Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: Annals *Reports*

Reverse geroscience: how does exposure to early diseases accelerate the age-related decline in health?

Ronald A. Kohanski,[1] Steven G. Deeks,[2] Claudia Gravekamp,[3] Jeffrey B. Halter,[4] Kevin High,[5] Arti Hurria,[6] Rebecca Fuldner,[1] Paige Green,[7] Robin Huebner,[8] Francesca Macchiarini,[1] and Felipe Sierra[1]

[1]Division of Aging Biology, National Institute on Aging, NIH, Bethesda, Maryland. [2]Department of Medicine, University of California San Francisco, San Francisco, California. [3]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York. [4]Geriatrics Center and Institute of Gerontology, University of Michigan, Ann Arbor, Michigan. [5]Department of Internal Medicine, Section on Infectious Diseases, Wake Forest School of Medicine, Winston-Salem, North Carolina. [6]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, California. [7]Biobehavioral and Psychologic Branch, National Cancer Institute, NIH, Bethesda, Maryland. [8]Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland

Address for correspondence: Felipe Sierra, Division of Aging Biology, National Institute on Aging, NIH, Bethesda, MD. sierraf@nia.nih.gov

Aging is the major risk factor for both the development of chronic diseases and loss of functional capacity. Geroscience provides links among the biology of aging, the biology of disease, and the physiology of frailty, three fields where enormous progress has been made in the last few decades. While, previously, the focus was on the role of aging in susceptibility to disease and disability, the other side of this relationship, which is the contribution of disease to aging, has been less explored at the molecular/cellular level. Indeed, the role of childhood or early adulthood exposure to chronic disease and/or treatment on accelerating aging phenotypes is well known in epidemiology, but the biological basis is poorly understood. A recent summit co-organized by the National Institutes of Health GeroScience Interest Group and the New York Academy of Sciences explored these relationships, using three chronic diseases as examples: cancer, HIV/AIDS, and diabetes. The epidemiological literature clearly indicates that early exposure to any of these diseases and/or their treatments results in an acceleration of the appearance of aging phenotypes, including loss of functional capacity and accelerated appearance of clinical symptoms of aging-related diseases not obviously related to the earlier event. The discussions at the summit focused on the molecular and cellular relationships between each of these diseases and the recently defined molecular and cellular pillars of aging. Two major conclusions from the meeting include the desire to refine an operational definition of aging and to concomitantly develop biomarkers of aging, in order to move from chronological to physiological age. The discussion also opened a dialogue on the possibility of improving late-life outcomes in patients affected by chronic disease by including age-delaying modalities along with the standard care for the disease in question.

Keywords: geroscience; aging; cancer; HIV; AIDS; diabetes

Introduction

Aging is often accompanied by multiple chronic diseases, a state called multimorbidity.[1] It is widely recognized that multimorbidity is the result of the functional decline that occurs in all organisms as a function of age. This leads to an enhanced susceptibility to those diseases for which an individual is most predisposed on the basis of his/her genes and environment.[2] Consequently, aging is acknowledged as the major risk factor for most chronic diseases and disabilities. Aging is not itself a disease but rather a natural process, and impressive progress has been made recently in understanding the biology, genetics, and physiology of aging. Furthermore, in a variety of species, the rate of aging is subject to modulation by several behavioral, genetic, and—more

doi: 10.1111/nyas.13297

recently—pharmacological interventions.[3] Interestingly, interventions that can significantly extend life span most often succeed in also improving at least some aspects of health at older ages. These may be viewed as slowing the rate of aging, since the improved health seems to occur primarily in the older animals. While it is unlikely that any single intervention will improve all aspects of aging physiology, the search continues to find interventions or combinations of interventions where the benefits will outcompete the risks.[4]

This progress in understanding and manipulating the rate of aging has made possible the emergence of geroscience, a field that aims at exploring the molecular and cellular elements that lie at the intersections among basic aging biology, aging physiology, and chronic disease.[6] Indeed, the geroscience hypothesis states that, by reducing the rate of aging, it should be possible to delay or slow down the appearance and progression of most age-related chronic diseases, in parallel. At the onset, the goal of geroscience was to try to unravel the biological basis for why aging is the major risk factor for disease. However, health is more than just the absence of disease, and an exclusive focus on diseases might not be the ideal way to proceed. In fact, it can be argued that focusing most of the resources for biomedical research on those diseases that are major killers might not be desirable if other aspects of health and well-being are neglected. In that context, it is important to acknowledge that aging is also a major risk factor for the loss in functionality that leads to an inability to perform the activities of daily living, with a corresponding decrement in quality of life. So, realizing that aging is the main driver for the general loss of functional capacity and the development of aging phenotypes, even in the absence of overt disease, the field has been moving toward focusing more on health, whereby aging is not solely a major risk factor for disease but also a major risk factor for loss of health in a broader context. In addition, researchers in the basic biology of aging who are working on health span are coming to appreciate what gerontologists recognize in their clinical practice: good health is viewed differently at different ages, and this presents another challenge for geroscience.

Research in aging biology has allowed the definition of a series of the so-called "pillars of aging," a handful of molecular and cellular processes whose dysfunction as a result of aging is thought to drive the age-related functional loss and appearance of aging phenotypes.[7–9] The relevance of each of these pillars to disease susceptibility was the topic of the first Geroscience Summit, held at the National Institutes of Health (NIH) Campus in 2013 and titled "Advances in geroscience: Impact on Healthspan and Chronic Disease." The outcomes of that meeting have been published.[10] When the time came to organize a Second Geroscience Summit, a different tack was chosen: instead of focusing on aging as a major risk factor for disease, a decision was made to address the opposite side of the coin: how do exposures to early disease (or their treatments) affect the pillars of aging, thus paving the way to accelerated development of aging phenotypes and chronic disease? Asking this question was reasonable given a substantial volume of epidemiological data, and the question still fits within the conceptual frame of the pillars of aging, since the pillars do include an "other biology" category. Inclusion of other biology as a pillar acknowledges the fact that not all drivers of the aging process might be known at this time, and there are likely to be additional, as-yet poorly understood modifiers. On the basis of the epidemiological data, exposure to chronic or life-threatening diseases in early or middle life could be one such as-yet poorly defined additional pillar.

As a result, and in conjunction with the New York Academy of Sciences, the Trans-NIH Geroscience Interest Group organized a Second Geroscience Summit, held in New York City in April 2016, titled "Disease Drivers of Aging." In order to focus the discussion, only three disease clusters were chosen as test cases: cancer, HIV/AIDS, and diabetes. It is a well-known epidemiological fact that cancer or HIV/AIDS survivors are affected by premature frailty and early appearance of a number of chronic diseases that normally affect older adults. Childhood cancers are a minor but emotionally devastating subset of all cancers.[11–14] Because life-saving cancer therapy has been available for decades, many childhood cancer patients are now middle aged or older, and the epidemiological data clearly indicate adverse effects later in life, often in tissues and systems not obviously affected by the initial insult or targeted by the initial treatment. Similarly, development of effective therapies against HIV/AIDS means that patients are surviving in large numbers, and many of them are now reaching older ages, having been exposed to the disease earlier in

life, and to long-term treatments, a situation that differs from the example of cancer.[13] The case of diabetes is slightly different: while sequelae of diabetes can indeed be lethal, palliative methods have been available for long enough that we do not regularly refer to these patients as survivors, yet diabetes has long been proposed to be an accelerated aging phenotype.[15] Indeed, many of the metabolic changes observed in diabetes mimic observations made in the aged, though in some cases with differences on the exact physiopathology.[16]

While the epidemiological data for apparent acceleration of aging phenotypes are compelling in all three cases, not much is known about the molecular and cellular drivers of this effect. The goal of the Second Geroscience Summit was therefore to address this issue: how do these diseases and/or their treatments affect the known pillars of aging? And a related question: are these effects transiently present only while the disease condition is present, or do the diseases/treatments leave a permanent imprint in the aging pillars, which could explain molecularly why affected individuals are handicapped later in life. A discussion of major issues in each of these domains is presented in this report.

Diseases accelerate the appearance of aging phenotypes in humans

Cancer

The majority of cancer diagnoses and cancer deaths occur in individuals age 65 and older. Given the association between cancer and aging and the aging of the U.S. population, we are in the midst of a substantial rise in the number of new cases of cancer diagnosed in the United States. There will be a projected 67% increase in cancer incidence in adults age 65 years and older between 2010 and 2030.[17] While cancer was once a deadly disease, improvements in early diagnosis and treatment are resulting in a substantial growth in the number of cancer survivors, estimated at eight million presently in the United States and growing to 11 million by 2020.[18] Hence, the impact of both cancer and its treatment on the aging process is an area of increasing importance.

There are several reasons why cancer therapies may affect the aging process. First, the mechanism of action of cancer therapeutics is primarily aimed at targeting one or more of the pillars of aging, such as genomic instability, epigenetic alterations, and cellular senescence, with the intent to target the tumor; however, the host is likely to sustain a bystander effect. Second, unlike most therapeutic approaches, the doses of the systemic therapies against cancer are often determined by the maximum tolerated dose (the highest dose of the cancer therapeutic that can be delivered to target the tumor without the patient experiencing extreme side effects) rather than the minimum effective dose. Third, and most important for this discussion, the studies evaluating the efficacy and toxicity of cancer therapeutics are often performed in younger adults, rather than in older adults who are the majority of those with cancer.[19,20] Therefore, it is not surprising that many cancer treatments result in both short- and long-term side effects, which may manifest as accelerated aging, with older adults at particular risk.[21–24]

There are emerging data suggesting that cancer therapy may be associated with an accelerated aging phenotype. These data come primarily from the pediatric literature, where pediatric cancer survivors are noted to have an increase in chronic conditions (second malignancies, congestive heart failure, myocardial infarction) and frailty.[11,12,25] In older adults, the accelerated aging phenotype manifests as an increased number of comorbidities,[26] increased mobility limitations and limitations in activities in daily living,[27] poorer mental and physical health-related quality of life,[28,29] and declines in neuropsychological function.[24] Objective measures of physiological health further support the development of an accelerated aging phenotype among patients receiving systemic cancer therapy (chemotherapy/endocrine therapy) demonstrated by a decline in exercise capacity as measured by VO_{2peak}[30–32] and a maximal cycle ergometer test.[33]

At a molecular or cellular level, the impact of cancer or cancer therapy on the patient is still a relatively unexplored area, as most cancer research is focused on the impact of the therapy on the tumor. However, there is emerging *in vitro* and human data suggesting that chemotherapy is associated with aging.[34,35] Studies in humans demonstrate that a potential biomarker of aging, *p16ink4a* expression measured in peripheral blood T cells, is increased among patients who receive adjuvant chemotherapy for breast cancer. The rise in *p16ink4a* expression is 0.81 $\log_2$ order of magnitude (corresponding to a 14.7 year increase in chronological age) immediately after treatment, with the impact sustained 12 months after treatment.[35] VEGF-A and MCP1

(senescence-associated cytokines) also increase with chemotherapy, while no change in telomere length was noted.[35] Other studies, however, have shown that chemotherapy affects telomere length[36] and is associated with telomere shortening in peripheral blood mononuclear cells,[37] as well as in hematopoietic stem cells.[38] The oldest patients may be at greater risk, as telomere shortening was shown to be greater in older patients given combined chemotherapy and radiation for head and neck cancer when compared with younger patients.[39]

Furthermore, there is a complex relationship between aging, cancer, cancer therapeutics, cellular senescence, and inflammation. Aging itself is associated with a chronic low grade inflammation ("inflammaging"), which may contribute to the development of chronic diseases, including cancer.[40] Furthermore, cancer in and of itself may lead to immune activation and systemic inflammation, which can induce damage both locally as well as at a distance.[41,42] Cancer therapeutics induce cellular senescence and the development of a senescence-associated secretory phenotype, which is associated with the secretion of growth factors, proinflammatory cytokines, and proteases.[43,44] Together, this can create a tissue microenvironment that may promote the development of cancer and other chronic diseases, as well as accelerate the aging process.[45]

One potential alternative of treating cancer that may not accelerate the aging process—or at least lessen it—is cancer immunotherapy. After the exciting breakthrough with checkpoint inhibitors—anti-PD-L1 and anti-CTLA4 antibodies—in patients with melanoma, lung cancer, leukemia, and kidney cancer,[46] cancer immunotherapy has been considered as one of the most promising therapies to treat metastatic cancer. Cancer immunotherapy is less harsh than chemotherapy or radiation. Although cancer immunotherapy is less likely than chemotherapy to accelerate aging, the long-term effects of cancer immunotherapy on aging need to be studied. However, cancer immunotherapy is less effective at old versus young ages, owing to T cell unresponsiveness caused by various age-related changes in the immune system. This includes lack of naive T cells, defects in activation pathways of T cells and antigen-presenting cells, and age-related changes in the tumor microenvironment.[47–50] Most cancer therapies are developed in young animals, including cancer immunotherapies. Since immunotherapy is recognized as a potentially important treatment for cancer in the near future, and since most cancer patients are old, analyzing cancer immunotherapies in older animals becomes an unavoidable need to bring the success of cancer immunotherapy to a higher level. Chemotherapeutics induce a proinflammatory cytokine–driven milieu in the tumor microenvironment that leads to accelerated aging. Examples are the production of interleukin 6 (IL-6) and transforming growth factor β, both produced by tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment.[51] However, several chemotherapeutics eliminate TAMs and MDSCs and thus reduce the production of these proinflammatory cytokines in the tumor microenvironment.[51–54] These cytokines also strongly induce immune suppression and T cell unresponsiveness.

Genomic instability is a hallmark of aging, and this leads to loss of antigens and escape of tumor cells from the immune system. Developing therapies that induce immunogenic tumor cell death, combined with immune adjuvants, will lead to the presentation of all antigens expressed by the patients' own tumors to the immune system.[55] If one antigen is lost through genomic instability, there is always another antigen present on the tumor cells that can be recognized by T cells. While this type of immunotherapy may prevent the escape of tumor cells from the immune system, it does not prevent or delay genomic instability. Finally, more targeted therapies with fewer side effects on normal tissues are important alternatives to prevent or delay accelerated aging. To analyze whether these alternative therapies indeed have a reduced potential to induce accelerated aging, they need to be studied over the long term. Such studies need to be carefully designed in aging animals to determine the potential of accelerated aging at various time points in life and to separate the complex relationships among aging, cancer, cancer therapeutics, cellular senescence, and inflammation.

There are many unanswered questions regarding cancer, cancer therapeutics, and accelerated aging. First, research is needed to further elucidate the biologic basis of how cancer or cancer therapies directly affect the pillars of aging. Second, how much of this damage is due to the tumor itself versus the

specific therapies? Third, what is the trajectory of accelerated aging from cancer and cancer therapies, who is most at risk, and is there a specific tipping point that places a host at increased vulnerability? Fourth, how do we prevent or reverse an accelerated aging trajectory? Oncology is a perfect model to study these questions. There are few other examples in medicine where a significant stressor (such as chemotherapy) is applied that unmasks the individual's biologic reserve, placing them at risk of accelerated aging. The stressor is then withdrawn, allowing for potential reversal (resilience) from the biologic insult. A deeper understanding of the biologic basis underlying this clinically common phenomenon would inform our approach to both cancer therapeutics and aging alike.

HIV/AIDS

When used optimally, antiretroviral therapy (ART) suppresses HIV replication indefinitely. Although durable suppression of the virus essentially eliminates the risk of developing AIDS-related complications and prolongs life, it does not fully restore health. For reasons that are the focus of extensive investigation, antiretroviral drug–treated adults are more likely to acquire an aged clinical phenotype faster than age-matched adults living without HIV. This is true regardless of how one defines the aged phenotype—by disease accumulation, functional decline, impaired physical and cognitive function, multimorbidity, development of geriatric syndromes, or self-reported quality of life.

Rates of chronic illnesses—hypertension, diabetes, cardiovascular disease, osteoporosis/bone fractures, chronic obstructive pulmonary disease, kidney disease, liver disease, and many cancers—are approximately 1.5- to twofold higher in HIV-infected compared with uninfected adults.[56–58] For example, in one cohort study, 30–35% of subjects aged 50–65 years have two or more comorbid conditions (in addition to HIV), compared with approximately 10% in that age range for HIV-uninfected adults.[58]

Perhaps the most compelling evidence suggesting that HIV affects healthy aging comes from a series of observations indicating that frailty (or frailty-like syndromes) and other geriatric syndromes are more prevalent among those with HIV. Indeed, the rates reported for those with HIV between 50 and 55 years are comparable to those in the 70+ year range in the general population. This is true even after controlling for many potential confounders, including drug use, other exposures, psychosocial factors, socioeconomic status, and other key variables.[59] In a recent study of men 50 years and older in San Francisco,[60] prefrailty (56%), difficulty with instrumental activities of daily living (46%), and cognitive impairment (47%) were the most common geriatric syndromes, and risk factors were lower for nadir CD4 count, non-white race, and increasing number of comorbidities.

These cross-sectional data have led the popular press and the community to the concern that HIV somehow accelerates aging. Longitudinal data to support this concept are limited, however. Among men with and without HIV followed in the MACS cohort, gait speeds in HIV infected and uninfected adults were comparable at about age 50 years, but thereafter, the rate of decline in normal walking speed is increased in HIV-infected versus uninfected adults. The median age at which walking speed falls below 1 m/s was 57 years in those with HIV compared with 66 years in those without HIV.[61]

HIV-associated neurologic dysfunction (including dementia) was widespread and devastating as a consequence of HIV in the pretreatment era. The neurologic syndromes that persist or emerge during ART are more subtle and generally referred to as *HIV-associated neurocognitive disorder* (HAND). Several factors likely contribute to this syndrome, including irreversible damage produced by HIV before treatment (HIV infects many cells within the central nervous system), antiretroviral toxicity, HIV-associated inflammation, and the presence of other comorbidities.[62,63]

Self-reported health impairments in domains noted with advancing age are increased in those with HIV: psychosocial stress, fatigue, and poor perception of health. Major depressive disorders and comorbid medical conditions, lower reported premorbid functioning, neurocognitive impairment, and nadir CD4 count are the strongest predictors of poor self-reported health and functional status.[64,65]

Important overarching issues in HIV/aging research.

HIV associated immune dysfunction. Infection with HIV is a dynamic event. Viral replication is overwhelming during the first few weeks of infection, with viral copies in the peripheral blood that

approach 10^8 to 10^9/mL. HIV replication during this time causes rapid depletion of tissue-based $CD4^+$ T cells (the primary target for the virus), high level inflammation, and tissue fibrosis. Ongoing harm from HIV replication persists until ART is started, at which time the immune system begins to slowly recover. This treatment-associated recovery is often incomplete, however. Lymphoid tissue fibrosis persists indefinitely. Subtle immunodeficiency is common, even as one's peripheral $CD4^+$ T cell counts are normalized. Inflammation within the innate and adaptive immune system remains elevated. Biomarkers associated with persistent activation of monocytes/macrophages (e.g., IL-6, sCD14) and the adaptive immune system (e.g., the CD4/CD8 ratio) typically persist during ART and are consistently associated with progression to all-cause morbidity. Collectively, this persistent immunologic dysfunction predicts and presumably contributes to a higher risk of a number of diseases common in older people, including cardiovascular disease, cancer, liver and kidney dysfunction, neurologic decline, and infectious complications, such as zoster.

Antiretroviral drug toxicity. ART is now indicated for essentially everyone living with HIV, even those living in resource-poor areas of the world. The effectiveness of these drugs in preventing AIDS, prolonging life, and reducing transmission is no longer questioned. Still, these drugs are not benign, and all may have subtle toxicities that could prevent healthy aging. All reverse transcriptase inhibitors impair mitochondrial replication, but the effect varies by the specific drug, so exposure to one generation of drug is very different than another (e.g., stavudine versus tenofovir vary by nearly 1000-fold with regard to mitochondrial DNA polymerase inhibition). Individual drugs also have toxicities that may be important; for example, tenofovir has bone and kidney-related side effects that are unique, while many protease inhibitors lead to hyperlipidemia and an increased risk of diabetes. These drugs often have complex drug–drug interactions that affect the efficacy of those additional drugs commonly used in older individuals. Polypharmacy is a common predictor of poor health outcomes in the general population and will almost certainly prove to be a major factor in healthy aging in those with HIV.

Cohort effects. Treatment strategies have evolved dramatically over the past 25 years. During the early treatment era, antiretroviral drugs were often toxic and generally not used until people had more advance disease. The treatments being used today are initiated as early as possible and are generally much safer. Accordingly, HIV cohorts from the 1980s are very different than those from the 1990s and the 2000s. As an example, a 70-year-old HIV-infected adult in 2016 who was infected in 1982 and diagnosed in 1988 is likely to have been exposed to multiple antiretroviral drugs with poorly controlled viral replication. In fact, he/she would be a survivor from a cohort where the vast majority did not survive and hence more likely to be resilient than those in the broader population. In contrast, a 70 year old who acquired the infection in 1998 and was diagnosed in 2005 is likely to have been treated with well-tolerated ART at an earlier stage of infection.

Potential confounders. Acquisition of HIV is associated with many risk behaviors, and those factors may differentially influence aging. (e.g., IV drug use, cancer-causing coinfections such as human papilloma virus or hepatitis B/C). Further, other risk factors (e.g., cigarette smoking, isolation from family/social support) do not increase the risk of HIV acquisition, but because they are more prevalent in HIV^+ subjects, it is critical to control such factors through appropriate study design.

Common pathways of aging: synergies with HIV infection.

Aging biology and geroscience. Substantial progress in our understanding of the basic biology of aging and of geroscience has allowed the definition of a few hallmarks or pillars that appear to drive the process.[7,8,10] In the next few paragraphs, we will consider how each of these pillars is affected by HIV infection and/or ART.

Inflammation and senescence. As in aging, ongoing, low-level inflammation is a hallmark of chronic HIV infection, even for those receiving ART, and inflammation is a risk factor for cardiovascular disease, HAND, geriatric syndromes, and other aspects of the aged phenotype.[56,58,66,67] The source of this inflammation is not certain, but three primary areas of focus are discussed below.

Though typically suppressed below measured levels in the blood by ART, HIV production, and perhaps replication, is not completely eradicated by treatment. Several anatomic compartments harbor virus that is continually produced and perhaps continues to infect other tissues.[68] These reservoirs may

be a source of inflammation, and, through a vicious cycle, inflammation is a trigger to low-level HIV production and replication. The importance of low-level viral replication in causing non-AIDS morbidity is perhaps best demonstrated by recent studies of reduced hospitalization and cardiovascular event rates by ART in those rare untreated individuals who have no detectable viremia (the so-called elite controllers).[69]

HIV leads to massive T cell turnover and immune exhaustion, contracted naive T cell populations, and expanded memory T cell populations (especially those T cells directed toward other chronic viruses, like cytomegalovirus (CMV)). This occurs at a younger age than in those without HIV[70] and is only partially mitigated by ART.[71] It has been known for many years that aging results in a similar phenotype, characterized by accumulation of more terminally differentiated $CD8^+$ T cells in peripheral blood. T cell activation—perhaps due to reservoirs of HIV replication—appears to be critical to the accumulation of these T cells.[72] Dysfunctional T cells with an inflammatory phenotype (which are often referred to as *senescent*) accumulate in response to a number of chronic viral infections, including CMV and HIV. These cells have short telomeres, poor telomerase activity, and typically secrete high levels of inflammatory cytokines. These senescent cells in and of themselves may cause age-related disease, such as osteoarthritis.[73] Elimination of senescent cells via senolytics—drugs that are able to push senescent cells to apoptosis—may have profound antiaging effects.[74]

After the initial HIV infection, gut lymphoid tissue is decimated and recovery after ART is incomplete,[75] leading to increased translocation of microbes and microbial products that incite inflammation. Altered gut immune response is also associated with changes in the gut microbiome that may play a role in HIV-related inflammation.[76,77] A large number of studies are now examining ways to modulate the microbiome and microbial translocation through probiotics and other interventions. The gut microbiome also has profound effects on liver metabolic pathways and may be of major importance in the metabolic changes noted below.

Epigenetics. DNA methylation is a good marker of biologic (versus chronologic) age and is associated with physical and cognitive functions.[78] HIV infection leads to methylation at many of the same, and some unique, sites as noted with aging, and HIV accelerates the rate of age-related DNA methylation changes in multiple cell types.[79,80] Depending on the study, this acceleration is on the order of 5–14 years in peripheral blood mononuclear cells and is true in different age cohorts (ages 20–24 and 48–56). These data suggest that the initial HIV "hit" may be most responsible for this change, rather that prolonged exposure to HIV and/or ART, and that there is little or no cohort effect in this phenomenon.[80] There is a strong correlation between advanced DNA methylation and the accumulation of senescent T cells in the peripheral blood.[79] Other investigators have shown DNA methylation patterns that are 5–7 years more advanced than expected for the chronological age of the individual.[81]

Stress response. Maladaptation of the stress response is apparent in people with chronic or overwhelming stress and may be relevant in HIV infection.[82] Resilience is the capacity to appropriately respond and recover from stress and is linked to both the perception of an event as stressful and the biologic changes that respond to and appropriately terminate a stress response. Many HIV-associated factors could conceivably affect resilience, including socioeconomic factors (poor social support systems, poverty), depression, substance use, polypharmacy, and persistent end-organ damage (e.g., neuropathy, myopathy, mild cognitive impairment (MCI), vascular disease, and the metabolic syndrome). Social isolation may be a particularly relevant contributor to poor resilience in HIV-infected older adults owing to inadequate social support and the stigma of having HIV infection, which itself may be perceived as a stress. Finally, there are also data suggesting that HIV proteins themselves may influence the stress response.[83]

Metabolism. HIV and its treatment are associated with marked changes in metabolism, particularly of glucose and fatty acids,[84] and glucose intolerance and frank diabetes mellitus are frequent. Some of this is very likely related to ART side effects. The well-described lipodystrophy syndrome that resulted after ART in the 1990s and early 2000s is much less common with newer drugs, but marked changes in body composition/weight gain, particularly in the period shortly after starting ART, are common and confer much of the diabetes mellitus risk.[85] This is particularly true in those already overweight at the time of ART initiation.[86] In addition,

metabolic changes in lipid and glucose metabolism are commonly associated with many antiretroviral drugs.[87] Liver disease, predominantly fatty liver, is also very common in those living with HIV.[88]

Macromolecular damage. HIV and ART have major effects on mitochondrial health and replication.[89] As noted previously, the effect on mitochondrial DNA polymerase varies greatly by individual drugs even within a class, but once mitochondrial deletion mutations or other macromolecular changes occur they can be propagated throughout the life span of the cell, leading to impaired stress responses, poor resilience, early senescence, and metabolic derangements. Telomerase activity is impaired by HIV, common coinfections (e.g., CMV), and ART.[90] These effects and increased rates of cell turnover result in premature telomere shortening in those with HIV, particularly in T cells.[91] Telomerase also has profound effects on mitochondrial health that may play a role in premature aging in those with HIV.[92]

Proteostasis. HIV also has marked effects on autophagy and other proteostatic networks within and between cells.[93,94] These effects are propagated by specific, HIV-encoded protein products (nef and env) but may differentially affect specific cell types.[93]

In summary, studying the interactions between HIV and aging requires careful attention to the biology of the virus and its impact on immunity, as well as potential confounders, such as ART, cohort effects, and common risk factors for disease (e.g., cigarette smoking, social isolation). The interaction of HIV biology with the biology of aging is likely to shed light on both HIV and geroscience, and HIV^+ subjects are an excellent population in which to consider antiaging interventions to assess their effect on the development of the aged phenotype.

Diabetes

Type 2 diabetes, by far the most common type in older adults, is an age-related disease. The prevalence of diabetes is 33% among people in the United States aged 65 years or older, and in addition nearly 50% of older people meet criteria for prediabetes.[95] The incidence of newly diagnosed diabetes is the highest among those aged 65–79 years. Older adults with diabetes mellitus are susceptible to all the usual complications of diabetes (reviewed in Ref. 96). Rates of end-stage renal disease, loss of vision, myocardial infarction,[97] stroke, peripheral vascular disease, and peripheral neuropathy all increase with age in the absence of diabetes. However, the presence of diabetes greatly increases the risk for these health problems in older adults (summarized in Ref. 98), a clear basis for viewing diabetes as a driver of age-related diseases.

On the other hand, generalizations need to be examined in detail, since some features of diabetes that appear to resemble accelerated aging in fact have important pathophysiological differences from aging; some features of diabetes do not appear to accelerate aging. For example, some severe microvascular complications of diabetes, such as proliferative retinopathy and end-stage nephropathy (Kimmelstein–Wilson lesions), are pathologically distinct from eye and kidney changes with age in the absence of diabetes. Another relevant example is insulin resistance, which contributes to hyperglycemia in human type 2 diabetes. However, insulin resistance is also an adaptive/protective response, and animal models of insulin resistance often live significantly longer.[99] Conversely, numerous models with enhanced insulin sensitivity live normal or shorter life spans. The intersection between insulin resistance and aging may not be relevant to accelerated aging in diabetes, although impaired insulin secretion in diabetes may share common mechanisms with aging.

The pathophysiology of type 2 diabetes is unknown, but it appears to occur as a result of a complex interaction among genetic, lifestyle, and aging influences (see Fig. 2 in Ref. 138). A central feature of this model is a decline of β cell function and insulin secretion with aging, consistently observed in rodents and humans.[100] Aging effects include a decline of both pancreatic islet β cell proliferation and β cell turnover.[101,102] One example is the inability of old mice to increase islet mass and β cell proliferation in response to a high-fat diet, as is observed in young mice.[103] Exposure to high concentrations of glucose *in vitro* can lead to apoptosis of β cells, evidence of glucose toxicity,[100] to which older rodents are more susceptible.[101]

Pancreatic islet β cell proliferation appears to be dependent on cell cycle regulation. There is a substantial increase in expression of the cell cycle regulator p16 in islet tissue from older mice who demonstrate the age-related decline in islet proliferation. Overexpression of p16 markedly reduces islet proliferation in younger mice to a level similar to

that observed in older mice, and knockout of p16, preventing p16 from increasing with aging, appears to reverse the age-related decline of islet cell proliferation in this model.[104] Furthermore, p16 is one of the proteins produced from the *CDKN2a* locus. Genetic variation at this locus has emerged as a consistent association with type 2 diabetes risk from genome-wide scanning studies in humans.[105–108]

Findings from humans parallel age-related changes observed in rodents, including diminished insulin secretion *in vitro* and *in vivo*, diminished proliferative capacity, and increased sensitivity to the apoptotic effects of high glucose exposure.[100,109] In the setting of the age-related impairment of β cell function, there is a maladaptive response to lifestyle-related insulin resistance, leading to more impaired insulin secretion and progression to impaired glucose tolerance (prediabetes) and type 2 diabetes.[110] Glucose toxicity from chronic exposure to hyperglycemia, in turn, can contribute directly to insulin resistance and to further impairment of pancreatic β cell function. In this way, hyperglycemia of diabetes may drive further worsening of β cell function and proliferation associated with aging.

Diabetes links directly to the seven pillars of aging: epigenetics, inflammation/senescence, proteostasis, stem cells, metabolism, stress response, and macromolecular damage. Thus, diabetes may augment/enhance the pillars of aging, leading to premature or accelerated appearance of multiple age-specific conditions.

Hyperglycemia in diabetes is a disturbance of metabolism that alters proteins (acromolecular damage) and proteostasis by creating advanced glycation end products, which increase oxidative stress, leading to activation of kinases and increased production of proinflammatory mediators.[111] These pathways also deplete endothelial and neural nitric oxide, leading to endothelial dysfunction.

Type 2 diabetes increases the risk for both vascular dementia and Alzheimer's disease.[96,112–114] Diabetes is also associated with an increased risk of MCI[115] and an increased rate of conversion from MCI to dementia.[116] Diabetes and Alzheimer's disease pathology can exert synergistic effects with age on the brain vasculature, blood flow, and delivery of substrates necessary for cognition.[117] Hyperglycemia increases production of AGEs and their receptors in the brain, and both type 2 diabetes and Alzheimer's disease can reduce brain cholesterol synthesis. People with diabetes may have brain areas of glucose hypometabolism, gray matter atrophy, and reduced blood flow in a pattern similar to that seen with Alzheimer's disease.[117,118] Both peripheral insulin resistance and brain insulin resistance have been hypothesized to play important roles in neurocognitive dysfunction and dementia.[119] For example, mice with knockout of the insulin receptor in the brain show increased tau phosphorylation. Postmortem brain tissue has shown the presence of some biochemical features reminiscent of insulin resistance in the hippocampal formation of persons with AD compared with normal controls, and this insulin resistance is associated with pathology that involves both Aβ oligomers and fibrillar amyloid plaques.

There are notable age-associated changes in specific aspects of cardiac structure and cardiovascular function. Diabetes also has a major impact on the heart[120,121] and can accelerate the changes with aging. For example, diabetes can dramatically worsen age-related changes in diastolic dysfunction.[120,121]

Similarly, there are substantial interactions of aging and diabetes on blood vessels. Inflammation and oxidative stress associated with aging and diabetes appear to play synergistic roles in the vasculature. Aging arteries exhibit a chronic inflammatory profile resulting from increased superoxide availability similar to that seen with diabetes, leading to intrinsic cell stiffness in the vascular smooth muscle and endothelial dysfunction.[122,123] There may also be an important role for adult stem cells located in perivascular areas in the endothelial dysfunction.

Increased leukocyte trafficking in response to hyperglycemia and insulin resistance has been linked with damage to blood vessels and surrounding tissue in diabetes, owing to the production of toxic mediators by activated leukocytes.[124–127] In addition, an inflammatory response characterized by enhanced endothelial adhesiveness and increased leukocyte–endothelium interactions occurs in the microvasculature during metabolic disorders such as diabetes. Loss of physiologic endothelial nitric oxide appears to be an important mechanism for this vascular inflammation,[127–129] which is likely to be a key contributing factor to accelerated aging. More work is needed to understand the cellular mechanisms by which diabetes causes microvascular dysfunction.

Another example of how diabetes may drive age-related deterioration is in the kidney. Older age is a risk factor for end-stage kidney disease, the most common cause of which is diabetes. Conversely, diabetes induces kidney cell senescence independent of age.[130] Diabetes is associated with increased oxidative stress in the kidney that is augmented by aging.[131] In both diabetes and aging, monocyte infiltration is commonly seen in the kidney. Kidney cell nuclear localization of NF-κB, a master regulator of cytokine expression, is increased in aging rodents.[132] An inflammatory response appears to contribute to the demise of type 2 diabetic mice. Infusion of early endothelial outgrowth cells seems to improve senescence, induce autophagy, and ameliorate kidney injury in diabetic mice,[133] and infusion of bone marrow cells from young mice ameliorates senescent changes in the kidney in old mice.[134] Thus, stem cells may play a role in protecting against kidney damage in aging diabetic mice. In addition, DNA damage occurs in the kidney in diabetes and aging. Epigenetic acetylation markers are increased within genes related to inflammation in peripheral blood monocytes from diabetic patients with renal and retinal damage.[135]

Finally, the glucose-lowering drugs metformin[136] and acarbose[137] both extend life span in animal models. While the mechanism by which they do it is not clear, these findings suggest a significant overlap between the molecular underpinnings of diabetes and those of aging. Further studies on how these drugs interact with each of these processes will likely shed further light on the complex interrelations between type 2 diabetes mellitus and aging.

Discussion

The summit provided ample time for in-depth discussion of many aspects of the interrelations between disease and aging. Necessarily, not all these elements have been included in this summary. However, several major overarching points became clear during these discussions. First and foremost, it has become apparent that, while geroscience offers a window into the mechanistic overlap between aging and chronic disease, the initial focus on aging being the main risk factor for disease needs to be revisited in at least two ways. First, as exemplified by the title of the summit, the relationship is a two-way street: not only is aging the major risk factor for disease, but diseases might also be major risk factors for accelerating physiological aging phenotypes. Second, the geroscience hypothesis should expand to encompass aging physiology as well as chronic disease, resulting in a greater emphasis on health in general.

Several groups have recently identified a finite number of major pillars that are either known or suspected of driving the aging process.[9,10] As the discussions in New York City indicate, many of these pillars are directly or indirectly affected by exposure to chronic diseases and/or their treatments. As a result, it is reasonable to suspect that these pillars are involved in the development of diverse comorbidities later in life, leading to diminished health and quality of life in patients experiencing those diseases. As such, it becomes clear that the physiological impact of diseases (as well as treatments against them), such as cancer, HIV, diabetes, and many others can result in an acceleration of the phenotypes associated with natural aging. Among those phenotypes, an increased susceptibility to additional major chronic diseases is paramount. In this sense, the geroscience hypothesis closes the loop between aging and chronic disease, suggesting that interventions designed to slow the rate of aging may ameliorate the long-term outcome of chronic diseases and their therapeutic management. This may be particularly the case when those diseases affect individuals at an earlier age. Of course, many questions remain.

- A deeper understanding is still needed about the basic biology of each disease and of aging. While it is often argued that an understanding of the basic biology is not necessarily a *sine que non* for development of effective interventions, it is clear that a further understanding of both disease and aging at the molecular and cellular levels will help us better develop comprehensive approaches to treating chronic diseases.
- A further examination of the role of aging and disease in defining the "genes × environment = phenotype" equation for each disease's susceptibility is also a need. It is interesting to consider that while aging increases susceptibility to most such diseases, individuals vary in this regard on the basis of each individual's specific genes and environmental context, which leads to the development of different diseases in each individual. In this regard, early exposure to a particular disease might cause a preferential exacerbation of one or more pillars

of aging, and, as such, the susceptibility later in life might be skewed toward diseases that depend more heavily on those pillars that were affected. This should be an area to investigate in further detail via detailed epidemiological and clinical approaches.

- Do these diseases change the rate of aging or the starting set-point? As discussed earlier, it has been suggested that, at least in the case of HIV/AIDS, infection with the virus leads to an immediate resetting of at least some parameters that define aging, apparently with little or no effect on the later trajectory of the parameter. It is currently unknown whether a similar situation occurs in additional parameters or in other diseases. For example, it is known that cancer chemo- and radiotherapies lead to a rapid accumulation of senescent cells. Many of these are cleared over time by the immune system, but there are residual cells not cleared that could have effects on tissue physiology later in life, including the possibility of senescence-driven senescence in neighboring cells. This in turn could increase susceptibility to diseases that depend heavily on cell senescence, such as diabetes, osteoarthritis, atherosclerosis, fibrosis, sarcopenia, or others.
- Early exposure to disease should be considered as a possible confounder in studies of interventions that may slow the rate of aging. Because these early exposures might activate some individual aging pillars more than others, it is important to consider that responsiveness to any given intervention will then be dependent on early exposures. On the brighter side, a further understanding of these interrelationships should facilitate personalized interventions geared to the needs of each individual.

In closing, there is an important consideration that begs for focused research: should age-retarding interventions be administered in conjunction with disease-fighting therapies? As has been discussed, all therapies are expected to leave sequelae, and these are likely to affect the individual's susceptibility to additional diseases later in life. This is particularly relevant in cases such as cancer, where the traditional armamentarium focuses on trying to destroy a cell that, other than its unbridled capacity for proliferation, very much resembles other dividing cells in the body. The secondary effects of these therapies have long been recognized as being close to unacceptable. As major strides are being made to identify interventions that address the aging process directly, it becomes a burning question to consider whether any such interventions would be advisable in patients suffering from diseases known or suspected to lead to accelerated aging. Would it be advisable, for example, to provide senolytics (as defined above, and after proper vetting of their modes of actions and secondary effects) to cancer patients concomitantly or immediately following chemo- or radiotherapy?

The shared physiological end result of natural aging and disease-accelerated aging provide yet another opportunity for cross-disciplinary collaborations, one of the goals of the organizers of the summit, the Trans-NIH GeroScience Interest Group. Recognizing that health encompasses more than absence of disease, a concerted effort in this area should provide benefits for disease patients and the elderly alike, further advancing the goal of biomedicine: to provide health to the entire spectrum of the human population.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Gerteis, J. *et al.* 2014. *Multiple Chronic Conditions Chartbook.* AHRQ Publications No. Q14-0038. Rockville, MD: Agency for Healthcare Research and Quality.
2. Barnes, P.J. *et al.* 2015. Mechanisms of development of multimorbidity in the elderly. *Eur. Respir. J.* **45:** 790–806.
3. Johnson, T.E. 2013. 25 years after age-1: genes, interventions and the revolution in aging research. *Exp. Gerontol.* **48:** 640–643.
4. Longo, V.D. *et al.* 2015. Interventions to slow aging in humans: are we ready? *Aging Cell* **14:** 497–510.
5. Sierra, F. 2016. The emergence of geroscience as an interdisciplinary approach to the enhancement of health span and life span. *Cold Spring Harb. Perspect. Med.* **6:** a025163.
6. Austad, S.N. 2016. The geroscience hypothesis: is it possible to change the rate of aging? In *Advances in Geroscience.* F. Sierra & R. Kohanski, Eds.: 1–36. Springer.
7. López-Otín, C. *et al.* 2013. The hallmarks of aging. *Cell* **153:** 1194–1217.
8. Burch, J.B. *et al.* 2014. Advances in geroscience: impact on healthspan and chronic disease. *J. Gerontol. A. Biol. Sci. Med. Sci.* **69**(Suppl. 1): S1–S3.
9. López-Otín, C. *et al.* 2016. Metabolic control of longevity. *Cell* **166:** 802–821.

10. Kennedy, B.K. *et al.* 2014. Geroscience: linking aging to chronic disease. *Cell* **159:** 709–713.
11. Oeffinger, K.C. *et al.* 2006. Chronic health conditions in adult survivors of childhood cancer. *N. Engl. J. Med.* **355:** 1572–1582.
12. Mohile, S.G. *et al.* 2009. Association of a cancer diagnosis with vulnerability and frailty in older Medicare beneficiaries. *J. Natl. Cancer Inst.* **101:** 1206–1215.
13. Miller, C.J. *et al.* 2014. Adjudicated morbidity and mortality outcomes by age among individuals with HIV infection on suppressive antiretroviral therapy. *PLoS One* **9:** e95061.
14. Deeks, S.G. & A.N. Phillips. 2009. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ* **338:** a3172.
15. Morley, J.E. 2008. Diabetes and aging: epidemiological overview. *Clin. Geriatr. Med.* **24:** 395–405.
16. Barzilai, N. *et al.* 2012. The critical role of metabolic pathways in aging. *Diabetes* **61:** 1315–1322.
17. Smith, B.D. *et al.* 2009. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J. Clin. Oncol.* **27:** 2758–2765.
18. Parry, C. *et al.* 2011. Cancer survivors: a booming population. *Cancer Epidemiol. Biomarkers Prev.* **20:** 1996–2005.
19. Scher, K.S. & A. Hurria. 2012. Under-representation of older adults in cancer registration trials: known problem, little progress. *J. Clin. Oncol.* **30:** 2036–2038.
20. Talarico, L. *et al.* 2004. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J. Clin. Oncol.* **22:** 4626–4631.
21. Hurria, A. *et al.* 2016. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *J. Clin. Oncol.* **34:** 2366–2371.
22. Extermann, M. *et al.* 2012. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer* **118:** 3377–3386.
23. Pinder, M.C. *et al.* 2007. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J. Clin. Oncol.* **25:** 3808–3815.
24. Lichtman, S.M. *et al.* 2012. Paclitaxel efficacy and toxicity in older women with metastatic breast cancer: combined analysis of CALGB 9342 and 9840. *Ann. Oncol.* **23:** 632–638.
25. Mulrooney, D.A. *et al.* 2009. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ* **339:** b4606.
26. Baker, F. *et al.* 2003. Health-related quality of life of cancer and noncancer patients in Medicare managed care. *Cancer* **97:** 674–681.
27. Keating, N.L. *et al.* 2005. Physical and mental health status of older long-term cancer survivors. *J. Am. Geriatr. Soc.* **53:** 2145–2152.
28. Reeve, B.B. *et al.* 2009. Impact of cancer on health-related quality of life of older Americans. *J. Natl. Cancer Inst.* **101:** 860–868.
29. Weaver, K.E. *et al.* 2012. Mental and physical health-related quality of life among U.S. cancer survivors: population estimates from the 2010 National Health Interview Survey. *Cancer Epidemiol. Biomarkers Prev.* **21:** 2108–2117.
30. Courneya, K.S. *et al.* 2007. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J. Clin. Oncol.* **25:** 4396–4404.
31. Hornsby, W.E. *et al.* 2014. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. *Acta Oncol.* **53:** 65–74.
32. Segal, R.J. *et al.* 2009. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J. Clin. Oncol.* **27:** 344–351.
33. van Waart, H. *et al.* 2015. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. *J. Clin. Oncol.* **33:** 1918–1927.
34. Buttiglieri, S. *et al.* 2011. The aging effect of chemotherapy on cultured human mesenchymal stem cells. *Exp. Hematol.* **39:** 1171–1181.
35. Sanoff, H.K. *et al.* 2014. Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer. *J. Natl. Cancer Inst.* **106:** dju057.
36. Beeharry, N. & D. Broccoli. 2005. Telomere dynamics in response to chemotherapy. *Curr. Mol. Med.* **5:** 187–196.
37. Yoon, S.Y. *et al.* 2007. Telomere length shortening of peripheral blood mononuclear cells in solid-cancer patients undergoing standard-dose chemotherapy might be correlated with good treatment response and neutropenia severity. *Acta Haematol.* **118:** 30–37.
38. Diker-Cohen, T. *et al.* 2013. The effect of chemotherapy on telomere dynamics: clinical results and possible mechanisms. *Leuk. Lymphoma* **54:** 2023–2029.
39. Unryn, B.M. *et al.* 2006. Acceleration of telomere loss by chemotherapy is greater in older patients with locally advanced head and neck cancer. *Clin. Cancer Res.* **12:** 6345–6350.
40. Franceschi, C. & J. Campisi. 2010. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J. Gerontol. A Biol. Sci. Med. Sci.* **69**(Suppl. 1): S4–S9.
41. Redon, C.E. *et al.* 2010. Tumors induce complex DNA damage in distant proliferative tissues *in vivo*. *Proc. Natl. Acad. Sci. U.S.A.* **107:** 17992–17997.
42. Mantovani, A. *et al.* 2008. Cancer-related inflammation. *Nature* **454:** 436–444.
43. Watt, D.G. *et al.* 2015. Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. *Surgery* **157:** 362–380.
44. Kim, J.H. *et al.* 2014. Mechanisms of radiation-induced normal tissue toxicity and implications for future clinical trials. *Radiat. Oncol. J.* **32:** 103–115.
45. Velarde, M.C. *et al.* 2013. Senescent cells and their secretory phenotype as targets for cancer therapy. *Interdiscip. Top. Gerontol.* **38:** 17–27.
46. Couzin-Frankel, J. 2013. Breakthrough of the year 2013. Cancer immunotherapy. *Science* **342:** 1432–1433.
47. Gravekamp, C. 2011. The impact of aging on cancer vaccination. *Curr. Opin. Immunol.* **23:** 555–560.

48. Gravekamp, C. 2009. The importance of the age factor in cancer vaccination at older age. *Cancer Immunol. Immunother.* **58:** 1969–1977.
49. Chandra, D. *et al.* 2013. Myeloid-derived suppressor cells have a central role in attenuated *Listeria monocytogenes*-based immunotherapy against metastatic breast cancer in young and old mice. *Br. J. Cancer* **108:** 2281–2290.
50. Castro, F. *et al.* Vaccination with Mage-b DNA induces CD8 T-cell responses at young but not old age in mice with metastatic breast cancer. *Br. J. Cancer* **101:** 1329–1337.
51. Suzuki, E. *et al.* 2005. Gemcitabine selectively eliminates splenic Gr-1+/CD11b+ myeloid suppressor cells in tumor-bearing animals and enhances antitumor immune activity. *Clin. Cancer Res.* **11:** 6713–6721.
52. Gabrilovich, D.I. and S. Nagaraj 2009. Myeloid-derived suppressor cells as regulators of the immune system. *Nat. Rev. Immunol.* **9:** 162–174.
53. Li, H. *et al.* 2009. Cancer-expanded myeloid-derived suppressor cells induce anergy of NK cells through membrane-bound TGF-β1. *J. Immunol.* **182:** 240–249.
54. Serafini, P. *et al.* 2008. Myeloid-derived suppressor cells promote cross-tolerance in B-cell lymphoma by expanding regulatory T cells. *Cancer Res.* **68:** 5439–5449.
55. Kroemer, G. *et al.* 2013. Immunogenic cell death in cancer therapy. *Ann. Rev. Immunol.* **31:** 51–72.
56. Hearps, A. *et al.* 2016. HIV and aging: parallels and synergistic mechanisms leading to premature disease and functional decline. In *Advances in Geroscience.* F. Sierra & R. Kohansky, Eds.: 509–550. Springer International.
57. Althoff, K.N. *et al.*; Veterans Aging Cohort Study (VACS). 2015. Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. *Clin. Infect. Dis.* **60:** 627–638.
58. High, K.P. *et al.*; OAR Working Group on HIV and Aging. 2012. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *J. Acquir. Immune Defic. Syndr.* **60**(Suppl. 1): S1–S18.
59. Erlandson, K.M. *et al.* 2014. Functional impairment, disability, and frailty in adults aging with HIV-infection. *Curr. HIV/AIDS Rep.* **11:** 279–290.
60. Greene, M. *et al.* 2015. Geriatric syndromes in older HIV-infected adults. *J. Acquir. Immune Defic. Syndr.* **69:** 161–167.
61. Schrack, J.A. *et al.* 2015. Multicenter AIDS cohort study. Accelerated longitudinal gait speed decline in HIV-infected older men. *J. Acquir. Immune Defic. Syndr.* **70:** 370–376.
62. Chan, P. *et al.* 2016. Cognitive impairment and persistent CNS injury in treated HIV. *Curr. HIV/AIDS Rep.* **13:** 209–217.
63. Saylor, D. *et al.* 2016. HIV-associated neurocognitive disorder—pathogenesis and prospects for treatment. *Nat. Rev. Neurol.* **12:** 234–248.
64. Morgan, E.E. *et al.* 2012. Synergistic effects of HIV infection and older age on daily functioning. *J. Acquir. Immune Defic. Syndr.* **61:** 341–348.
65. Rodriguez-Penney, A.T. *et al.* 2013. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. *AIDS Patient Care STDS* **27:** 5–16.
66. So-Armah, K.A. *et al.*; VACS Project Team. 2016. Do biomarkers of inflammation, monocyte activation, and altered coagulation explain excess mortality between HIV infected and uninfected people? *J. Acquir. Immune Defic. Syndr.* **72:** 206–213.
67. Hearps, A.C. *et al.* 2014. Inflammatory co-morbidities in HIV+ individuals: learning lessons from healthy ageing. *Curr. HIV/AIDS Rep.* **11:** 20–34.
68. Svicher, V. *et al.* 2014. HIV compartments and reservoirs. *Curr. HIV/AIDS Rep.* **11:** 186–194.
69. Crowell, T.A. & H. Hatano. 2015. Clinical outcomes and antiretroviral therapy in 'elite' controllers: a review of the literature. *J. Virus Erad.* **1:** 72–77.
70. Appay, V. & D. Sauce. 2016. Assessing immune aging in HIV-infected patients. *Virulence* **16:** 1–10.
71. Eberhard, J.M. *et al.* 2016. Partial recovery of senescence and differentiation disturbances in $CD8^+$ T cell effector-memory cells in HIV-1 infection after initiation of antiretroviral treatment. *Clin. Exp. Immunol.* **186:** 227–238.
72. Cobos Jiménez, V. *et al.*; AGEhIV Study Group. 2016. T-cell activation independently associates with immune senescence in HIV-infected recipients of long-term antiretroviral treatment. *J. Infect. Dis.* **214:** 216–225.
73. Xu, M. *et al.* 2016. Transplanted senescent cells induce an osteoarthritis-like condition in mice. *J. Gerontol. A Biol. Sci. Med. Sci.* pii: glw154.
74. Zhu, Y. *et al.* 2015. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell* **14:** 644–658.
75. Deleage, C. *et al.* 2016. Impact of early cART in the gut during acute HIV infection. *JCI Insight* **1:** e87065.
76. Wang, H. & D.P. Kotler. 2014. HIV enteropathy and aging: gastrointestinal immunity, mucosal epithelial barrier, and microbial translocation. *Curr. Opin. HIV AIDS* **9:** 309–316.
77. Trøseid, M. *et al.* 2014. Microbial translocation and cardiometabolic risk factors in HIV infection. *AIDS Res. Hum. Retroviruses* **30:** 514–522.
78. Marioni, R.E. *et al.* 2015. The epigenetic clock is correlated with physical and cognitive fitness in the Lothian Birth Cohort 1936. *Int. J. Epidemiol.* **44:** 1388–1396.
79. Rickabaugh, T.M. *et al.* 2015. Acceleration of age-associated methylation patterns in HIV-1-infected adults. *PLoS One* **10:** e0119201.
80. Gross, A.M. *et al.* 2016. Methylome-wide analysis of chronic HIV infection reveals five-year increase in biological age and epigenetic targeting of HLA. *Mol. Cell* **62:** 157–168.
81. Horvath, S. & A.J. Levine. 2015. HIV-1 infection accelerates age according to the epigenetic clock. *J. Infect. Dis.* **212:** 1563–1573.
82. Weinstein, T.L. & X. Li. 2016. The relationship between stress and clinical outcomes for persons living with HIV/AIDS: a systematic review of the global literature. *AIDS Care* **28:** 160–169.
83. Panagiotakopoulos, L. *et al.* 2015. HIV-1 proteins accelerate HPA axis habituation in female rats. *Physiol. Behav.* **150:** 8–15.
84. Willig, A.L. & E.T. Overton. 2016. Metabolic complications and glucose metabolism in HIV infection: a review of the evidence. *Curr. HIV/AIDS Rep.* **13:** 289–296.
85. Herrin, M. *et al.* 2016. Weight gain and incident diabetes among HIV-infected veterans initiating antiretroviral

therapy compared with uninfected individuals. *J. Acquir. Immune Defic. Syndr.* **73:** 228–236.
86. Yuh, B. *et al.* 2015. Weight change after antiretroviral therapy and mortality. *Clin. Infect. Dis.* **60:** 1852–1859.
87. Calza, L. *et al.* 2016. Clinical management of dyslipidaemia associated with combination antiretroviral therapy in HIV-infected patients. *J. Antimicrob. Chemother.* **71:** 1451–1465.
88. Pérez-Matute, P. *et al.* 2013. Role of mitochondria in HIV infection and associated metabolic disorders: focus on non-alcoholic fatty liver disease and lipodystrophy syndrome. *Oxid. Med. Cell. Longev.* **2013:** 493413.
89. Payne, B.A. *et al.* 2015. Mitochondrial DNA mutations in ageing and disease: implications for HIV? *Antivir. Ther.* **20:** 109–120.
90. Torres, R.A. & W. Lewis. 2014. Aging and HIV/AIDS: pathogenetic role of therapeutic side effects. *Lab. Invest.* **94:** 120–128.
91. Effros, R.B. 2011. Telomere/telomerase dynamics within the human immune system: effect of chronic infection and stress. *Exp. Gerontol.* **46:** 135–140.
92. Xie, Z. *et al.* 2015. Early telomerase inactivation accelerates aging independently of telomere length. *Cell* **160:** 928–939.
93. Espert, L. *et al.* 2015. Autophagy in *Mycobacterium tuberculosis* and HIV infections. *Front. Cell. Infect. Microbiol.* **5:** 49.
94. Dinkins, C. *et al.* 2015. Roles of autophagy in HIV infection. *Immunol. Cell Biol.* **93:** 11–17.
95. Menke, A. *et al.* 2015. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. *JAMA* **314:** 1021–1029.
96. Kirkman, M.S. *et al.* 2012. Diabetes in older adults: a consensus report. *J. Am. Geriatr. Soc.* **60:** 2342–2356.
97. Booth, G.L. *et al.* 2006. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet* **368:** 29–36.
98. Halter, J.B. *et al.* 2014. Diabetes and cardiovascular disease in older adults: current status and future directions. *Diabetes* **63:** 2578–2589.
99. Barzilai, N. & L. Ferrucci. 2012. Insulin resistance and aging: a cause or a protective response? *J. Gerontol. A Biol. Sci. Med. Sci.* **67:** 1329–1331.
100. Halter, J.B. 2011. Aging and insulin secretion. In *Handbook of the Biology of Aging.* 7th ed. E.J. Masoro & S.N. Austad, Eds.: 373–384. Elsevier Inc.
101. Maedler, K. *et al.* 2006. Aging correlates with decreased β-cell proliferative capacity and enhanced sensitivity to apoptosis: a potential role for Fas and pancreatic duodenal homeobox-1. *Diabetes* **55:** 2455–2462.
102. Rankin, M. & J. Kushner. 2009. Adaptive β-cell proliferation is severely restricted with advanced age. *Diabetes* **58:** 1365–1372.
103. Tschen, S.-I. *et al.* 2009. Age-dependent decline in β-cell proliferation restricts the capacity of β-cell regeneration in mice. *Diabetes* **58:** 1312–1320.
104. Krishnamurthy, J. *et al.* 2006. $p16^{ink4a}$ induces an age-dependent decline in islet regenerative potential. *Nature* **443:** 453–457.
105. Saxena, R. *et al.* 2007. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* **316:** 1331–1336.
106. Scott, L.J. *et al.* 2007. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* **316:** 1341–1345.
107. Steinthorsdottir, V. *et al.* 2007. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. *Nat. Genet.* **39:** 770–775.
108. Zeggini, E. *et al.* 2007. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* **316:** 1336–1341.
109. Chang, A.M. *et al.* 2006. Impaired beta-cell function in human aging: response to nicotinic acid-induced insulin resistance. *J. Clin. Endocrinol. Metab.* **91:** 3303–3309.
110. Chang, A.M. & J.B. Halter. 2003. Aging and insulin secretion. *Am. J. Physiol. Endocrinol. Metab.* **284:** E7–E12.
111. Brownlee, M. 2005. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* **54:** 1615–1625.
112. Craft, S. 2009. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch. Neurol.* **66:** 300–305.
113. Biessels, G.J. *et al.* 2006. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol.* **5:** 64–74.
114. Gudala, K. *et al.* 2013. Diabetes mellitus and risk of dementia: a meta-analysis of prospective observational studies. *J. Diabetes Investig.* **4:** 640–650.
115. Cheng, G. *et al.* 2012. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern. Med. J.* **42:** 484–491.
116. Cooper, C. *et al.* 2015. Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. *Am. J. Psychiatry* **172:** 323–334.
117. Takeda, S. *et al.* 2010. Diabetes-accelerated memory dysfunction via cerebrovascular inflammation and Aβ deposition in an Alzheimer mouse model with diabetes. *Proc. Natl. Acad. Sci. U.S.A.* **107:** 7036–7041.
118. Baker, L.D. *et al.* 2011. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch. Neurol.* **68:** 51–57.
119. Luke, E. *et al.* 2016. Complex mechanisms linking neurocognitive dysfunction to insulin resistance and other metabolic dysfunction. *Version 2. F1000Res.* **5:** 353.
120. From, A.M. *et al.* 2009. Changes in diastolic dysfunction in diabetes mellitus over time. *Am. J. Cardiol.* **103:** 1463–1466.
121. Huebschmann, A.G. *et al.* 2011. Exercise attenuates the premature cardiovascular aging effects of type 2 diabetes mellitus. *Vasc. Med.* **16:** 378–390.
122. Dai, D.F. *et al.* 2012. Mitochondria and cardiovascular aging. *Circ. Res.* **110:** 1109–1124.
123. North, B.J. & D.A. Sinclair. 2012. The intersection between aging and cardiovascular disease. *Circ. Res.* **110:** 1097–1108.
124. Panes, J. *et al.* 1996. Diabetes exacerbates inflammatory responses to ischemia–reperfusion. *Circulation* **93:** 161–167.
125. Salas, A. *et al.* 1998. Mechanisms responsible for enhanced inflammatory response to ischemia–reperfusion in diabetes. *Am. J. Physiol.* **275:** H1773–H1781.

126. Wang, Q. *et al.* 2014. Myeloperoxidase deletion prevents high-fat diet-induced obesity and insulin resistance. *Diabetes* **63:** 4172–4185.
127. Valerio, A. *et al.* 2006. TNF-α downregulates eNOS expression and mitochondrial biogenesis in fat and muscle of obese rodents. *J. Clin. Invest.* **116:** 2791–2798.
128. Kim, F. *et al.* 2008. Vascular inflammation, insulin resistance, and reduced nitric oxide production precede the onset of peripheral insulin resistance. *Arterioscler. Thromb. Vasc. Biol.* **28:** 1982–1988.
129. Kubes, P. *et al.* 1991. Nitric oxide: an endogenous modulator of leukocyte adhesion. *Proc. Nat. Acad. Sci. U.S.A.* **88:** 4651–4655.
130. Satriano, J.H. *et al.* 2010. Transition of kidney tubule cells to a senescent phenotype in early experimental diabetes. *Am. J. Physiol. Cell Physiol.* **299:** C374–C380.
131. Wu, J.R. *et al.* 2010. Induction of diabetes in aged C57B6 mice results in severe nephropathy. *Am. J. Pathol.* **176:** 2163–2176.
132. Li, F. *et al.* 2013. Autophagy attenuates diabetic glomerular damage through protection of hyperglycemia-induced podocyte damage. *PLoS One* **8:** e60546.
133. Patschan, D.K. *et al.* 2014. eEOC-mediated modulation of endothelial autophagy, senescence, and EnMT in murine diabetic nephropathy. *Am. J. Physiol. Renal Physiol.* **307:** F686–F694.
134. Yang, H.-C. *et al.* 2011. Cells derived from young bone marrow alleviate renal aging. *J. Am. Soc. Nephrol.* **22:** 2028–2036.
135. Miao, F. *et al.* 2014. Evaluating the role of epigenetic histone modifications in the metabolic memory of type 1 diabetes. *Diabetes* **63:** 1748–1762.
136. Martin-Montalvo, A. *et al.* 2013. Metformin improves healthspan and lifespan in mice. *Nat. Commun.* **4:** 2192.
137. Harrison, D.E. *et al.* 2014. Acarbose, 17-α-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. *Aging Cell* **13:** 273–282.
138. Hodes, R.J. *et al.* 2016. Disease drivers of aging. *Ann. N.Y. Acad. Sci.* **1386:** 45–68.