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Review

Translating advances from the basic biology of aging into clinical application

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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.

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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.

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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

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productive and needs to be supported, not reduced. Although a degree of consideration about relevance for hypothesis-driven research is perhaps reasonable, the current tendency by many funding agencies in many countries to force hypothesis-driven aging research to become highly application-directed could be counterproductive.

The aging field has moved into developing interventions that enhance healthspan in experimental animals, particularly over the past 4 years. Novel pharmacologic interventions are being explored that have potential to extend lifespan, delay cancers, dementias, and possibly other age-related diseases, and promote resilience in experimental animals, in addition to any effects on lifespan. These include rapamycin, JAK1/2 inhibitors, senescence-associated secretory phenotype and protein aggregation inhibitors, and other, as yet unpublished approaches (Harrison et al., 2009; Laberge et al., 2012; Lucanic et al., 2011; Verstovsek et al., 2010). Based on the finding that eliminating senescent cells increases healthspan in progeroid mice, screens to discover small molecules and biologicals that target senescent cells are underway. Discovery efforts to characterize factors released by stem cells from young individuals that potentially restore function in older individuals are also underway.

While many of these findings are very recent and in some cases not yet published, it is likely that the aging field will soon find itself at the point of beginning to translate interventions from lower mammals to humans. Successfully translating interventions effective in experimental animals into clinical application is very difficult, time-consuming, and expensive (Fig. 1). It can take over 17 years to complete translation, even in fields with an established translational tradition, such as infectious diseases or oncology. The process involves pre-clinical basic studies demonstrating efficacy and safety as well as definition of pharmacokinetics in mammals, generally in at least two species and using good laboratory practices (GLP) conditions, as specified by regulatory agencies (Steinmetz and Spack, 2009). It is important to select clinical outcome measures that have been validated, are reproducible, can be measured in a short time-frame, are as non-invasive as possible, and are accepted by regulatory agencies. Iterative bench-to-bedside coupled to "reverse translational" bedside-to-bench developmental phases are likely to be necessary, especially for investigational new drugs (INDs). This requires an equal partnership between basic biologists and clinicians with a strong basic biology background. Intellectual property protection at a very early stage is necessary to motivate the commercial collaborations necessary to bring agents into the clinic. Without early attention to protecting intellectual property, the chances of getting a treatment to patients are greatly reduced. Finally, early attention to marketing and potential interest of payers for treatments can help to motivate commercialization and getting treatments into the clinic.

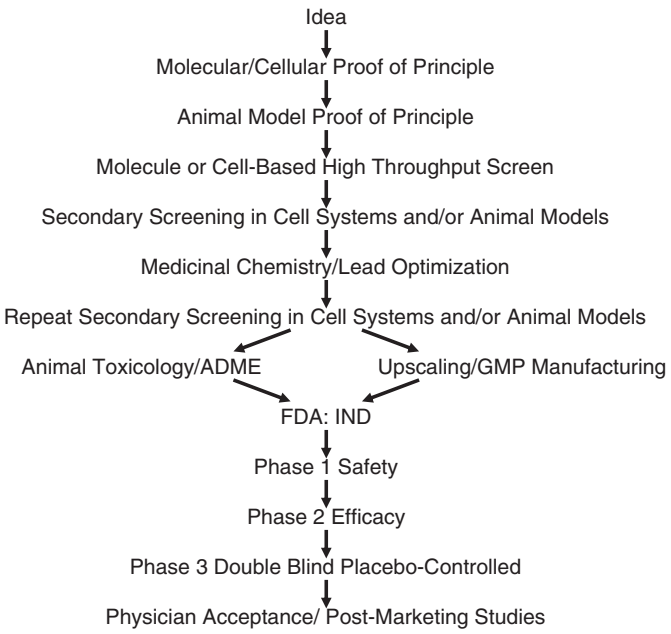

Fig. 1. The path from an idea about an intervention to clinical application. ADME refers to pharmacokinetic studies of absorption, distribution, metabolism, and excretion. GMP refers to "good manufacturing practices". FDA refers to Food and Drug Administration. IND refers to investigational new drug.

5. Initial clinical studies

While progress over the past few years in developing successful interventions that target basic aging processes in mice has been impressive, the way forward to translation into humans has not yet been fully mapped. We need innovative, new solutions to the limitations in experimental paradigms, infrastructure, strategies, and personnel that will be required for successful translation in the near future.

The field of translating the biology of aging into clinical interventions is in its infancy. Few drug intervention trials of any type have been conducted in elderly populations, as elderly subjects have generally been excluded from clinical trials, especially those involving completely new formulations. However, initial trials have commenced in humans using some of the approaches that have been shown to enhance life- or healthspan in rodents using drugs already approved for other indications. These drugs are being used to target aspects of age-related dysfunction or particular chronic diseases. For example, at least three clinical trials of rapamycin in Alzheimer's disease and another for frailty are currently underway or about to begin. Resveratrol congeners are being developed to treat type 2 diabetes (Baur et al., 2012). JAK1/2 inhibitors, which interfere with IL-6 signaling, appear to ameliorate frailty in elderly patients with myelofibrosis, a hematologic disease associated with inflammation marked by high circulating IL-6, without affecting the clonal hyperproliferation that is the underlying cause of the hematologic disorder (Geron et al., 2008; Pardanani et al., 2011; Tefferi and Pardanani, 2011; Verstovsek et al., 2010).

At least three potential drug development paradigms can be envisaged for whether interventions based on targeting fundamental aging processes improve function (Table 1). The first is to determine if these treatments ameliorate dysfunction due to chronic, age-related diseases using well-defined endpoints. For example, effects of interventions could be determined on HbA_1C or fasting glucose in age-related type 2 diabetes. Other examples could be improvements in psychometric indices of cognitive function in dementias or primary tumor size or rate of metastatic spread in cancers. The second set of paradigms is to study effects on disease events more narrowly associated with the agent being

Table 1
Potential paradigms for translating interventions that extend health- or life-span in experimental animals into clinical treatments.

Amelioration of age-related diseases
Cancer: growth or metastases
Cognitive or neurological dysfunction due to Alzheimer's or other neurodegenerative diseases
Atherosclerosis: vessel flow or patency, calcification, acute coronary syndrome, cardiac function
Diabetes (particularly that associated with obesity or metabolic syndrome): HbA1C, HOMA index, glucose or insulin clamps
Niche indications specifically targeted by the intervention
Myelofibrosis with elevated IL-6 by JAK1/2 inhibitors
Senolytics for fracture non-union
Amelioration of frailty (in pre-frail, as opposed to very frail, subjects)
Short term
Chemotherapy constitutional side effects
Recovery from elective surgery
Duration of rehabilitation required after myocardial infarction or hip fracture
Intermediate term
Prevention of nursing home admission

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tested. An example might be resolution of fracture non-union, which is associated with local increases in senescent cells, with senolytic agents (Bajada et al., 2009). The third approach is to test if agents can reduce aspects of frailty. For example, effects of agents could be tested on strength, endurance, nausea, and appetite after chemotherapy, time needed for return of function and wound healing after elective surgery, or delay of imminent nursing home admission in pre-frail, at-risk elderly subjects. These approaches would be more feasible than using long-term, unproven, or problematic endpoints, such as lifespan in humans.

Outcomes that are acceptable to regulatory agencies will be needed for clinical trials of drugs that target fundamental aging mechanisms. Little work has been done on surrogate outcomes for frailty and age-related disability or on validating biomarkers from drug studies in young subjects for use in the elderly. Endpoint and pre-clinical testing paradigms need to be developed in aging animal models for initial pre-clinical studies. These need to be based on the clinical endpoints to be used in subsequent trials in elderly subjects. Ideally, already established endpoints that the FDA recognizes, such as measures of glucose tolerance, muscle strength, or cognitive function could be used. Work needs to continue on developing other, possibly more relevant biomarkers, such as indices of frailty, to the point that the FDA can accept them.

6. Investigators needed for translational aging research

In the US, there are 7000 American Board of Internal Medicine-certified geriatricians (source: Association of Directors of Geriatric Academic Programs). Fewer than a dozen have R01 grants from the Division of Aging Biology at the National Institutes of Health. Indeed, worldwide there are few clinical geriatricians who are also basic aging researchers. This is very unlike many other biomedical fields, such as endocrinology, in which many academic clinicians also conduct basic laboratory research. Few geriatricians attend meetings in the basic biology of aging. Furthermore, basic biologists rarely attend clinical geriatrics meetings. In addition, unlike infectious disease specialists or oncologists, few geriatricians have experience with translating INDs into clinical application. This means that there is a critical shortage of investigators with the combination of basic biological and clinical skills necessary to design and conduct the pre-clinical and clinical studies and to navigate the regulatory framework necessary to translate recent advances.

We need to begin to train a new group of investigators in the basic biology of aging who have a thorough grasp of translational strategies and clinical geriatrics. We need a group of geriatricians with sufficient understanding of the both basic biology of aging and clinical trial methodology to lead the process of taking INDs through pre-clinical studies, clinical trials, and the regulatory approval process. It will take well over 5 years for these investigators to be ready, even if we can entice trainees into this area and begin intensive training programs right away. In the meantime, we need to devise collaborative strategies that bring trios of basic biologists, geriatricians, and clinical trial investigators together to start the process of translating new agents as they become available. We also need to consider developing clinical trial networks, perhaps emulating the successful approaches taken by the networks established in the cancer field.

A major barrier in the US to attracting trainees into careers combining clinical geriatrics with the biology of aging is the very poor reimbursement for geriatric clinical services, resulting in a general shortage of geriatricians (Committee on the Future Health Care Workforce for Older Americans, 2008). Geriatricians actually earn less than general internists, even though American Board of Internal Medicine certified that geriatricians need to complete training as general internists before they do additional training in geriatric medicine. Because of this, much of the energy of leaders in academic geriatric medicine has to be devoted to devising ways to improve practice efficiency and volume to compensate for poor reimbursement, rather than concentrating on other academic issues, such as developing methods to translate fundamental aging processes into the clinic.

Despite this, it is encouraging that trainees are beginning to embark on the training needed to conduct translational aging research. This seems to be related to the recent, high profile advances in basic aging biology, especially interventions that enhance health- and life-span in mammals. A number of steps need to be taken to help these trainees in their careers, including development of well-thought out curricula, securing funding for training programs, enhancing the reimbursement system for geriatrician/basic scientists, and developing a much fairer and supportive scientific review process for the grants for which these investigators will need to compete. Currently, many grant review committees are quite hostile to translational research, even if this is not intentional. The system is stacked against such applications, in part because basic scientists reviewing these grants do not understand the clinical components and the clinicians do not understand the basic science components. With page limitations, these applications have less room to describe the basic science component than purely basic grants being reviewed by the same group, with the same being true of the clinical component of the grant. Trainees are very aware of this issue, and considerable thought is needed to find ways to address this in order to attract trainees into the field and to get the research going.

7. Conclusions

We are on the verge of a new era in the basic biology of aging, an era in which we can finally contemplate beginning clinical translation for a range of applications. While interventions with potential to delay age-related dysfunction appear to be at hand, creation of new experimental paradigms with relevant, measureable outcomes, funding, and training for personnel with new skills are needed soon. All this has to be done without taking resources away from the current descriptive and mechanistic approaches in the aging biology field that led to these important advances.

Can every age-related change be reversed? Some involve progenitor depletion, some involve chronic inflammation, and others involve extracellular matrix and structural changes (e.g., cataracts, osteoporosis). Different mechanisms are implicated to different degrees in different organs and cell types. This suggests that several therapeutic strategies may need to be combined to be maximally effective: no one strategy is very likely to be a panacea. A process involving at least two steps may ultimately be needed, based on the longstanding surgical principle of first removing dead material and then replacing with good tissue. The first step may involve removing senescent cells, ameliorating the senescence-associated secretory phenotype and reducing inflammation, and removing cytotoxic lipids and lipofuscin, protein aggregates, damaged macromolecules, and advanced glycation endproducts. The second step may involve transplanting tissues, differentiated cells, or stem cells or restoring endogenous progenitor function to repopulate damaged tissues. Advances are being made in each of these areas, and highly effective combined approaches, while currently science fiction, may not be that far off.

If any or all of this comes to fruition and is translated into clinical treatments successfully, we may be able to delay chronic age-related diseases as a group, rather than picking them off one-at-a-time, delay or reverse frailty, and even extend health- or lifespan. If these speculations come about, there will be myriad economic and social consequences, for which the public is not prepared. To quote Pliny the Elder, the only certainty is that there is nothing certain.

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