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Review

Translating advances from the basic biology of aging into clinical application

James L. Kirkland *

Robert and Arlene Kogod Center on Aging, Mayo Clinic, 200 First Street, S.W., Rochester, MN 55902, USA

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ABSTRACT

Recently, lifespan and healthspan have been extended in experimental animals using interventions that are potentially translatable into humans. A great deal of thought and work is needed beyond the usual steps in drug development to advance these findings into clinical application. Realistic pre-clinical and clinical trial paradigms need to be devised. Focusing on subjects with symptoms of age-related diseases or frailty or who are at imminent risk of developing these problems, measuring effects on short-term, clinically relevant outcomes, as opposed to long-term outcomes such as healthspan or lifespan, and developing biomarkers and outcome measures acceptable to regulatory agencies will be important. Research funding is a major roadblock, as is lack of investigators with combined expertise in the basic biology of aging, clinical geriatrics, and conducting investigational new drug clinical trials. Options are reviewed for developing a path from the bench to the bedside for interventions that target fundamental aging processes.

1. Introduction

The elderly are the fastest growing segment of the population. With advancing age, chronic diseases become increasingly prevalent. Aging is the single largest risk factor for stroke, heart attacks, cancers, diabetes, and most other chronic diseases (Research, 2012). Numbers of chronic diseases *per individual* increase with aging, causing loss of independence, frailty, and increased risk of death.

Rather than extending lifespan at all costs, the elderly appear to be more interested in an increased healthspan, the portion of the life-span during which function is sufficient to maintain autonomy, control, independence, productivity, and well-being, although few hard data are available about this important issue. Loss of autonomy and control predict mortality (Fry and Debats, 2006). Furthermore, the elderly are not fatalistic: they are not resigned to an old age of frailty (Fry, 2000). Although much more study is needed about what the elderly hope to gain from biomedical research, it seems that there is public interest in supporting research to enhance healthspan and compress the period of morbidity near the end of life. Prompted in part by an NIH conference in 2008, the basic biology of aging field has started to shift into placing increased emphasis on studying healthspan in animal models, rather than focusing almost exclusively on lifespan (Kirkland and Peterson, 2009; Tatar, 2009).

2. Healthspan

Limits to healthspan include disability, frailty, chronic diseases, and of course lifespan. Disability refers to functional deficits that are sequelae of diseases earlier in life, accidents, or developmental disorders. Frailty is an age-related clinical syndrome that entails loss of resilience and failure to recover from acute problems, such as pneumonia, stroke, influenza, heart attacks, dehydration, or fractures (Bandeen-Roche et al., 2006, 2009; Fried et al., 2001; Kanapuru and Ershler, 2009; Leng et al., 2007; Qu et al., 2009; Rockwood et al., 2006; Walston et al., 2002, 2006, 2009). Frailty can be diagnosed through clinically validated scales that are reasonably, but not completely, sensitive and specific. These scales involve combinations of assessments of weakness, fatigue, weight loss, low activity, and chronic disease and disability burden (Bandeen-Roche et al., 2006; Fried et al., 2001; Lucicesare et al., 2010; Rockwood and Mitnitski, 2011). Scales and biomarkers of frailty need to be developed for use in experimental animal models. This should be feasible in mammals, particularly since it has even been possible to develop parameters for evaluating frailty in an invertebrate, *Caenorhabditis elegans* (Iwasa et al., 2010).

The prevalence of frailty increases with aging (Bandeen-Roche et al., 2006, 2009; Fried et al., 2001; Kanapuru and Ershler, 2009; Leng et al., 2007; Lucicesare et al., 2010; Qu et al., 2009; Rockwood and Mitnitski, 2011; Rockwood et al., 2006; Walston et al., 2002, 2006, 2009). It predisposes to chronic diseases, loss of independence, and high mortality. Frailty is linked to the "geriatric syndromes" of sarcopenia, immobility, falling, cachexia, depression, and confusion, as well as the chronic inflammation implicated in the genesis of chronic disease. Age-related chronic diseases and frailty combine to result in poor response to treatments, such as chemotherapy, surgery,

Abbreviations: Senolytic, an agent that targets senescent cells; ADME, absorption, distribution, metabolism, and excretion of a drug; SASP, senescence-associated secretory phenotype; mTOR, mammalian target of rapamycin; JAK, Janus-activated kinase; GLP, good laboratory practices; GMP, good manufacturing practices; FDA, Food and Drug Administration; IND, investigational new drug.

* Tel.: +1 507 266 9151; fax: +1 507 293 3853.
E-mail address: Kirkland.james@mayo.edu.

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organ or stem cell transplantation, and rehabilitation. They can initiate a downward spiral of dysfunction that progresses rapidly to loss of independence, institutionalization, and death. Intriguingly, chronic inflammation is closely associated with frailty, most age-related chronic diseases, including dementias, depression, atherosclerosis, cancers, and diabetes, as well as advanced old age and cellular senescence. Whether and how chronic inflammation causally links these processes remains to be determined (Brown et al., 2001; Bruunsgaard and Pedersen, 2003; Bruunsgaard et al., 2003; Cesari et al., 2003; Ferrucci et al., 1999; Harris et al., 1999; Howren et al., 2009; Hu et al., 2004; Kanapuru and Ershler, 2009; Leng et al., 2007; Margolis et al., 2005; O'Connor et al., 2010; Pai et al., 2004; Pradhan et al., 2001; Schetter et al., 2010; Spranger et al., 2003; Srikrishna and Freeze, 2009; Tuomisto et al., 2006; Walston et al., 2002).

3. Do we have translatable interventions?

Although aging has long been recognized as the leading risk factor for chronic diseases and frailty, it has only recently become widely viewed as a potentially modifiable risk factor. Supporting this view are findings that: 1) maximum lifespan is extended and age-related diseases are delayed across species by a number of single gene mutations (Bartke, 2011), suggesting that the pathways affected by these mutations could be therapeutic targets. 2) Humans who live beyond age 100, a partly heritable trait, frequently have delayed onset of age-related diseases and disabilities (Lipton et al., 2010), leading to compression of morbidity and enhanced healthspan. 3) Rapamycin increases lifespan in mouse models (Harrison et al., 2009) and appears to delay cancers and age-related cognitive decline (Majumder et al., 2012). 4) Caloric restriction, which increases maximum lifespan, is associated with delayed onset of multiple chronic diseases in animal models (Anderson and Weindruch, 2012). 5) Factors produced by stem cells from young individuals ameliorate dysfunction in older individuals (Conboy et al., 2005; Lavasani et al., 2012). 6) Senescent cell accumulation is associated with chronic inflammation, which in turn promotes many age-related chronic diseases and frailty (Laberge et al., 2012). Importantly, senescent cell elimination enhances healthspan in mice, at least in progeroid mice (Baker et al., 2011). A pipeline is developing of yet more interventions that appear to enhance lifespan in rodent models. Many of these are promising, but not yet published.

Since interventions that increase lifespan and healthspan in mammals now exist, it appears plausible that, by targeting fundamental mechanisms of aging, clinical interventions might be developed that could delay or prevent age-related diseases and disabilities as a group, rather than one at a time. Even if a major chronic disease such as atherosclerotic heart disease was eradicated, as transformative as such an advance would be, it would only add 2 or 3 years to life expectancy (Fried et al., 2009; Olshansky et al., 1990). However, attacking the intersection between fundamental aging mechanisms and processes that lead to chronic diseases could delay age-related diseases and disabilities. This would have a substantially larger impact on healthspan and health costs than curing any one major chronic disease.

Targeting the intersection between aging and predisposition to chronic diseases would circumvent a problem encountered in studying the pathogenesis of many of these diseases in humans. Many chronic diseases, such as Alzheimer's or atherosclerosis, are restricted to humans or a very limited number of species. Many human age-related chronic diseases only become manifest clinically after the disease has advanced considerably at the molecular and cellular levels. Both these points make delineation of initiating or upstream etiological mechanisms very challenging because of difficulty in obtaining appropriate tissue samples for analysis sufficiently early during disease development. Targeting upstream, fundamental aging processes that predispose to these diseases in humans could circumvent these difficulties. Despite the huge potential promise of this approach, the financial, infrastructure, and personnel resources needed for basic and translational aging research are insufficient. A strategy to optimize resource development is needed to accelerate progress and avoid duplication.

Promising interventions that could enhance healthspan and delay age-related chronic diseases as a group appear to be at or close to the point of being ready for initial translational studies. More solid data testing the hypothesis that these interventions do, in fact, delay multiple age-related diseases in mouse models are needed. Experimental animal models of human chronic diseases need to be developed more fully with respect to application in the context of aging. Particularly in the case of genetically-modified animal models, it is important to conduct studies in old animals, rather than in young animals with accelerated onset of conditions modeling human age-related diseases. Use of old animals is more likely to phenocopy the systemic aging context in which chronic disease occurs in humans.

Since multiple, potentially effective interventions are emerging, there will be an opportunity to select those that are more readily translatable. Some, such as lifestyle interventions, are particularly challenging (e.g., caloric restriction in the context of an obesity epidemic). Desirable characteristics of interventions to be suitable for translation include: 1) low toxicity and few side effects, 2) effectiveness by oral as opposed to parenteral administration, 3) low dosing frequency (i.e., relatively long half-life), 4) stability, 5) scalability and low manufacturing cost, 6) detectability in blood, and 7) very importantly, effectiveness of interventions if initiated in later life or once symptoms have started to develop. Interventions that need to be applied in childhood or early adulthood, when subjects are still asymptomatic, in order to affect health much later in life would be very difficult to translate into humans. To be acceptable to regulatory bodies, such interventions would need to have virtually no side effects. Furthermore, it would take decades to demonstrate efficacy. Such interventions would be of little or no interest to the pharmaceutical industry because of time and expense required for clinical trials and expiration of patents during the time it takes to take drugs through clinical trials and regulatory approval processes. Similarly, lifestyle interventions that need to be initiated in early life would be difficult to implement.

4. Recent changes in the biology of aging field

The aging field has moved from description of effects of aging through hypothesis-driven mechanistic studies into development of interventions in experimental animals. A phase of translating these interventions from the bench to the bedside and, eventually, clinical application, is about to begin. In making these transitions, it is important to sustain or increase funding for important descriptive, mechanistic, and animal intervention work in aging, since the discovery pipeline must be maintained and even expanded.

Although “descriptive” is sometimes used as a pejorative term by scientific review committees, descriptive or discovery research leading to hypothesis generation has become highly sophisticated and of great relevance to the aging field. New descriptive approaches include sequencing, genome-wide association studies, epigenetic, microRNA, transcriptional, proteomic, and metabolomic profiling, organism-, cell-, and target molecule-based high throughput screens, bioinformatics, and system biological and epidemiological techniques. Multiple drug discoveries have come from descriptive approaches, especially high-throughput screening. There is a need in the aging field to continue or increase support for descriptive research, not reduce it, in order to maintain the intervention discovery pipeline.

The mechanism-based, hypothesis-driven approach has been the mainstay of basic aging research for the past couple of decades. Frequently, hypothesis-driven research is not focused solely on potential application or relevance. Many transformative discoveries leading to interventions did not originate from goal-directed research. Mechanism-based, hypothesis-driven, non-application-directed research has been