Clinical Section / Viewpoint

Gerontology

Gerontology
DOI: 10.1159/000442746

Received: July 17, 2015
Accepted: November 25, 2015
Published online: December 17, 2015

Living Long and Well: Prospects for a Personalized Approach to the Medicine of Ageing

Georg Fuellen[a] Paul Schofield[l, m] Thomas Flatt[k] Ralf-Joachim Schulz[e] Fritz Boege[g] Karin Kraft[b] Gerald Rimbach[h] Saleh Ibrahim[i] Alexander Tietz[f] Christian Schmidt[c] Rüdiger Köhling[d] Andreas Simm[j]

[a]Institute for Biostatistics and Informatics in Medicine und Ageing Research (IBIMA), [b]Chair of Complementary Medicine, [c]Office of the Medical Director, and [d]Oscar Langendorff Institute of Physiology, Rostock University Medical Center, Rostock, [e]Department of Geriatric Medicine, St. Marien-Hospital, and [f]Gesellschaft für Gesundes Altern und Prävention, Cologne, [g]Institute of Clinical Chemistry and Laboratory Diagnostics, Medical Faculty, Heinrich Heine University, Düsseldorf, [h]Institute of Human Nutrition and Food Science, University of Kiel, Kiel, [i]Lübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, and [j]Clinic for Cardiothoracic Surgery, University Hospital Halle, Halle (Saale), Germany; [k]Department for Ecology and Evolution, University of Lausanne, Lausanne, Switzerland; [l]Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK; [m]The Jackson Laboratory, Bar Harbor, Maine, USA

Key Words
Health span · Healthy ageing · Cohort study · Model organism · Bioinformatics

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 as well as 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 they 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 the two, a comprehensive picture of the various determinants of ageing and 'health span' can be studied in detail, and an appreciation of the relevance of results from model organisms to humans is emerging. 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 the success of preventive interventions, we argue that there is a pressing need for an individualized evaluation of interventions such as physical exer-

This paper is 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'.

KARGER

E-Mail karger@karger.com
www.karger.com/ger

0304–324X/15/0000–0000$39.50/0

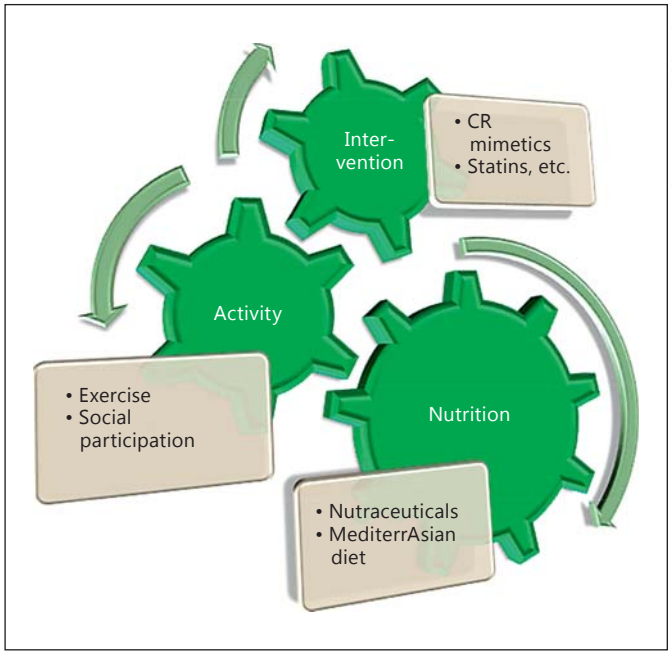
Georg Fuellen
Institute for Biostatistics and Informatics in Medicine and Ageing Research (IBIMA)
Rostock University Medical Center, Ernst-Heydemann-Strasse 8
DE–18057 Rostock (Germany)
E-Mail fuellen@alum.mit.edu

cise, nutrition, nutraceuticals and calorie restriction mimetics as well as psychosocial and environmental factors, separately and in combination. The expected extension of the health span enables us to refocus health care spending on individual prevention, starting in late adulthood, and on the brief period of morbidity at very old age.

Introduction

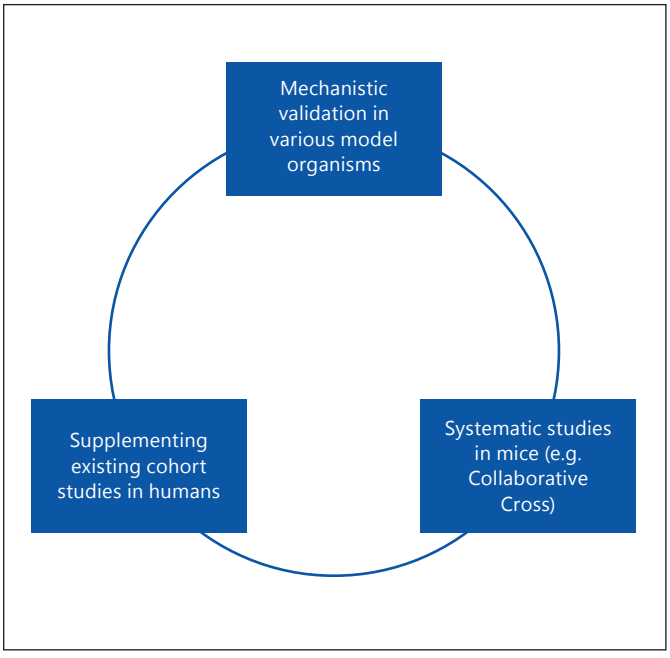
The need for ageing research is growing rapidly. Trends predicted from the EUROPOP survey suggest that the proportion of the population aged 65 years and over will rise from 17% in 2010 to 30% in 2060, with those aged over 80 years increasing from 5 to 12% over the same period (http://futurage.group.shef.ac.uk/roadmap.html).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

Therefore, based on the recent convergence of personalized medicine and ageing research in human and model organisms, we suggest in this viewpoint paper that a successful research agenda for the next decade should be based on three pillars (fig. 2): (1) extending,



Color version available online

Fig. 1. Health span extension includes activity, diet and other interventions, each of which are expected to be most effective if personalized (alone and in combination). For the 'MediterrAsian' diet, see [67]. CR = Calorie restriction.



Color version available online

Fig. 2. Robust research on health span 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.

complementing and integrating the knowledge base assembled in existing human cohort studies; (2) running closely similar studies in animal models, and (3) understanding the biology of ageing through the detailed investigation of findings in humans 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'; 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 lies in technical limitations: human marker measurements are rarely comparable across decades. Also, by selecting blood as the most easily assayable biological fluid, other organs affected by age are ignored. 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 a low body mass index or blood pressure may indicate a lower biological age for younger people and the opposite for the very old [8, 9]. 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+ studies [10, 11], necessarily focus on old-age multimorbidity rather than on the full spectrum of ageing processes over a human life course. Nevertheless, listings of biomarkers validated for humans in longitudinal studies were compiled; they include interleukin 6 (IL-6) and some hormones [7, 12], as well as, more recently, galactosylated N-glycans [13], plasma N-terminal pro-B-type natriuretic peptide [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 data sets in order to allow a differentiation and classification of patients within cohorts is the key to personalized medicine. Longitudinal cohort studies, such as the Framingham Heart Study [20] and the Study of Health in Pomerania (SHIP) [21] 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 morbidities associated with it. Moreover, longitudinal cohort studies in 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 [29–31] have yielded many insights in recent years. Some of them converge on exercise and diet and their associated pathways. In particular, one of the recurring themes 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 life spans and health spans alike [26]. Dietary restriction may be the best path towards this goal, even though its long-term effects on humans are ultimately unknown. Pragmatically speaking, its downside is that it requires behavioral modifications and great willpower, triggering the search for calorie-restriction mimetics, i.e. small molecules that produce comparable effects, with some of them promising early results [33]. Importantly, the effects of dietary restriction are not uniform; in the case of mice and primates, the results of dietary restriction vary by genotype (or strain or subspecies), diet and/or environment, and dietary restriction was sometimes found to be detrimental [34], just as the effects of its mimetics vary [35]. The effects of dietary components vary as well; for instance, 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 mice and humans depend on the *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 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 Data Sets

The most visible sign of the convergence of personalized medicine and ageing research is the recent start-up of Human Longevity Inc. (http://www.humanlongevity.com/) by Craig Venter, aiming at finding genomic, metabolomic, microbiomic and other determinants of health in hundreds of thousands of volunteers. Along similar lines, the Institute for Systems Biology in Seattle is now pursuing the 100K Wellness Project (http://research.systemsbiology.net/100k/). As time goes by, longitudinal cohort studies will by necessity be 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 permit a systematic dissection of the molecular architecture of ageing. For example, around 30 strains of mice have recently been studied at the Nathan Shock Center of the Jackson Laboratory [29], and phenotypic and/or genetic data are now being analyzed together with life span data [9, 40, 41]. Efforts such as the Collaborative Cross [42] allow genome-wide association study-like trials in mice as well as the subsequent detailed study of mechanistic insights and, more generally, the modeling of approaches to personalized medicine in animals. Here, we can investigate in great detail the individual differences in the biology of ageing on the cell, tissue and organ level. On each of these levels, the speed of ageing can vary substantially, and this may, for instance, be reflected epigenetically [15, 16]. More generally, as described in the Introduction, biomarkers of ageing are usually found while 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 as well as on their severity and timing, many of these risks are turning out to be modified by subjects' 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 diseases 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, the 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 receptor D_4 *(DRD4)* knockout mice do not show the increased longevity observed 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 showed consistency with a parallel human cohort, presenting an excellent paradigm for future work [47]. An individual environmental impact may be reflected epigenetically [15]. Such epigenetic individuality is influenced in part by biographical parameters, reflecting the psychosocial environment, social participation and education, and the way this allostatic load has been 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 permit well-founded comparisons 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 the use of data from diseased animal tissue to extrapolate them 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 allow 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 in order to describe phenotypes and diseases [50]. Furthermore, recent promising developments in systems biology and systems medicine include simulation studies of ageing-related pathways and multilevel modeling of the large number of interacting processes involved [51]. Such studies help to disentangle the network of interdependent biological processes that underlie ageing, and to distinguish between correlation and causality, following the example of cancer research, where computational studies help to distinguish 'passenger' from 'driver' mutations [52]. Whereas many cancers are characterized by gross modifications of cell and organ physiology (e.g. due to chromosomal aberrations), ageing

processes are subtler, triggering weaker patterns and signals in terms of phenotype and molecular mechanisms, and on a longer timescale. Therefore, the sound integration of data using the techniques of data semantics and ontologies is important in ageing research [53–56] to maximize our chances of detecting meaningful patterns and signals.

The Implementation of Any Recommendations for Health Span Extension Must Be Easy and Safe

Many people show close adherence to moderate modifications of exercise and dietary patterns, motivated by their personal instinct or subjective feelings of benefit. The correct use of 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 their age and gender, compared to subjects consuming <100 g/day, although a good plasma micronutrient status can be achieved through targeted counseling [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 their 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, the quality and safety of nutraceuticals and food supplements are not controlled as strictly as drugs. Here, subjective feelings have to be supplemented with or substituted by sound scientific evidence regarding benefits, subject to a personalized approach. The polypill concept [62] is often criticized exactly because it does not consider the specifics of 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 attacks and strokes, employing one statin and three blood pressure-reducing agents at around half the standard dose; in a personalized instantiation, it can be considered a model for active interventions to stay healthy for longer periods of time.

[1] For example, a 6-year study on the prevention of dementia failed to show positive effects, possibly due to increasing nonadherence [68] (fig. 2 therein).

Sound Scientific Evidence for Health Span Effects of Interventions in Humans Is Becoming Available

Conclusive evidence for therapeutic or prophylactic effects of interventions on the human health span is going to be difficult to establish, since longitudinal intervention studies (starting in midlife) would take around half a century to complete. Moreover, interventions designed for presumably healthy people need specific justification and should have no discernible negative side effects. However, a significant postponement of ageing-associated disease and morbidity is a distinctly positive aim that should not be abandoned without due consideration. Fortunately, there are a couple of convincing arguments that indicate a high likelihood of success in finding valid means for achieving health span extensions [25], with people in their late adulthood as the target group. First, very 'mild' forms of health span-extending interventions have already been practiced for a long time; their systematic and personalized improvement is already half the battle. Such interventions 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 further significant extension of their health span 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 health spans in numerous animal species including mammals – benefitting rhesus monkeys, for example (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]. Combining interventions is important, though, since most of the supplementation trials with single compounds and/or single lifestyle preventive strategies have largely been unsuccessful so far [61]. Third, centenarians frequently feature very late onsets of age-related diseases and disabilities [64], demonstrating that the goal of health span extension can indeed be accomplished at a 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 the stratification of populations with regard to the efficacy of therapeutic and prophylactic interventions. It is critical to record environmental parameters as well as the characteristics of stress, activity and personal history for human studies and to conduct detailed analyses 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 an 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 any individual.

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

Economic Implications

Slowing ageing and extending health spans has profound economic implications. Importantly, maintaining health and fitness for a longer time period allows later retirement and more senior-level contributions to society (http://www.healthyageing.eu/). Furthermore, with the growing shortage of young employees there is a great need for people working until the age of 70 years or more, especially in service industries such as medicine. Most importantly, however, increases in health span are among the few contributors to lowering health care costs in a predictable way by postponing most of the demand until very old age [65]. The current repair-oriented approaches adopted in cancer, cardiovascular diseases, neurodegeneration and other areas may then slowly but steadily be refocused on serving populations at an increasingly advanced age who stay healthy well beyond their 90s. In summary, the social, economic and health-related benefits resulting from prolonging health spans are 'longevity dividends' [66].

Acknowledgements

G.F. was supported in part by the BMBF Verbundprojekt ROSAge, FKZ 0315892A and the EU Horizon 2020 research and innovation program under grant agreement No. 633589; A.S. was supported in part by the state of Saxony-Anhalt.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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–R752.
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 Moeller M, Hirose M, Mueller S, Roolf C, Baltrusch S, Ibrahim S, Junghanss C, Wolkenhauer O, Jaster R, Köhling R, Kunz M, Tiedge M, Schofield PN, Fuellen G: Inbred mouse strains reveal biomarkers that are pro-longevity, antilongevity or role switching. Aging Cell 2014;13:729–738.
9 Martin-Ruiz C, von Zglinicki T: Biomarkers of healthy ageing: expectations and validation. Proc Nutr Soc 2014;73:422–429.
10 Lagaay AM, van Asperen IA, Hijmans W: The prevalence of morbidity in the oldest old, aged 85 and over: a population-based survey in Leiden, The Netherlands. Arch Gerontol Geriatr 1992;15:115–131.
11 Collerton J, Barrass K, Bond J, Eccles M, Jagger C, James O, Martin-Ruiz C, Robinson L, von Zglinicki T, Kirkwood T: The Newcastle 85+ Study: biological, clinical and psychosocial factors associated with healthy ageing: study protocol. BMC Geriatr 2007;7:14.
12 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.

13 Dall'Olio F, Vanhooren V, Chen CC, Slagboom PE, Wuhrer M, Franceschi C: N-glycomic biomarkers of biological aging and longevity: a link with inflammaging. Ageing Res Rev 2013;12:685–698.
14 van Peet PG, de Craen AJ, Gussekloo J, de Ruijter W: Plasma NT-proBNP as predictor of change in functional status, cardiovascular morbidity and mortality in the oldest old: the Leiden 85-plus Study. Age (Dordr) 2014;36:9660.
15 Horvath S: DNA methylation age of human tissues and cell types. Genome Biol 2013;14:R115.
16 Weidner CI, Lin Q, Koch CM, Eisele L, Beier F, Ziegler P, Bauerschlag DO, Jöckel KH, Erbel R, Mühleisen TW, Zenke M, Brümmendorf TH, Wagner W: Aging of blood can be tracked by DNA methylation changes at just three CpG sites. Genome Biol 2014;15:R24.
17 Hamburg MA, Collins FS: The path to personalized medicine. N Engl J Med 2010;363:301–304.
18 Snyder M: iPOP and its role in participatory medicine. Genome Med 2014;6:6.
19 McEwen BS, Getz L: Lifetime experiences, the brain and personalized medicine: an integrative perspective. Metabolism 2013;62(suppl 1):S20–S26.
20 Mahmood SS, Levy D, Vasan RS, Wang TJ: The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet 2014;383:999–1008.
21 Völzke H, Alte D, Schmidt CO, et al: Cohort profile: the study of health in Pomerania. Int J Epidemiol 2011;40:294–307.
22 Wichmann HE, Kaaks R, Hoffmann W, Jöckel KH, Greiser KH, Linseisen J: The German National Cohort (in German). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012;55:781–787.
23 Gems D, Partridge L: Genetics of longevity in model organisms: debates and paradigm shifts. Annu Rev Physiol 2013;75:621–644.
24 Behrens A, van Deursen JM, Rudolph KL, Schumacher B: Impact of genomic damage and ageing on stem cell function. Nat Cell Biol 2014;16:201–207.
25 Kirkland JL: Translating advances from the basic biology of aging into clinical application. Exp Gerontol 2013;48:1–5.
26 Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW, Weindruch R: Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 2009;325:201–204.
27 Mattison JA, Roth GS, Beasley TM, Tilmont EM, Handy AM, Herbert RL, Longo DL, Allison DB, Young JE, Bryant M, Barnard D, Ward WF, Qi W, Ingram DK, de Cabo R: Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. Nature 2012;489:318–321.
28 Nebel A, Kleindorp R, Caliebe A, Nothnagel M, Blanché H, Junge O, Wittig M, Ellinghaus D, Flachsbart F, Wichmann HE, Meitinger T, Nikolaus S, Franke A, Krawczak M, Lathrop M, Schreiber S: A genome-wide association study confirms *APOE* as the major gene influencing survival in long-lived individuals. Mech Ageing Dev 2011;132:324–330.
29 Yuan R, Peters LL, Paigen B: Mice as a mammalian model for research on the genetics of aging. ILAR J 2011;52:4–15.
30 Bartke A: Single-gene mutations and healthy ageing in mammals. Philos Trans R Soc Lond B Biol Sci 2011;366:28–34.
31 Miller RA, Harrison DE, Astle CM, Floyd RA, Flurkey K, Hensley KL, Javors MA, Leeuwenburgh C, Nelson JF, Ongini E, Nadon NL, Warner HR, Strong R: An Aging Interventions Testing Program: study design and interim report. Aging Cell 2007;6:565–575.
32 Johnson SC, Rabinovitch PS, Kaeberlein M: mTOR is a key modulator of ageing and age-related disease. Nature 2013;493:338–345.
33 Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin MJ, Schwab M, Pollak M, Zhang Y, Yu Y, Becker KG, Bohr VA, Ingram DK, Sinclair DA, Wolf NS, Spindler SR, Bernier M, de Cabo R: Metformin improves healthspan and lifespan in mice. Nat Commun 2013;4:2192.
34 Liao CY, Johnson TE, Nelson JF: Genetic variation in responses to dietary restriction – an unbiased tool for hypothesis testing. Exp Gerontol 2013;48:1025–1029.
35 Miller RA, Harrison DE, Astle CM, Baur JA, Boyd AR, de Cabo R, Fernandez E, Flurkey K, Javors MA, Nelson JF, Orihuela CJ, Pletcher S, Sharp ZD, Sinclair D, Starnes JW, Wilkinson JE, Nadon NL, Strong R: Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. J Gerontol A Biol Sci Med Sci 2011;66:191–201.
36 Kyrø C, Olsen A, Landberg R, et al: Plasma alkylresorcinols, biomarkers of whole-grain wheat and rye intake, and incidence of colorectal cancer. J Natl Cancer Inst 2014;106:djt352.
37 Gardener SL, Rainey-Smith SR, Barnes MB, Sohrabi HR, Weinborn M, Lim YY, Harrington K, Taddei K, Gu Y, Rembach A, Szoeke C, Ellis KA, Masters CL, Macaulay SL, Rowe CC, Ames D, Keogh JB, Scarmeas N, Martins RN: Dietary patterns and cognitive decline in an Australian study of ageing. Mol Psychiatry 2015;20:860–866.
38 Collerton J, Martin-Ruiz C, Kenny A, Barrass K, von Zglinicki T, Kirkwood T, Keavney B: Telomere length is associated with left ventricular function in the oldest old: the Newcastle 85+ Study. Eur Heart J 2007;28:172–176.
39 Bertram L, Böckenhoff A, Demuth I, Düzel S, Eckardt R, Li SC, Lindenberger U, Pawelec G, Siedler T, Wagner GG, Steinhagen-Thiessen E: Cohort profile: the Berlin Aging Study II (BASE-II). Int J Epidemiol 2014;43:703–712.
40 Yuan R, Meng Q, Nautiyal J, Flurkey K, Tsaih SW, Krier R, Parker MG, Harrison DE, Paigen B: Genetic coregulation of age of female sexual maturation and lifespan through circulating IGF1 among inbred mouse strains. Proc Natl Acad Sci USA 2012;109:8224–8229.
41 Bogue MA, Peters LL, Paigen B, Korstanje R, Yuan R, Ackert-Bicknell C, Grubb SC, Churchill GA, Chesler EJ: Accessing data resources in the mouse phenome database for genetic analysis of murine life span and health span. J Gerontol A Biol Sci Med Sci 2014, Epub ahead of print.
42 Threadgill DW, Churchill GA: Ten years of the Collaborative Cross. G3 (Bethesda) 2012;2:153–156.
43 Nithianantharajah J, Hannan AJ: The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. Prog Neurobiol 2009;89:369–382.
44 Tosto G, Reitz C: Genome-wide association studies in Alzheimer's disease: a review. Curr Neurol Neurosci Rep 2013;13:381.
45 Lewejohann L, Reefmann N, Widmann P, Ambree O, Herring A, Keyvani K, Paulus W, Sachser N: Transgenic Alzheimer mice in a semi-naturalistic environment: more plaques, yet not compromised in daily life. Behav Brain Res 2009;201:99–102.
46 Barnum CJ, Pace TW, Hu F, Neigh GN, Tansey MG: Psychological stress in adolescent and adult mice increases neuroinflammation and attenuates the response to LPS challenge. J Neuroinflammation 2012;9:9.
47 Grady DL, Thanos PK, Corrada MM, Barnett JC Jr, Ciobanu V, Shustarovich D, Napoli A, Moyzis AG, Grandy D, Rubinstein M, Wang GJ, Kawas CH, Chen C, Dong Q, Wang E, Volkow ND, Moyzis RK: *DRD4* genotype predicts longevity in mouse and human. J Neurosci 2013;33:286–291.
48 Kienhuis AS, van de Poll MC, Wortelboer H, van Herwijnen M, Gottschalk R, Dejong CH, Boorsma A, Paules RS, Kleinjans JC, Stierum RH, van Delft JH: Parallelogram approach using rat-human in vitro and rat in vivo toxicogenomics predicts acetaminophen-induced hepatotoxicity in humans. Toxicol Sci 2009;107:544–552.
49 Hoehndorf R, Hiebert T, Hardy NW, Schofield PN, Gkoutos GV, Dumontier M: Mouse model phenotypes provide information about human drug targets. Bioinformatics 2014;30:719–725.
50 Machado CM, Rebholz-Schuhmann D, Freitas AT, Couto FM: The semantic web in translational medicine: current applications and future directions. Brief Bioinform 2015;16:89–103.
51 Kriete A, Lechner M, Clearfield D, Bohmann D: Computational systems biology of aging. Wiley Interdiscip Rev Syst Biol Med 2011;3:414–428.

52 Pon JR, Marra MA: Driver and passenger mutations in cancer. Annu Rev Pathol 2015;10: 25–50.
53 Sundberg JP, Berndt A, Sundberg BA, Silva KA, Kennedy V, Bronson R, Yuan R, Paigen B, Harrison D, Schofield PN: The mouse as a model for understanding chronic diseases of aging: the histopathologic basis of aging in inbred mice. Pathobiol Aging Age Relat Dis 2011;1:10.3402/pba.v1i0.7179.
54 Johnson SC, Dong X, Vijg J, Suh Y: Genetic evidence for common pathways in human age-related diseases. Aging Cell 2015;14:809–817.
55 Cen W, Freitas AA, de Magalhaes JP: Predicting the pro-longevity or anti-longevity effect of model organism genes with new hierarchical feature selection methods. IEEE/ACM Trans Comput Biol Bioinform 2015;12:262–275.
56 Callahan A, Cifuentes JJ, Dumontier M: An evidence-based approach to identify aging-related genes in *Caenorhabditis elegans*. BMC Bioinformatics 2015;16:40.
57 Anlasik T, Sies H, Griffiths HR, Mecocci P, Stahl W, Polidori MC: Dietary habits are major determinants of the plasma antioxidant status in healthy elderly subjects. Br J Nutr 2005;94:639–642.
58 Polidori MC, Praticó D, Mangialasche F, Mariani E, Aust O, Anlasik T, Mang N, Pientka L, Stahl W, Sies H, Mecocci P, Nelles G: High fruit and vegetable intake is positively correlated with antioxidant status and cognitive performance in healthy subjects. J Alzheimers Dis 2009;17:921–927.
59 Polidori MC, Carrillo JC, Verde PE, Sies H, Siegrist J, Stahl W: Plasma micronutrient status is improved after a 3-month dietary intervention with 5 daily portions of fruits and vegetables: implications for optimal antioxidant levels. Nutr J 2009;8:10.
60 Mecocci P, Tinarelli C, Schulz RJ, Polidori MC: Nutraceuticals in cognitive impairment and Alzheimer's disease. Frontiers Pharmacol 2014;5:147.
61 Polidori MC, Schulz RJ: Nutritional contributions to dementia prevention: main issues on antioxidant micronutrients. Genes Nutr 2014;92:382.
62 Wald DS, Morris JK, Wald NJ: Randomized Polypill crossover trial in people aged 50 and over. PLoS One 2012;7:e41297.
63 Rickman AD, Williamson DA, Martin CK, Gilhooly CH, Stein RI, Bales CW, Roberts S, Das SK: The CALERIE Study: design and methods of an innovative 25% caloric restriction intervention. Contemp Clin Trials 2011; 32:874–881.
64 Andersen SL, Sebastiani P, Dworkis DA, Feldman L, Perls TT: Health span approximates life span among many supercentenarians: compression of morbidity at the approximate limit of life span. J Gerontol A Biol Sci Med Sci 2012;67:395–405.
65 Goldman DP, Cutler D, Rowe JW, Michaud PC, Sullivan J, Peneva D, Olshansky SJ: Substantial health and economic returns from delayed aging may warrant a new focus for medical research. Health Aff (Millwood) 2013;32: 1698–1705.
66 Olshansky SJ, Perry D, Miller RA, Butler RN: Pursuing the longevity dividend: scientific goals for an aging world. Ann NY 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.
68 Jerant A, Chapman B, Duberstein P, Robbins J, Franks P: Personality and medication nonadherence among older adults enrolled in a six-year trial. Br J Health Psychol 2011;16: 151–169.