Journal of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
2009. Vol. 64A, No. 2, 209–212
doi:10.1093/gerona/gln063


Advance Access publication on February 9, 2009

Special Issue: Biology of Aging Summit

Perspective

# Healthspan, Translation, and New Outcomes for Animal Studies of Aging

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Dramatic advances in understanding mechanisms of aging have recently been made in model systems. Interventions have been devised that successfully enhance survival. Major issues still in need of resolution include whether these interventions not only increase survival but also enhance function, delay frailty, and can be translated into clinical application. It seems there are basic biologic findings close to being ready for translation. However, a number of barriers exist to translating these findings into realistic clinical interventions. Steps and resources needed include measuring not only survival but also impact of interventions on age-related disability, frailty, and onset of disease in model systems; development of clinically relevant measures of disability, frailty, and disease for each animal model and genetically tractable animal models of frailty; training and career-long funding mechanisms for geriatricians in basic science research and for basic scientists in geriatric issues; translationally capable review and funding mechanisms; emphasis on studies of interventions that can be initiated in later life for preventing or reversing disability; genetic association studies in humans to identify new candidate genes and pathways that correlate with disability, frailty, and age-related disease onset as well as longevity; study of exposure to environmental agents or toxins early in life on survival, disability, frailty, and disease in later life.

**Key Words:** Healthspan—Translation—Animal studies of aging.

*Infirmity doth still neglect all office*
*Whereto our health is bound; we are not ourselves*
*When nature, being oppress'd, commands the mind*
*To suffer with the body*
(William Shakespeare, King Lear, Act 2 Scene 4)

DRAMATIC, important advances in understanding mechanisms of aging have recently been made using both experimental animal models and cultured cells. The field has moved beyond descriptive studies to exciting research in interventions that successfully enhance survival, potentially having the promise to completely transform our lives. Major issues are whether these interventions not only increase survival but also enhance function, delay frailty, and can be translated into the clinic. This raises several key questions: (a) Do we have in hand basic biology that can be translated? (b) What barriers exist to translating basic knowledge about mechanisms underlying age-related dysfunction in model systems into realistic clinical interventions? (c) What resources are needed to translate basic findings into clinical application? Discussion of each of these questions follows.

## Do We Have in Hand Basic Biology That Can Be Translated?

Interventions have been discovered that increase maximum life span in experimental animals. These include caloric restriction, drugs, and mutations in several pathways (including growth hormone/insulin-like growth factor-1 [IGF-1]/insulin/insulin receptor substrate-1 [IRS-1]/protein kinase B [AKT]/Foxo, sirtuin, cellular stress response components, and mammalian target of rapamycin [mTOR]). Some of these mutations coincide with polymorphisms associated with familial longevity in humans (eg, in the IGF-1 receptor causing reduced IGF-1 signaling). Drugs based on some of these pathways are being developed. Some are close to clinical application for disease-specific indications (eg, sirtuin ligands for obesity-related diabetes).

Some interventions, for example, caloric restriction or sirtuin ligands, might need to be applied for many years in humans, perhaps even from early adulthood, to impact maximum survival substantially. An important issue is whether long-term interventions, such as using caloric restriction mimetics, are practical in humans. To be acceptable for use in younger, asymptomatic individuals with the expectation of a much later impact on survival, a lifestyle intervention or drug would have to be effective and have few or no side effects. Studies to achieve regulatory approval could take decades. This is not attractive to the pharmaceutical industry. Where interventions have more immediate effects for specific indications, such as sirtuin ligands in treating diabetes in obese individuals or statins for hyperlipidemia, an effect on life span might eventually become

apparent in postmarketing analyses. This backdoor approach might eventually yield either lifestyle interventions or drugs indicated for increasing survival. However, it does not seem realistic to set out to develop interventions that would have to be administered from early life in healthy humans.

Interventions that could be applied over a short period may -flammation by inhibiting nuclear factor-kappa B (NFκB). Perhaps caloric restriction, enhancing sirtuin activity, reducing IGF-1 exposure, or other interventions effective over the long term might have beneficial short-term effects in humans. Indeed, studies of short-term caloric restriction have favorably influenced predisposition to age-related disease in humans (1). Thus, interventions that extend over a substantial portion of the animals' life span and result in an increase in life span in these animals may be appropriate to test in short-term studies in humans. This could be especially true where age-related disabilities exist that can be targeted by the intervention (eg, cardiovascular or metabolic disease), with concurrent study of additional age-associated end points to ask if the intervention also has effects on multiple age-associated pathologies.

## What Barriers Exist to Translating Basic Understanding of Mechanisms Underlying Age-Related Dysfunction in Model Systems to Realistic Clinical Interventions?

Many barriers exist to translating basic findings concerning longevity into clinical application. It is difficult to envisage how long-term lifestyle or drug interventions could be implemented, and in the case of drugs, how they would receive regulatory approval. Another key issue is that elderly individuals often say they would rather keep on feeling healthy than merely live longer. Thus, maximizing healthspan and preventing dysfunction are at least as important, perhaps more important, than extending life span at all costs. Geriatricians and others providing health care for the elderly have long recognized that disability, frailty, and age-related disease onset are the critical end points that need to be addressed in older populations. Clinicians have made considerable progress in devising criteria and scales for measuring frailty and function. Many of these indicators of frailty and function could be adapted for use in experimental animals, a step that needs to be taken.

Most investigators in the basic science of aging use survival curves and maximum life span as key end points for studies of effects of interventions, rather than healthspan or function. The focus by basic researchers on life span and the greater focus by clinicians on frailty and age-associated disability is reflective of a gulf between basic scientists in the biology of aging and clinicians caring for the elderly. Only a handful of geriatricians have federal research grants in basic biologic aspects of aging. Many hold federal funding in other areas: in the basic biology of specific age-related diseases or disabilities, clinical physiology, clinical trials, epidemiology, or health policy, but not in basic biology of aging. Clinicians have infrequently been included in basic biology of aging meetings. Perhaps because of this, it is rare that discussion of rational clinical application of basic findings about the biology of aging occurs at these meetings.

Steps to address this disconnect are required. The need to translate findings from the bench to the bedside is overwhelming given impressive recent advances in our understanding of mechanisms of longevity in model organisms, increases in numbers of older people, and accelerating economic strains on health care systems. Many more investigators trained and funded to conduct translational research will be required within the next decade. This could be achieved by creating incentives for trainees in geriatrics to develop skills needed to investigate the basic biology of aging. Trainees in the basic biology of aging could be given clinical experience and learn about regulatory processes for drug development. However, simply enhancing opportunities for training is not sufficient. To draw trainees into the nexus of the basic biology of aging and clinical application, career-long mechanisms for their support need to be established. These include grant review by peers who themselves conduct translational research.

## Healthspan

A concern of health providers is whether increasing longevity will increase disability and health costs. It is not clear whether increasing lifespan will be associated with a pushing of morbidity out until near the end of life (compression of morbidity), or with increased disability and health care costs for society (expansion of morbidity) (2). This continuing controversy raises the concern that life-extending interventions might cause increased disability coupled with unsustainable increases in personal and health care costs. Some solace may be taken from data indicating that the prevalence of chronic disability in the elderly is decreasing (3).

To test the hypothesis that living to advanced old age results in a high level of disability, a longitudinal survey of the 1905 Danish birth cohort from 1998 to 2005 measured independence (including basic activities of daily living [ADL score, grip strength], cognitive function [mini-mental state test score, cognitive composite score) and depression (4). Very little decline in the proportion of independent subjects was found in four assessments between ages 92 and 100. This was because dependent subjects had higher mortality than independent subjects. Because the prevalence of independence declined only slightly between ages 92 and 100, the period of disability before death may change very little. This indicates that health care costs may not rise through the 10th decade (see also article by Miller, [5]). Although most people will experience physical decline before death, the duration of this period of disability before death may not increase with increased longevity. Others found that the cumulative health care costs for people in good health at age

70 are not greater than for less healthy people, despite greater longevity of the healthy group (6). Thus, there is some hope that interventions that increase survival could delay onset of age-related disability, but this needs to be tested for each intervention.

Basic biologists could do much to test whether compression of morbidity results from interventions that increase life span through experimental animal studies. So far, very little information about the relation of life-extending interventions in animal models to health and function in late life is available because most studies have focused only on survival. Studies of caloric restriction in rodents indicate this could be true for this intervention, at least in the laboratory environment. It is less clear that such interventions will increase survival, let alone function, in the wild. We need to go back and ask if interventions that increase maximum survival in fact increase healthspan. This is not self-evident. For example, interfering with mTOR might enhance maximum life span under laboratory conditions but could have adverse effects on muscle function. Interfering with cellular stress response pathways may increase maximum survival but could predispose to increased morbidity due to infections. Interfering with IGF-1 signaling might increase survival but could impede brain development and cognitive function.

## Frailty

Basic biologists stand to learn much from clinicians about frailty, an outcome potentially important to study in response to interventions targeting fundamental aging mechanisms. The term "frailty" has been used to characterize the most vulnerable subset of older individuals (7). Frailty becomes evident over time as increased vulnerability to physiological stress, with reduced ability to maintain or regain homeostasis after a destabilizing event. Frailty usually describes a condition in which a critical number of impairments occur in parallel, becoming evident after a threshold is reached, and if a stress such as an infection or injury is applied.

Definitions of the frailty syndrome include various combinations of the following indicators: weakness, fatigue, weight loss, impaired balance, decreased physical activity, slowed motor performance, social withdrawal, mild cognitive dysfunction, and increased vulnerability to physiological stresses. Screening criteria for frailty have been proposed that include at least three of the following: weakness, weight loss, slowed mobility, fatigue, and low levels of activity. Subjects meeting at least three of these criteria have increased inflammatory biomarkers, glucose metabolism impairment, markers of clotting, falls, disability, hospitalization, and mortality.

Formal screening tools for frailty in humans are currently being developed and validated. These tools could be adapted for use in animal models (see also article by Tatar, [8]). For example, muscle weakness, weight loss of no clear etiology, slowed performance, and low levels of activity could be determined in rodents using such measures as body weight; food intake; body composition by dual-energy x-ray absorptiometry, computed tomography, and magnetic resonance imaging; activity (spontaneous and induced); grip strength; grooming; and cognitive testing. Inflammatory mediators, insulin responsiveness, and procoagulant factors could be measured. The impact of interventions on frailty could be further evaluated by imposing stresses to animals, such as drug-induced oxidative stress, infections, or cold or heat exposure. Ideally, a set of measurements of healthspan, frailty, and function could be devised, standardized, and validated for each experimental animal model, as has been done for many functional domains by clinicians working with older humans. If experimental animal models of accelerated and delayed frailty can be developed, they would be useful resources for studies of interventions affecting fundamental aging processes.

## What Resources are Needed to Translate Basic Findings into Clinical Application?

In addition to developing animal models of frailty and disability, other resources that would advance the field include tools to measure healthspan in these animals, a cadre of investigators trained to translate basic findings about the biology of aging into clinical action, and methods for supporting these investigators by setting apart funds and establishing peer review mechanisms for them.

Support is needed for generation of additional targets for developing short-term interventions. This could be done through genetic approaches to identify candidate genes that correlate with extended longevity in humans, now that such approaches have become more technically feasible. The target pathways identified could be validated in short-term intervention studies in animals. Interventions could be developed based on these pathways and then translated to humans. Support is needed for studies in animal models and humans linking clinical pathology to molecular and cellular changes in model systems and cell culture (eg, senescence, hormonal, stress, damage). The impact of exposure to environmental conditions, agents, or toxins in early life to subsequent development of age-related diseases, frailty, and disability in animal models needs to be studied. This approach could have substantial public health ramifications through identifying potential environmental accelerants of age-related dysfunction.

## Recommendations

Based on the foregoing, the recommendations are as follows:

1. Studies of interventions in fundamental aging mechanisms in experimental animal models should measure not only survival but also impact on delaying disability, frailty, and onset of age-related disease.

2. Physiological measures in model systems need to be developed, validated, standardized, and linked to clinically relevant human pathophysiology. To begin this, basic biologists, geriatricians, bioengineers, pathologists, and veterinarians need to be brought together. A set of clinically relevant measures of age-related disability, frailty, and disease needs to be developed for each animal model.
3. Genetically tractable models of age-related disability, frailty, and disease are needed. Rodents, flies, and worms are particularly suitable. This could be achieved by supporting reverse translation of age-related phenotypes identified in humans into animal models.
4. Training programs and career-long funding mechanisms for geriatricians in basic science research and for basic scientists in geriatric issues need to be developed.
5. Translationally capable study sections and supportive aging Small Business Innovation Research grant review processes need to be in place. Investigator support in obtaining Investigational New Drug approvals, as available through the National Cancer Institute, would aid in efforts to translate interventions.
6. Study of interventions that can be initiated in later life for preventing or reversing frailty and disability need to be emphasized over less feasible life-long interventions.
7. Support is needed for genetic association studies in humans to identify new candidate genes, and validate candidate genes and pathways that correlate with extended longevity, disability, frailty, and age-related disease onset.
8. Effects of exposure to environmental agents or toxins early in life need to be examined on survival as well as disability, frailty, and disease in later life.

## Acknowledgments

The authors thank all the participants in this very lively discussion that occurred within the context of the Biology of Aging Summit in September 2008.

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*Received December 9, 2008*
*Accepted December 10, 2008*
*Decision Editor: Huber R. Warner, PhD*