GeroScience (2017) 39:1–5
DOI 10.1007/s11357-016-9954-6

EDITORIAL

Geroscience and the trans-NIH Geroscience Interest Group, GSIG

Felipe Sierra · Ron Kohanski

Published online: 10 January 2017

Abstract Age is by far the major risk factor for most chronic diseases. This has been common knowledge since time immemorial. Aging encompasses the biological changes most often seen as declines of function and increasing burden of disease. The close linkage of these two has led people to believe that aging, like age, is immutable. It is only recently that research into the basic molecular and cellular mechanisms of aging has led to potential interventions that increase lifespan and appear to increase healthspan, as well. Geroscience is an interdisciplinary field that aims to understand the relationship between the biology of aging and the biology of age-related diseases. The "geroscience hypothesis" posits that manipulation of aging will delay (in parallel) the appearance or severity of many chronic diseases because these diseases share the same underlying major risk factor (age). The hope is that this will lead to health improvements in the older population with perhaps greater efficiency than can be achieved through the successful cure and management of diseases of aging as they arise individually or as comorbidities.

With those concepts in mind, the Geroscience Interest Group (GSIG) was launched as a trans-institute interest group within the NIH in November 2012. Here, we discuss the genesis of the trans-NIH group and the most salient activities that have occurred in the last 5 years.

F. Sierra (✉) · R. Kohanski
Division of Aging Biology, National Institute on Aging, NIH, Bethesda, MD, USA
e-mail: sierraf@nia.nih.gov

Keywords Geroscience · Aging · Healthspan · Longevity

Background

During a 2010 workshop titled "Indicators of Aging" organized by the Alliance for Aging Research, a discussion was held about the idea that aging is at the core of all chronic diseases, and one of us (FS) mentioned, without much pre-conceptualization, that since aging biology is at the core of all the diseases that concern them, then every institute within the NIH should have a Division of Aging Biology. The idea remained and over discussions between both authors in the ensuing months, this concept was further developed as a possible activity to be proposed across the entire NIH. As we refined the ideas and prepared to engage others, it became obvious that geroscience, as proposed in a successful application to the NIH by Gordon Lithgow et al. from the Buck Institute was a proper name for the initiative.

Additional discussions with the NIA Director, Dr. Richard Hodes, led to a plan to make a trial proposal to a small group of institute directors. The presentation in September 2011 led to a unanimous and enthusiastic response, and within a week or so, other institute directors had been contacted, and the response was again positive. Thus was born the Trans-NIH Geroscience Interest Group, GSIG (the acronym GIG had already been taken by the Genetics Interest Group, which is why an extra S is included), which currently includes

participation of institute director-designated representatives from 22 NIH Institutes.

Interestingly, the concepts of geroscience have long been understood both by scientists and the general public, as well as literature and the arts. However, the concept was slow in gaining recognition in medical spheres because of the ingrained notion that age is not a modifiable factor. While this is obviously true for chronological age (as the passage of time) it is also well recognized that good health at older ages can be attained by relatively simple interventions (which as behavioral changes, appear difficult for many people). Acceptance of age as the major risk factor for chronic diseases is implicit in the recommendations we receive if we visit a medical doctor for any malady: in addition to disease-specific interventions (statins, metformin, antidepressants), we are often counseled to "eat well, exercise moderately, and refrain from smoking." These are non-specific recommendations aimed at "healthier aging," but physicians seem loath to say so directly. What has changed the perceptions is the astonishing advances made in the last couple of decades by scientists focused on understanding the basic biological underpinnings of the aging process, independently of disease. This has led to a few publications, including those from the GSIG, that have attempted to classify the main hallmarks or pillars currently believed to be the main drivers of the aging process (López-Otín et al. 2013, Kennedy et al. 2014). These conceptual advances have worked synergistically with reports from the NIA-supported Interventions Testing Program, which aims to test, in a variety of animal models, mostly pharmacological interventions that lead to an increase in both lifespan and healthspan (Warner et al. 2000, Strong et al. 2016).

Early activities

Acceptance of the geroscience concept within the NIH proceeded at such a fast pace that an action plan was much less developed than the conceptual arguments used to form the group. An important strategic point was to keep the initial goals simple and attainable. This required a focus primarily on informational activities that would not require significant dollar investments on the part of participating institutes. Also, because the entire concept had been developed as a means to capitalize on the advances in basic aging research, the initial goal statement included in the web site (https://gsig.irp.nia.nih.gov) indicated that the focus was to be on basic biology, although we recognized the translational value of the effort. The immediate goal was to exchange ideas and inform each other of the ways in which different NIH institutes and centers could profit from paying more attention to aging as a modifiable risk factor for their diseases of interest. This led to monthly internal discussions, as well as a well-received seminar series that is open to the public.

Among other activities early on was a workshop focused on inflammation and age-related diseases, held at the NIH Campus in September 2012 (Howcroft et al. 2013). This in turn led to the publication of a funding opportunity (a program announcement) joined by 10 of the GSIG member Institutes. In the meantime, work began on preparing a major summit. Preparations for the summit included discussions both within the NIH and with a selected team of external advisors about the major topics to be discussed. These discussions led to the identification of seven pillars of aging, which formed the backbone for the summit. Interestingly, at about the same time, a group of European scholars published a paper titled *The Hallmarks of Aging* (López-Otín et al. 2013), which had significant overlaps with the GSIG effort. We referred to the GSIG paper as "pillars", to distinguish them from the "hallmarks". The summit itself was held in the biggest auditorium of the NIH Campus in October/November of 2013, and it was titled "Advances in Geroscience: Impact on Healthspan and Chronic Disease". The 44 scientific presentations were bookended by opening remarks from the NIH Director Dr. Francis Collins and closing remarks by the NIA Director Dr. Richard Hodes. It was attended by close to 700 scientists from academia, industry, advocacy groups, and others. Immediately after the sessions, a select group met to discuss future goals and proposals, which led to the publication of a position paper in the journal *Cell* in 2014 (Kennedy et al. 2014). The success of that effort led to pressures for the group to organize more summits, and indeed, a second summit was held in New York City in April 2016. This effort was done in conjunction with the New York Academy of Sciences, and it was focused on the opposite side of the coin: what are the molecular and cellular mechanisms that explain why certain diseases can lead to an acceleration of the aging process? A report from the effort is currently in press (Hodes et al. 2016).

Current activities

Current efforts are focused primarily on three areas where the GSIG recognizes an urgent need for further research: development of more appropriate animal models, enhancing the focus of geroscience on health irrespective of disease, and identification of suitable molecular and cellular biomarkers of the aging process. Taken together, these efforts aim at developing a deeper understanding of the basic biology driving all chronic diseases, and harnessing that knowledge for the betterment of health and well-being.

Development of appropriate animal models There are many reasons that potentially explain the low rate of success in translating findings from animal models to humans. Foremost among them is the over-reliance on mice, and more specifically, on a single strain of mice, C57Bl/6. This has been discussed by many authors (http://www.slate.com/articles/health_and_science/the_mouse_trap/2011/11/lab_mice_are_they_limiting_our_understanding_of_human_disease_.html). Recently, the NIH has made an effort to focus on one important variable that might help in improving translatability of animal models: sex. Indeed, much research is done only in one sex (mostly males), or without reporting about the sex of the subjects, and the fact that physiology is quite different between males and females makes this a powerfully important experimental parameter. However, in our view, there was also a missed opportunity to emphasize research in age-relevant animals because the physiology of old animals is vastly different from that of their younger counterparts. The majority of laboratory studies using vertebrates are done with young animals which may be appropriate to model the biology of young humans. Conversely, older animals may be more appropriate for studies of human conditions and diseases prevalent in older humans, as suggested in some published work (Bouchlaka et al. 2013). However, there are two primary obstacles to such studies: cost and time. Nevertheless, investigations with older animals may be critical to advancing basic research and translational studies from animal models to older human populations. To test this assumption, the members of the GSIG published a request for applications RFA AG-16-020 and now support 12 demonstration projects (as test cases) to ask: 1. Does age of the model organism influence experimental outcomes? 2. Are older animals' better models in studies for conditions, interventions, diseases, or environmental exposures for which aging is a risk factor of the human condition? The participating NIH institutes include NCI, NIAID, NIDCR, NIEHS, and NINDR with matching funds from NIA.

In addition, there are efforts within the NIA (independent of GSIG) to develop better translational animal models for aging research, including pet dogs and marmosets. In both cases, these species have lifespans of 10–15 years, within the range of NIH-funded research programs (usually renewable in blocks of 5 years). Two attractive features of research on pet dogs are their close relationship with humans and the existence of multiple breeds, while marmosets are intriguing because they are non-human primates that—like dogs—share with humans many conditions and diseases of aging, and in which health can be assessed in quantitative ways. While these animals will not be manipulated genetically—as are laboratory mice—they are important "bridges" for translational studies.

On the other end of the spectrum—both evolutionarily and in terms of lifespan, it is also worth mentioning the recent development of the *Caenorhabditis* Interventions Testing Program (CITP). The genus is phylogenetically far from humans but genetically more diverse, allowing for testing the robustness of potential interventions.

Refocusing our efforts on health Geroscience sits at the intersection of aging and disease, and it is appropriate to ask where geroscience—as an emergent field—resides in the context of NIH and its development. Historically, the nineteenth century roots of the NIH are in health care (hygiene), and the public health service emerged from these roots on the cusp of the twentieth century (https://history.nih.gov/exhibits/history/index.html). The advances in basic biology during the early twentieth century brought together basic research and medical practice, attempting to produce vaccines and understand and treat cancer among other major health concerns. There followed an expansion of the NIH mostly through creation of disease-oriented institutes and centers, and the tissues and organs most directly affected by those diseases (some institutes, for example NIA, NICHD, NHGRI, NIGMS, and NIBIB, are based on different paradigms and are less focused on specific diseases). Each institute brings together basic research and technology in the context of clinically important health issues. This disease-orientation was driven by

the confluence of clinical considerations and public perceptions: diseases are clinically described, have biological causes, and the burdens imposed by them need to be lifted as best can be done by the available science and medicine for which the government provides support through the NIH and other entities.

How does geroscience fit in this milieu, since it is an emerging research discipline and not a research institute, and its scope includes many chronic and acute diseases as well as all organs, tissues and cells of the body? Geroscience hopes to address the clinically important issue of healthy aging which is of concern across all institutes of the NIH. The founding logic is that age is the major risk factor for chronic diseases and degenerative conditions. Age, as the immutable passage of time, is accompanied by "aging" which is the process of diverse biological change that underpins "age" as a risk. Although increased age is the parameter that can be epidemiologically linked to increased prevalence of chronic disease, aging is the underlying biological risk factor that can, at least to some extent, be modified—as is the case for other risk factors linked to specific diseases (e.g., smoking for lung cancer). Thus, altering aging—for which the biological mechanisms are of specific interest to the National Institute on Aging—will affect multiple chronic diseases, and each of those is within the purview of one or more of the 27 institutes and centers of the NIH. The GSIG is therefore riding a wave of scientific and clinical interest in aging at the NIH, which has nearly doubled research investment in aging over the past 5 years, across all institutes, even after excluding research on Alzheimer's disease, which has received an additional boost. One immediate goal of the GSIG is to help the NIH institutes maintain awareness of each other's programs involving aging and promote synergies among them, where appropriate, and always under the broad NIH goal of "turning discovery into health."

The GSIG was formed around the idea that aging affects multiple chronic diseases. Through discussions within the group we came to understand that many diseases appear to accelerate aging. Two prominent examples of what might be called "reverse geroscience" are found in the life histories of people surviving early childhood cancers (Weaver et al. 2016), and from people infected by HIV at any age (Erlandson et al. 2014). As an initial effort to better understand this side of the two-way street, the GSIG partnered with the New York Academy of Sciences to organize a summit on ways in which chronic diseases might accelerate the aging process. The above two disease categories, plus diabetes, were chosen as the topics for this Summit on Disease Drivers of Aging (April 2016). Importantly, and logically, among the unknowns in disease drivers of aging is distinguishing between the age-acceleration due to the disease itself from that due to the treatment. The goal was to discuss the molecular and cellular changes behind the epidemiologically identified health risks left behind after those chronic diseases are either cured or contained, leading to decreased quality of life and increased susceptibility to frailty and other conditions otherwise affecting people at much later ages.

One of several outcomes of this summit is the recognized need to better identify biomarkers of aging, if we are to determine in molecular and cellular terms how diseases and treatments accelerate aging. The issue of biomarkers of aging has been a long-standing concern. Earlier attempts to identify such biomarkers, dating back more than three decades, may have fallen short due to an emphasis on predicting time to death as the metric and limitations in technologies. There is a great deal of recent and promising research on biomarkers of aging, in the laboratory and in epidemiological studies, so the concept might be worth revisiting from the perspective of geroscience.

Identifying biomarkers of the aging process Stepping back to the 2013 Geroscience Summit, the GSIG played a crucial role in the identification and promotion of the concept of biological pillars of the aging process in relationship to chronic disease. It is widely recognized that this was one of the first steps in our efforts to organize a new and rational approach to understanding the intersection between the biology of aging and disease susceptibility. In parallel with ongoing research on the biology of aging, there should be identification and validation of biomarkers of aging. As just stated, this is not a new endeavor. In the clinic, a parameter often used is a frailty index (of which there are several versions, see Fried et al. 2001, Rockwood and Mitnitski, 2011. These are composite indices that to a greater or lesser extent emphasize physical capacity and mental acuity. Frailty tends to be diagnosed later in life, and can be used to predict further functional decline and mortality (all-cause as well as disease-specific mortality). As such frailty measures report existing "damage" at a given time and predict more "damage" within a relatively short time-

frame. The frailty indices raise important questions for biomarkers of aging as follows: 1. Which of the pillars of geroscience and other information from the basic biology of aging or disease can we use for translation of biomarkers of aging from laboratory animals to humans? 2. How early in life can these biomarkers have diagnostic or predictive value? 3. Once candidate biomarkers are proposed, how will they be validated? 4. How will biomarkers of aging differ from biomarkers of disease? 5. Will biomarkers of aging be interpretable as indices of healthy aging?

A look at the future

The field of geroscience has come a long way from its inception. Today, it is widely recognized among researchers in various fields of aging, ranging from basic biology to clinical and behavioral research. It is also becoming a known term among investigators working on a variety of chronic diseases that affect predominantly the elderly, as some geriatrics societies have spawned their own Geroscience Interest Groups. Being a new field, mentions in PubMed are still rare, but the rate of increase (only 4 in 2014, 7 in 2015, and 57 as of October 2016) projects a bright future for the field. Similarly, the number of workshops and sessions at multiple venues has increased substantially in the last couple of years, so that currently, the demand for representation and organization of activities has been stressing the capacity of NIH personnel. Fortunately, other individuals and organizations are taking the torch from the GSIG and carrying it further. In that sense, the renaming of the *Journal of the American Aging Association* as "GeroScience" is an enormous accolade and recognition for the fledging field. We are optimistic that the new direction of the journal will continue to attract high quality research for publication, and will act as a synergistic vehicle to move forward the field of geroscience.

References

Bouchlaka MN, Sckisel GD, Chen M, Mirsoian A, Zamora AE, Maverakis E, Wilkins DE, Alderson KL, Hsiao HH, Weiss JM, Monjazeb AM, Hesdorffer C, Ferrucci L, Longo DL, Blazar BR, Wiltrout RH, Redelman D, Taub DD, Murphy WJ (2013) Aging predisposes to acute inflammatory induced pathology after tumor immunotherapy. J Exp Med 210: 2223–2237

Erlandson KM, Schrack JA, Jankowski CM, Brown TT, Campbell TB (2014) Functional impairment, disability, and frailty in adults aging with HIV-infection. Curr HIV/AIDS Rep 11: 279–290

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, MA MB, Cardiovascular health study collaborative research group (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56A:M146–M156

Hodes RJ, Sierra F, Austad SN, Epel E, Neigh GN, Erlandson KM, Schafer MJ, LeBrasseur NK, Wiley C, Campisi J, Sehl ME, Scalia R, Eguchi S, Kasinath BS, Halter JB, Cohen HJ, Demark-Wahnefried W, Ahles TA, Barzilai N, Hurria A, Hunt PW (2016) Disease drivers of aging. Ann N Y Acad Sci 1386(1):45–68. doi:10.1111/nyas.13299

Howcroft TK, Campisi J, Louis GB, Smith MT, Wise B, Wyss-Coray T, Augustine AD, McElhaney JE, Kohanski R, Sierra F (2013) The role of inflammation in age-related disease. Aging 5:84–93

Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, Franceschi C, Lithgow GJ, Morimoto RI, Pessin JE, Rando TA, Richardson A, Schadt EE, Wyss-Coray T, Sierra F (2014) Geroscience: linking aging to chronic disease. Cell 159:709–713

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153:1194–1217

Rockwood K, Mitnitski A (2011) Frailty defined by deficit accumulation and geriatric medicine defined by frailty. Clin Geriatr Med 27:17–26

Strong R, Miller RA, Antebi A, Astle CM, Bogue M, Denzel MS, Fernandez E, Flurkey K, Hamilton KL, Lamming DW, Javors MA, de Magalhães JP, McCord JM, Miller BF, Müller MM, Nelson JF, Ndukum J, Rainger GE, Richardson A, Sabatini DM, Salmon AB, Simpkins JW, Steegenga WT, Nadon NL, Harrison DE (2016) Longer lifespan in male mice treated with a weakly-estrogenic agonist, an antioxidant, an α-glucosidase inhibitor or a Nrf2-inducer. Aging Cell 15:872–884

Warner HR, Ingram D, Miller RA, Nadon NL, Richardson AG (2000) Meeting report: program for testing biological interventions to promote healthy aging. Mech Aging Dev 115: 199–208

Weaver KE, Leach CR, Leng X, Danhauer SC, Klepin HD, Vaughan L, Naughton M, Chlebowski RT, Vitolins MZ, Paskett E (2016) Physical functioning among women 80 Years of age and older with and without a cancer history. J Gerontol A Biol Sci Med Sci 71(Suppl 1):S23–S30