Healthy aging: the ultimate preventative medicine

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Abstract

Age is the greatest risk factor for nearly every major cause of mortality in developed nations. Despite this, most biomedical research focuses on individual disease processes without much consideration of the relationships between aging and disease. Recent discoveries in the field of Geroscience, which seeks to understand biological mechanisms of aging, have provided insights into molecular processes that underlie biological aging and, perhaps more importantly, potential interventions to delay aging and promote healthy longevity. Here we describe some of these advances along with efforts to move Geroscience from the bench to the clinic. We also propose that greater emphasis should be placed on research into basic aging processes, because interventions that slow aging will have a greater impact on quality of life than disease-specific approaches.

The major focus of biomedical research has traditionally been on the pathogenesis and treatment of individual diseases, particularly those with large impacts upon morbidity and mortality. Within the United States National Institutes of Health there are institutes dedicated to research toward treatments for cancer (NCI), eye disease (NEI), heart, lung, and blood disease (NHLBI), infectious disease (NIAID), arthritis, musculoskeletal, and skin diseases (NIAMS), neurological disease and stroke (NINDS) and diabetes, digestive disease, and kidney disease (NIDDK). Even at the National Institute on Aging (NIA), more than one third of the 2014 research budget is allocated to a single target: Alzheimer’s Disease, and this percentage is expected to increase to more than 50% in 2015. This disease-specific focus has unquestionably had a profound impact on medical care and human health; many new treatments have been developed that are helping people live longer today than ever before. However, despite significant advances in management, we have been largely unsuccessful at postponing, ameliorating, or preventing the accumulation of morbidities during aging. As a consequence, people are living longer but often suffering from multiple diseases or disabilities of aging. This has important societal and economic implications. Many families struggle to care for elderly relatives who survive with reduced quality of life for years or even decades, while nations devote an increasing proportion of finite resources toward medical care for aging populations.

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These issues have, in part, spurred efforts to increase the recognition of the importance of basic research on the biology of aging. This has resulted in a series of major advances in a field once known as Biogerontology, but which has recently become known as Geroscience. Such work has demonstrated that biological aging is modifiable, and has provided tangible approaches to enhance healthy longevity. A promising new initiative, the NIH-wide Geroscience Interest Group, has been created to expedite collaborative efforts to discover the mechanisms of aging that constitute the major risk factor for virtually all of their focused disease interests (1). The underlying hypothesis is that delaying the rate of biological aging would simultaneously delay the onset and progression of each of these diseases, a prediction supported by experimental data in laboratory models (2). This has at least two major implications for translational biomedical research. First, it is critical to take into consideration the biological effects of aging when developing therapies for chronic disease, something that is often not appropriately controlled for in preclinical studies that use young animal models. Consider, for example, the efficacy of vaccine therapies, which generally work potently in young animals, but more poorly in the context of an aged immune system; most preclinical studies in this area use young animals, yet the corresponding clinical applications are, in many important cases, targeted toward the elderly. A specific case where this may have significant implications is in the development of cancer immunotherapies (3).

The second and most profound implication from the link between aging and disease is that successful modifications of the intrinsic rates of aging will provide a much more effective approach for improving healthy longevity, relative to strategies aimed at treating or curing an individual disease. This is because therapies aimed at a single chronic disease, even when maximally effective, are generally unable to impact other diseases of aging. The added value from targeting the underlying processes of aging directly, and thereby delaying multiple age-related declines in function, has been referred to as the “Longevity Dividend” (4). Efforts to quantify this dividend, based on projections from preclinical experimental data, predict significant benefits in individual quality of life (healthspan), as well as important society-wide economic and productivity gains (5).

Although it is clear that targeting aging directly is theoretically superior to treating individual chronic diseases, until recently translational approaches to achieve this goal have been just that - purely theoretical. This is now changing. Numerous studies over the past decade have identified key mechanisms of aging (6), along with targeted interventions that modulate those mechanisms and extend healthy longevity in laboratory model systems. Most excitingly, within the past few years we have begun to see the first steps toward translation of these laboratory discoveries into clinical applications.

Now we will focus on the initial forays into Translational Geroscience and the major challenges and opportunities they present. We have identified several interventional strategies for which there is evidence of attenuating or reversing biological aging in model systems, and may therefore have translational potential for improving human healthspan (Table 1). This is not an exhaustive list, nor is it a prediction of precisely where the field will go, but rather indicates those areas where there currently appear to be the most promise for development of effective interventions to enhance quality of life for people by delaying aging. Among the features that are likely to determine the broad utility of a particular
intervention for improving healthy longevity in people are (1) it must be relatively easy to implement, (2) it can be effective when started in mid-life or later, and (3) the benefits must outweigh the risks.

There are at least two major hurdles to overcome, however, before clinical interventions in aging can be rigorously validated in people. The first is the timescale over which human aging occurs. One way to assess the efficacy of an intervention for delaying biological aging is to demonstrate significant improvements in the progression of aging-related conditions. However, unless there are intermediate outcomes, this may require very long clinical trials since many aging-related conditions progress over decades. Recent advances toward the development of true biomarkers of biological aging rate (i.e. epigenetic or metabolomic signatures) may provide surrogate measures, although these will also need to be validated, at least initially, in a similar manner. These strictures are greatly relaxed, however, if the intervention can be shown to reverse physiological parameters of aging. While this is a higher bar to reach, there is evidence that it may be achieved by some interventions that target mechanisms of aging. For example, mTOR inhibitors such as rapamycin (see Table 1) can partially rejuvenate immune stem cell (7) and cardiac (8, 9) function in mice, and perhaps also restore immune function in elderly people (10).

The second major challenge for clinical assessment of interventions that modify biological aging, at least in the United States, is a regulatory one. At present, targeting basic processes of biological aging has an undefined regulatory path at the U.S. Food and Drug Administration (FDA). Thus, it may not yet be possible to receive FDA approval for an intervention whose primary indication is to delay the onset or rates or progression of processes of aging. However, a strategy has recently been proposed, in consultation with the FDA, to partially bypass these hurdles and assess the efficacy of metformin against human aging in a randomized, double-blind, 5–6 year clinical trial. The “Targeting Aging with Metformin” or “TAME” clinical trial seeks to enroll individuals who have already been diagnosed with any age-associated condition and to determine whether metformin is effective at delaying the diagnosis of other age-associated conditions (11). Because the time between diagnosis of the first and second age-associated condition will be compressed, the study is expected to detect delays of the order of 15–30% (depending upon the specific age-related condition) with 90% power. Should the results prove to delay the onset of disorders of aging significantly, the TAME study may provide a possible regulatory path forward for clinical trials of agents designed to retard biological aging.

As an intermediate to human clinical studies, we could apply Translational Geroscience to companion (pet) dogs (12). Dogs suffer from many of the same age-associated diseases and functional declines that impact humans, albeit at an accelerated rate, and veterinary practitioners are adept at recognizing and diagnosing geriatric diseases in dogs. Dogs also have substantial genetic and phenotypic diversity. Moreover, companion dogs and cats share the human environment to an extent unmatched by any other non-human animal. Significant increases in healthy longevity in companion dogs would not only provide important insights into similar efforts in people but would directly improve the quality of life for pet dogs and their owners. A pilot study assessing the effects of short-term rapamycin treatment on cardiac aging in middle-aged companion dogs is underway (13), and a longer-term
An intervention study has been proposed that would also assess the effects of rapamycin treatment on cancer incidence, cognitive decline, immune function, mobility, and life expectancy in middle-aged dogs (12).

We have briefly outlined the case for concerted efforts to determine the mechanisms by which intrinsic processes of aging lead to many of the most devastating human health disorders, including heart disease, diabetes, cancer and dementia. We have also pointed to promising advances in translational research with the potential to delay or conceivably prevent most such disorders. There is, however, a caveat that requires much more investigation – the degree to which interventions that slow the rate of aging and delay the onset of age-related disorders will be accompanied by a compression of morbidity. In other words, will such interventions regularly lead to an increase in the ratio of healthspan to lifespan? Will our medicated centenarians lead fulfilling lives with eventual sudden collapse, or will they suffer from proportionally protracted durations of chronic disease? While some research on centenarians does indeed suggest a compression of morbidity (14) and rapamycin, in particular, appears to disproportionately enhance many measures of healthspan in mice (15), future progress in Geroscience interventions will need to be carefully monitored.

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References


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### Table 1
Geroscience interventions with translational potential.

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<th>Intervention</th>
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<tr>
<td>Dietary restriction</td>
<td>Dietary restriction (DR) is the most studied intervention for delaying aging (16). Although not universally effective, a majority of studies have documented significant increases in both lifespan and healthspan when applied in laboratory models, including non-human primates (17). Limited studies also indicate significant health benefits in people who practice DR, including reversal of disease risk factors (16). Although DR is not a viable translational approach at the population level, research in this area has spurred the search for alternative dietary modifications (e.g. low protein diets) or small molecule DR mimetics (e.g. mTOR inhibitors, see below) that can provide health benefits of DR without requiring reduced food consumption.</td>
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<td>Exercise</td>
<td>There is a large body of literature supporting the health benefits of exercise that are consistent with the enhancement of healthspan (18, 19). However, poor compliance, especially in the elderly population, makes this challenging to apply. There is thus high interest in developing pharmacologic interventions that would synergize with lower levels of exercise.</td>
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<td>mTOR inhibitors</td>
<td>Rapamycin extends lifespan and promotes healthspan in mice, as well as simpler organisms. Treatment beginning late in life is sufficient to extend lifespan, reverse cardiac decline, and improve immune function in mice (20). A recent study also reported that a rapamycin derivative significantly boosts immune function in elderly people (10).</td>
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<td>Metformin and acarbose</td>
<td>Metformin and acarbose are widely used anti-diabetes drugs. Metformin improves healthspan in mice and may slightly extend lifespan (21), while acarbose robustly extends lifespan in male mice and modestly extends lifespan in female mice (22). In a non-randomized retrospective analysis, diabetic patients taking metformin have reduced mortality compared to diabetic patients not receiving metformin, and may live longer than non-diabetics not receiving metformin (23).</td>
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<td>NAD precursors and sirtuin activators</td>
<td>As discussed by Verdin and colleagues in their companion review, NAD precursors such as nicotinamide riboside and nicotinamide mononucleotide have been reported to improve healthspan in mouse models of muscle aging and cognitive decline. The mechanism of action is not clear, but may involve activation of sirtuin NAD-dependent protein deacetylases along with enhanced mitochondrial function. Other, possibly more specific, sirtuin activators also improve healthspan and slightly extend lifespan in mice (25).</td>
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<td>Modifiers of senescence and telomere dysfunction</td>
<td>Senescent cells accumulate during aging and secrete factors that promote inflammation and cancer (26). As discussed in the companion review by Blackburn and colleagues, telomere dysfunction is a major cause of cell senescence, and strategies to enhance telomerase function offer promise for improving healthspan, although the possibility of increased cancer risk must be addressed. Likewise, genetic and pharmacological strategies to target and kill senescent cells enhance both lifespan and markers of health in short-lived mice with high levels of senescent cells (28, 29).</td>
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<td>Hormonal and circulating factors</td>
<td>Age related changes in important hormones, including sex-steroids, growth hormone and IGF-1 are well documented; however, the risks and benefits of hormone supplementation in aging remain largely controversial (30). As discussed in the companion review by Goodell and Rando, heterochronic parabiosis experiments in which the circulatory system of an aged mouse is shared with that of a young mouse suggest that additional, more subtle humoral factors impact age-associated declines in several tissues including brain, muscle, liver, and heart (31). Some progress has been made to define these factors (32), and an effort is underway to determine whether transfusion of young plasma can delay Alzheimer’s disease (33).</td>
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<td>Mitochondrial targeted therapeutics</td>
<td>As discussed in the companion review by Hekimi and colleagues, mitochondrial dysfunction is a major contributor to aging and age-related diseases, although the mechanisms are more complex than initially suggested by the Harman’s Free Radical Theory of Aging (34). Attention is now directed to interventions that augment mitochondrial function, energetics and biogenesis, including mitochondrial targeted antioxidants and NAD precursors.</td>
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