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Introduction

It is Time to Embrace 21st-Century Medicine

Matt Kaeberlein, PhD*

*Address correspondence to Matt Kaeberlein, PhD, Department of Pathology, University of Washington, 1959 NE Pacific St, Seattle, WA 98195. E-mail: kaeber@uw.edu

Biomedical research and clinical practice have traditionally been focused on disease rather than health. We typically wait until people are sick before trying to cure their disease or alleviate their symptoms, rather than actively supporting health and wellbeing in the absence of disease. Current demographic trends toward older populations make this approach problematic. Instead of improving the quality of life, we may be extending the period of morbidity and frailty for millions of people. Twenty-first century medicine should adopt the strategy of directly targeting the molecular mechanisms that cause biological aging. Only in this way will it be possible to slow the onset and progression of multiple age-related diseases simultaneously, in order to extend the healthspan proportionately with the lifespan.

The world is getting older. Over the past century, life expectancies in developed countries have increased approximately 60% at the same time that birth rates have declined. The net effect of these trends is that nearly every nation is experiencing a dramatic "graying" of the population. Unfortunately, the increase in life expectancy does not appear to have been matched by increasing "health expectancy" (Nikolich-Žugich et al., 2016). The concept of the healthspan refers to the period of life spent free from chronic, age-related disease or disability (Kaeberlein, 2018), but increases in the human lifespan have not been matched by increases in the population healthspan (Olshansky, 2018). Instead, many people are living longer with one or, more often, multiple diseases of aging. In 2017, it was estimated that more than half of the global health burden among adults could be attributed to age-related diseases (Chang, Skirbekk, Tyrovolas, Kassebaum, & Dieleman, 2019), and this number is growing. The consequences of these demographic shifts and increases in comorbid survival are profound, with major economic and social implications.

The increase in the disease burden among older adults may be related to a "one disease at a time" approach to human medicine. Biomedical research and clinical practice are almost exclusively focused on treating individual diseases after people get sick. Even preventative approaches generally focus on a single disease, such as heart disease or Alzheimer's disease. The problem with this mindset is that age is the single greatest risk factor for many different diseases (Kaeberlein, 2017). Even if we were someday successful at curing cancer or heart disease, the impact on healthspan would be relatively small (Lombard, Miller, & Pletcher, 2016). This is because risks for all of the other diseases of aging continue to increase exponentially with age. Indeed, it has been estimated that curing all forms of cancer would increase the life expectancy for a typical 50-year-old woman in the United States by only 3–4 years (Martin, LaMarco, Strauss, & K, 2003), with an even smaller increase in the health expectancy, simply because only one (out of many) diseases of aging would be mitigated.

We now have an opportunity to take a much more effective approach to extending healthspan, by targeting the biological mechanisms of aging directly. Since the mid-1990s, immense progress has been made in understanding the molecular causes of biological aging, which have been formalized as nine "Hallmarks of Aging" (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). These hallmarks represent specific, biological processes that contribute to age-related functional declines and disease risk. Importantly, by targeting these hallmarks with medications or other interventions, it is now possible to slow the biological aging process and, in some cases, even reverse the functional declines that occur during aging. For example, the drug rapamycin, which targets multiple hallmarks of aging, has been shown to improve the aged heart, brain, and immune system in rodents, such that old animals treated with this drug have shown functional rejuvenation in these organs (Kaeberlein & Galvan, 2019). A derivative of rapamycin is now being studied in clinical trials in people to determine whether it has the same immune-boosting effects in the older adults, with initial results looking quite

promising (Mannick et al., 2018). This represents only one of several strategies for clinically targeting the Hallmarks of Aging, and it now seems certain that medicines to delay or reverse the biological aging process are only a matter of when, rather than if.

Targeting biological aging directly, which I refer to as 21st-century medicine, has many advantages over the traditional one-disease-at-a-time approach. The impacts on life and health expectancies from targeting aging are much greater than waiting until people get sick and trying to cure or ameliorate their individual diseases (Figure 1). Instead of increasing life expectancies by only a few years from curing one disease, delaying aging could increase life expectancies by a few decades. Importantly, those added years would be spent in relatively good health, because instead of only fixing one disease, all of the functional declines and diseases of aging would be targeted simultaneously. In addition to the impact on the quality of life, there are substantial economic benefits as well. It has been estimated that simply increasing health expectancy by a miniscule 2.2 years will yield more than $7.1 trillion in economic benefits to the United States from decreased health-care costs and increased productivity (Goldman et al., 2013). There is no question that curing an individual's disease is immensely important to that individual and their loved ones; however, at the population level, this approach is inefficient and, in some ways, counter-productive. Instead, we need to retool our thinking toward attenuating the underlying cause for the vast majority of chronic and lethal diseases.

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Fortunately, there is growing recognition within the biomedical research community of the central role that aging plays in many disease processes. This is important, as prior failures to appreciate this may have had a significant, detrimental impact on research progress over the past 30 years. For example, the development, dissemination, and widespread use of biologically young animal models in cancer research may underlie the failure of many cancer therapies to translate from preclinical to clinical success. Similar attempts to model age-related diseases in young animals have generally fared poorly in oral health (e.g., periodontal disease), Alzheimer's disease, and musculoskeletal disease research, among others. Importantly, a Geroscience Interest Group has been formed at the National Institutes of Health (NIH), with the mission to "enhance opportunities to explore the intersection between aging biology and the biology of diseases that are of interest to the various NIH Institutes and Centers" (National Institute on Aging, 2019). Initiatives such as this are needed, as the vast majority of federal funding for research on age-related diseases is not administered through the National Institute on Aging, but is instead administered through other NIH Institutes (Table 1). The trans-NIH Geroscience Interest Group, along with similar initiatives, can help NIH staff and scientists at each Institute to understand the important role that biological aging plays in their diseases of interest.

We are also beginning to see real progress on strategies that will allow for the regulatory approval of interventions designed to target biological aging. For example, a clinical trial to test whether the drug metformin can delay biological aging has been proposed and accepted by the United States Food and Drug Administration (FDA). The Targeting Aging with Metformin (TAME) trial will test whether metformin can delay the onset of multiple diseases

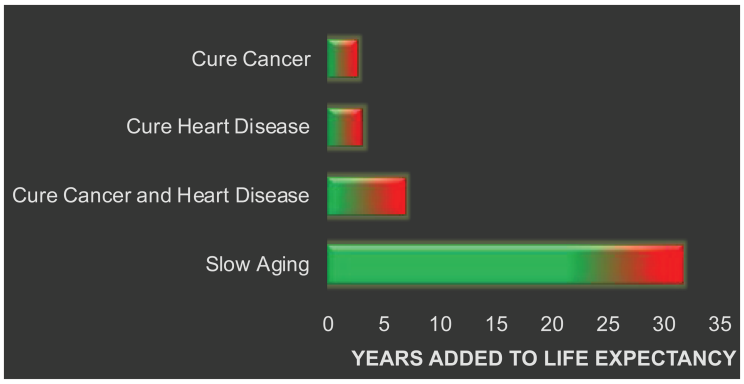

Figure 1. Slowing aging is more effective than curing disease. Displayed are the calculated impacts on life expectancy for a typical 50-year-old woman from curing cancer, heart disease, or both, relative to the impact of slowing aging. The figure was generated from data presented in Lombard et al. (2016). The coloring illustrates the hypothetical impact on health expectancy in each case, where green represents the absence of a comorbidity and the red represents a severe comorbidity.

Table 1. Age-Related Diseases by Primary National Institutes of Health Institute Responsible for Administering Research Funding

NCI — $6 billion
Neoplasms — Acute lymphoid leukaemia; acute myeloid leukaemia; benign and in situ intestinal neoplasms; bladder cancer; brain and nervous system cancer; breast cancer; chronic lymphoid leukaemia; chronic myeloid leukaemia; colon and rectum cancer; gallbladder and biliary tract cancer; Hodgkin lymphoma; kidney cancer; larynx cancer; lip and oral cavity cancer; liver cancer due to non-alcoholic steatohepatitis; liver cancer due to alcohol use; liver cancer due to hepatitis C; malignant skin melanoma; mesothelioma; multiple myeloma; myelodysplastic, myeloproliferative, and other hematopoietic neoplasms; non-Hodgkin lymphoma; non-melanoma skin cancer (basal-cell carcinoma); non-melanoma skin cancer (squamous-cell carcinoma); oesophageal cancer; other benign and in situ neoplasms; other leukaemia; other malignant neoplasms; ovarian cancer; pancreatic cancer; prostate cancer; stomach cancer; thyroid cancer; tracheal, bronchus, and lung cancer; and uterine cancer.
NEI — $0.7 billion
Sense organ diseases — Age-related and other hearing loss; age-related macular degeneration; cataract; glaucoma; other sense organ diseases; other vision loss; and refraction disorders.
NHLBI — $3.4 billion
Cardiovascular diseases — Atrial fibrillation and flutter; endocarditis; hypertensive heart disease; intracerebral haemorrhage; ischaemic heart disease; ischaemic stroke; myocarditis; non-rheumatic calcific aortic valve disease; non-rheumatic degenerative mitral valve disease; other cardiomyopathy; other cardiovascular and circulatory diseases; other non-rheumatic valve diseases; and peripheral artery disease.
Blood diseases — Other haemoglobinopathies and haemolytic anaemias.
Chronic respiratory diseases — Asbestosis; chronic obstructive pulmonary disease; coal worker pneumoconiosis; interstitial lung disease and pulmonary sarcoidosis; other pneumoconiosis; and silicosis.
NIA — $2.6 billion*
Dementias — Alzheimer's disease and other dementias.
NIAID — $5.3 billion
Communicable — Diarrhoeal diseases; encephalitis; lower respiratory infections; pneumococcal meningitis; and trachoma.
NIAMS — $0.6 billion
Musculoskeletal diseases — Congenital musculoskeletal and limb anomalies.
Skin and subcutaneous diseases — Cellulitis; decubitus ulcer; fungal skin diseases; other skin and subcutaneous diseases; and pyoderma.
NIDCR — $0.5 billion
Oral diseases (non-cancer) — Periodontal disease.
NIDDK — $2.1 billion
Diabetes and kidney diseases — Chronic kidney disease due to type 2 diabetes mellitus; chronic kidney disease due to glomerulonephritis; and chronic kidney disease due to other and unspecified causes.
Digestive diseases — Cirrhosis due to NASH; pancreatitis; paralytic ileus and intestinal obstruction; peptic ulcer disease; vascular intestinal disorders; and digestive congenital anomalies.
NIEHS — $0.8 billion
Injuries — Drowning; environmental heat and cold exposure; falls; foreign body in other body part; other transport injuries; and other unintentional injuries.
NINDS — $2.2 billion
Neurological disorders — Motor neuron disease; and Parkinson's disease.

Notes.The disease list has been modified from the 92 age-related diseases identified by Chang et al. (2019). The fiscal year 2018 budget allocation is shown for each NIH Institute (National Institutes of Health, 2019). *Of the $2.6 billion allocated to the NIA, approximately 2/3 is earmarked for Alzheimer's disease research. NASH = Nonalcoholic steatohepatitis; NCI = National Cancer Institute; NEI = National Eye Institute; NHLBI = National Heart Lung and Blood Institute; NIA = National Institute on Aging; NIAID = National Institute of Allergy and Infectious Disease; NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIDCR = National Institute of Dental and Craniofacial Research; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institutes of Health; NINDS = National Institute of Neurological Disorders and Stroke.

of aging simultaneously (Barzilai, Crandall, Kritchevsky, & Espeland, 2016). At the same time, several biotechnology companies are working toward the goal of treating age-related diseases through targeting the Hallmarks of Aging. For example, after two successful Phase II trials, resTORbio, Inc. has initiated a Phase III trial aimed at

restoring immune functions in the older adults. Another publicly traded company, Unity, Inc., is taking a different approach by developing drugs to clear senescent cells in aged individuals. Senescent cells accumulate in many tissues as we get older, and are believed to contribute to chronic inflammation, decreased organ functions, and increased cancer risks.

Despite the exciting progress, there is still much to be done before we can fully capitalize on the promise of 21st-century medicine. Many clinicians recognize that most of their sick patients are older, but remain unaware of the impact of biological aging on disease. There is also resistance among some in the medical community to treating otherwise "healthy" older people. While every intervention has potential side effects, this should be weighed against the possible benefits of improved functions for the aged heart, brain, lung, kidney, immune system, and so forth. We must keep in mind that, compared to a typical 30-year-old person, every 70-year-old person is likely to be functionally impaired. This can be seen for measures of physical fitness, from relatively extreme feats, such as marathon times, to more mundane tasks, like arm curls or step tests (Milanović et al., 2013). Nearly every organ system declines with age, which leads to functional impairments in a variety of measures, including the ability to fight off infections (immune), hearing, vision, memory, strength, and many others. While there are certainly rare 70-year-olds who can outperform the average 30-year-old for some of these measures, it is unlikely that there are any 70-year-olds who have not experienced functional declines relative to their own performance at 30. The potential benefits of broadly maintaining or restoring functions and preventing disease in older people should be appropriately weighed when considering potential risks.

Regulatory issues also present an ongoing challenge. This is true not only for establishing how medications that target aging will be approved for use by the FDA and equivalent bodies in other nations around the world, but also for preventing the misuse of such treatments and helping consumers separate the legitimate medications from the rampantly fraudulent claims of "anti-aging" therapies. Some of these are outright snake oil; however, there are a growing number of companies marketing anti-aging products in the gray area where the FDA has limited oversight, such as natural product supplements. Many of these are based on real scientific research, but have little or no evidence for efficacy in people and absolutely no data on the adverse events associated with long-term use. As the science in this area continues to advance, we will see even more of these unregulated products come to market, and the vast majority of the general public is ill-equipped to understand where these products fall on this spectrum.

Now is the time to begin preparing for the reality of effective approaches for delaying aging in people. Policy makers, research funders, regulatory officials, and medical professionals alike should understand that intervention in biological aging is not only possible, but is already making its way into the clinic and the unregulated marketplace. Within the next 5 years, we may see the first FDA-approved drugs that target the hallmarks of aging to improve age-related disorders. There will undoubtedly be challenges during this transition, but there are also immense opportunities. Serious consideration of these challenges and opportunities at the highest levels will help ensure that our society can reap the greatest benefits from 21st-century medicine.

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