11-13.

67 Pallauf K, Giller K, Huebbe P, Rimbach G: Nutrition and healthy ageing: Calorie restriction or polyphenol-rich "mediterrasian" diet? Oxid Med Cell Longev 2013;2013:707421.

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].

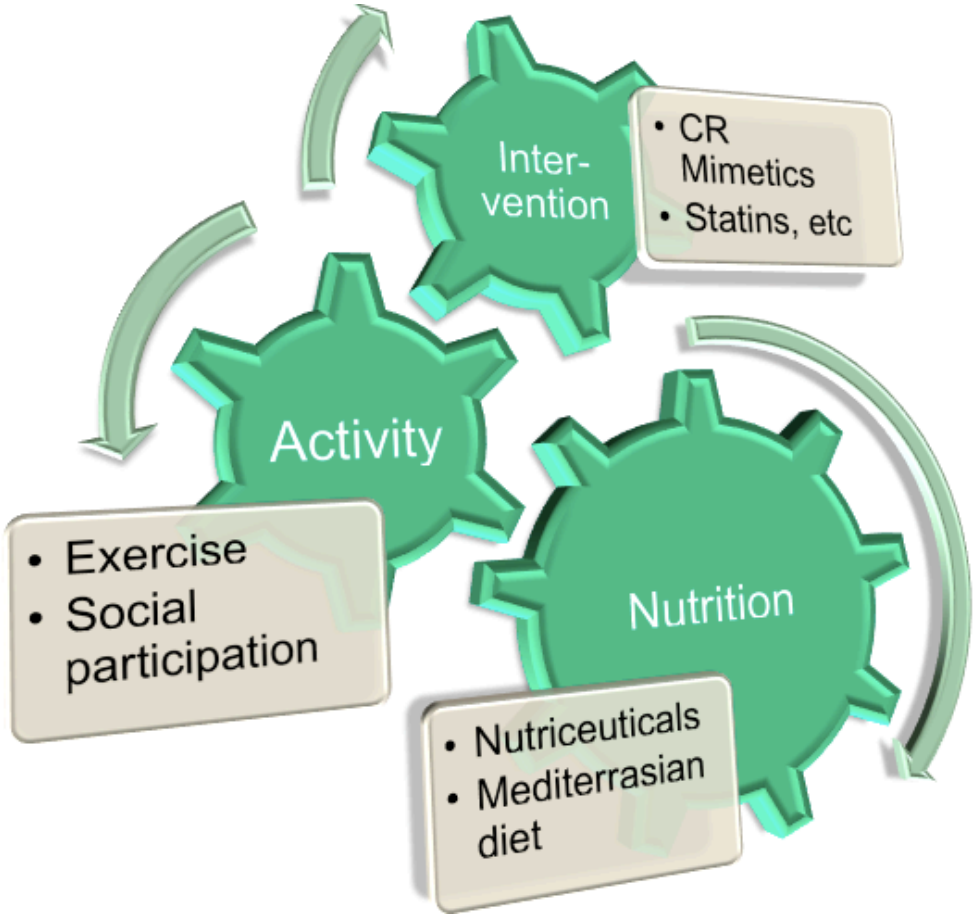

Fig. 2: Robust research on healthspan extension requires a solid base of systematic studies in humans and animals, and an understanding of the biology of ageing, that is, of the mechanisms underlying molecular ageing processes.