THE GERONTOLOGICAL SOCIETY OF AMERICA®

OXFORD

Special Issue: Moving Geroscience Into Uncharted Waters: Perspective

Barriers to the Preclinical Development of Therapeutics that Target Aging Mechanisms

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Received March 22, 2016; Accepted June 2, 2016

Decision Editor: Rafael de Cabo, PhD

Abstract

Through the progress of basic science research, fundamental mechanisms that contribute to age-related decline are being described with increasing depth and detail. Although these efforts have identified new drug targets and compounds that extend life span in model organisms, clinical trials of therapeutics that target aging processes remain scarce. Progress in aging research is hindered by barriers associated with the translation of basic science discoveries into the clinic. This report summarizes discussions held at a 2014 Geroscience Network retreat focused on identifying hurdles that currently impede the preclinical development of drugs targeting fundamental aging processes. From these discussions, it was evident that aging researchers have varied perceptions of the ideal preclinical pipeline. To forge a clear and cohesive path forward, several areas of controversy must first be resolved and new tools developed. Here, we focus on five key issues in preclinical drug development (drug discovery, lead compound development, translational preclinical biomarkers, funding, and integration between researchers and clinicians), expanding upon discussions held at the Geroscience Retreat and suggesting areas for further research. By bringing these findings to the attention of the aging research community, we hope to lay the foundation for a concerted preclinical drug development pipeline.

Keywords: Aging—Geroscience network—Preclinical drug development

Here, we summarize discussions held during a Geroscience Network Retreat focused on barriers to the preclinical development of therapeutics that target fundamental aging mechanisms. This retreat followed a conference, "Therapeutic Approaches for Extending Healthspan: The Next 10 Years" in May, 2014 at The Scripps Research Institute in Jupiter, Florida. The retreat, which brought together basic scientists working on strategies to extend health span and life span in model systems and clinicians who have conducted intervention studies in the elderly people, was funded through the National Institutes of Health (NIH) Geroscience Network, a consortium of 18 aging centers and academic groups across the United States, in partnership with groups in the European Union (Table 1). At the conference, participants (see Acknowledgements) gave presentations about their own experience with preclinical therapeutic development. Afterwards, at the Geroscience Network Retreat, group discussions were held to brainstorm and prioritize strategies for accelerating the preclinical pipeline of drugs that target fundamental aging mechanisms, rather than focusing on specific age-related diseases one at a time. Herein, we summarize and further prioritize these discussions, highlighting strategies to benefit ongoing and future efforts focused on the identification, development, and translation of therapies that simultaneously target multiple age-related dysfunctions and diseases.

As the mechanisms of age-related decline are elucidated in greater depth, the possibility of targeting fundamental aging

Table 1. Geroscience Network

Albert Einstein College	Stanford University
Buck Institute	University of Arkansas
European Union	University of Connecticut
Harvard University	University of Michigan
Johns Hopkins University	University of Minnesota
Mayo Clinic	University of Southern California
National Institute on Aging	University of Washington
The Scripps Research Institute	Wake Forest University
University of Alabama at Birmingham	University of Texas Health Science Center San Antonio

processes to delay, prevent, alleviate, or even reverse age-related chronic diseases is becoming a reality. Efforts by individual labs, as well as collaborative groups like the National Institute on Aging (NIA) Interventions Testing Program (ITP), have already led to the identification of compounds that extend life span and/or health span in a variety of model organisms. Despite these remarkable advances, human clinical trials of therapeutics that target basic aging processes are rare. It is clear that barriers between discovery and translation—"the valley of death"—are blocking needed progress in the field. Although this gap is a threat to developing many types of promising drugs, this is especially true of treatments affecting aging processes.

An effective preclinical pipeline for developing interventions that target fundamental aging processes could one day transform medicine. However, at the Geroscience Network retreat, it was evident that the best potential strategies for drug discovery and development were not perceived as uniform among those working in the field. In some sense this is not surprising, as researchers have yet to define what is needed to develop a mechanism-based aging therapeutic with clinical utility. Still, the discordance among leaders in the field was enlightening—revealing many unanswered questions and unmet challenges in the discovery and preclinical development of drugs that target mechanisms of aging. This article describes some of the key issues discussed at the Geroscience Network Retreat, including (i) best practices for drug discovery, (ii) lead compound development, (iii) translational preclinical biomarkers, (iv) funding and support for preclinical studies, and (v) the collaboration among researchers and clinicians.

Moving forward, communication among basic scientists, clinicians, clinical pharmacologists, pharmaceutical companies, funding organizations, and regulatory agencies such as the FDA, along with continued support for translational aging research, is needed to establish and promote a consistent and effective preclinical pipeline. By bringing this discussion to the forefront, we aim to facilitate more rapid bench-to-bedside and bedside-to-practice translation of basic science discoveries in the aging field.

Approach

Best Practices for Drug Discovery

The traditional drug discovery pipeline identifies chemical modulators of validated, single protein targets in mammalian cells that are directed toward treating a single disease. However, because aging is an organismal phenotype, the implementation of a traditional drug discovery approach has been problematic. Numerous interventions with potential to slow aging processes have been identified in non-mammalian model organisms. In these phenotypic screens, life span

or other outcomes related to health or aging are often used as an endpoint. This type of "black box" approach, where the molecular target is unknown, necessitates the use of new strategies to predict the translational potential of each identified hit effectively, some of which are considered in the following sections.

Invertebrate screens

Genetic studies in invertebrate model systems, such as the nematode worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, and yeast *Saccharomyces cerevisiae*, have been instrumental in defining the molecular determinants of aging (1). More recently, both targeted and unbiased chemical screens in invertebrates (eg, *C elegans*) have also begun to identify small molecules that influence aging processes (2). A select number of these hits have already been shown to extend life span in mammals and serve to validate the utility and physiological relevance of invertebrate screens in aging research (3). For novel, lifespan-extending compounds identified in invertebrate screens, defining the mechanism of action will be helpful in discovering additional drug targets. Of even greater importance will be the ability to demonstrate that hits extend health span, not just life span. To accomplish this task, measurements akin to human frailty, loss of resilience, or multiple comorbid conditions must first be developed and standardized in invertebrates.

Chemical epistasis studies in a genetically tractable, short-lived system, such as *C elegans*, could also be used to define the mechanism of action for compounds that target fundamental aging processes. Classically, epistasis is used to identify genetic interactions via phenotypic examination of null mutants. Similarly, chemical epistasis might be used to determine if a particular compound extends life span in the context of a genetically null organism, representative of known aging pathways. For example, failure of a compound to extend the life span of a *daf-16/foxo*-null mutant would suggest that the compound acts through an insulin-like signaling mechanism (4). One advantage to this type of genetic approach is that mechanistic information can be quickly obtained and used to direct further therapeutic development. A disadvantage of this approach is that not all fundamental mechanisms of aging are conserved from invertebrates to mammals; therefore, chemical interventions discovered in invertebrates must always be tested in mammalian systems. Unfortunately, life-span studies in mammals can be expensive and lengthy. Initial screens in invertebrate models need to be followed by confirmatory studies in mammalian systems (see *Mammalian screens*). Additional experiments to establish the evolutionary conservation of fundamental aging mechanisms would increase the power of such high-throughput invertebrate screens to identify high-confidence, actionable drug targets.

Mammalian screens

Although the use of invertebrate model organisms in drug discovery will likely increase the speed with which drugs to increase health span are discovered, these systems do not fully mimic the biological complexity of mammalian systems. For this, studies of life span and health span in rodents, which are expensive and time consuming, are necessary. Use of initial screens in invertebrates or cell culture models can help in deciding which agents to select for detailed analysis in mammals, in some cases beginning with small, proof-of-principle studies in mice. Use of endpoints other than effects of prolonged administration of candidate agents on life span could accelerate these studies. For example, studies on survival following administration of candidate drugs beginning in already old mice may

be a way to accelerate development. Such an approach would recapitulate observational studies in humans showing that metformin increases 5-year survival of elderly people ([5]). Rapamycin or JAK 1/2 inhibitors enhance health span even if started in old age in mice ([6]). Other clinically relevant endpoints of mouse secondary screening studies could include a combination of (i) health span measures in old mice, (ii) disease-related endpoints in mouse models of human age-related diseases or conditions, such as glucose tolerance in diet-induced obese mice or reduced spread of tumor allografts, or (iii) resilience/frailty measures, such as testing if the agents improve physical function in older mice stressed by chemotherapy or if they improve resistance to toxins. Treating these endpoints as composite outcomes, much like the approach used in clinical trials ([7]), could provide a means of more efficiently assessing significance. Efforts to define these measures in mouse models are ongoing with multiple measures of health span and functionally validated murine frailty indexes being recently reported ([8],[9]). However, there are still no established protocols from regulatory agencies dictating what invertebrate, cell culture, or mammalian preclinical studies are required to move interventions that target fundamental aging mechanisms along the translational pipeline. Establishing a coherent drug discovery pipeline for drugs that slow development of aging changes and developing a strategy for demonstrating the preclinical efficacy of candidates may help to accelerate, and direct, such protocols from the regulatory agencies.

Consideration of genetic and environmental diversity

The era of personalized medicine has made it clear that both genetics and environment influence therapeutic outcome. As single-nucleotide polymorphisms associated with age-related disease are elucidated, the development of preclinical models to mimic these genetic risk factors would be useful in intervention testing. With the acceleration of CRISPR/Cas technology, the establishment of such "genetic avatars" has become faster and more feasible as long as a syntenic locus is identified. Similar to genetic polymorphisms associated with aging, environmental and dietary exposures linked to general aging phenotypes (eg, high fat diet, smoking) could be integrated into preclinical models. These approaches could help identify molecular mechanisms associated with age-related disease while improving therapeutic efficacy in the target population.

Development of Lead Compounds

As the number of molecules that show effects on health span or life span in model organisms grows, there is a need to develop a consensus regarding which preclinical testing approaches best predict efficacy in humans. Such a consensus approach should take into account all available information about the evolutionary conservation of a lead compound's effects, its safety profile, and biodistribution. Depending upon the gathered information, multiple defined approaches with clinically relevant endpoints may be necessary to evaluate each hit. For example, a drug that kills senescent myocytes would demand different testing approaches than one that promotes neuronal synaptogenesis. This point brings up the issue that the relative effects of particular primary fundamental aging mechanisms in one tissue may differ from another. Therefore, a combination of drugs may be necessary to extend human health span. Moreover, given the genetic and environmental heterogeneity in human populations, it is unlikely that a single drug will be efficacious in all individuals. Thus, it will be necessary to identify a suite of drugs that effectively target different mechanisms of aging that can be applied in a personalized approach.

How might the efficacy of general aging interventions be examined in mammalian systems? As a first pass, toxicity and optimization studies could be evaluated in mammalian cell culture assays, as is typically done by the pharmaceutical industry. Here, the function of primary cell cultures subjected to genotoxic/oxidative stress or other primary culture models, including adult stem cell populations, isolated from older versus younger individuals, may work as predictors for in vivo efficacy screening. However, these in vitro systems will never model the complexity of living systems, and additional studies in animals are needed for drug approval. The most popular mammalian model system in aging research is the laboratory mouse (*Mus musculus*). Spearheaded by the NIA, the ITP has examined a number of promising molecules in mice ([10],[11]). Testing strategies used by the ITP have become a gold standard in the field, employing three independent, parallel trials in mice from a four-way cross (ie, an F2 cross of four inbred strains). Use of a four-way cross generates a more genetically diverse population of animals for interventional studies than with inbred strains; however, even this strategy cannot fully mimic the complex genetic diversity of the human population. Moreover, the time and costs associated with murine preclinical trials that involve prolonged administration of agents on life span as the outcome has greatly limited the number of compounds that can be tested by the ITP. This low throughput nature of the ITP is not conducive to drug screening and novel target identification. In fact, only compounds previously tested and recommended by the scientific community are candidates for the ITP program.

Some argue that the wealth of phenotypic, behavioral, and biochemical data available for mice of a single genetic background (via resources like The Jackson Laboratory Nathan Shock Center Phenome Database ([12])) might have utility in assessing health-span modulation. However, because one goal of preclinical testing is to examine whether an intervention has broad efficacy, this strain-specific approach could result in a loss of generality. An example of this comes from studies of dietary restriction in mice. Dietary restriction is recognized as one of the most robust means of extending life span in model systems from yeast, worms, and flies to laboratory mouse strains ([13],[14]). However, when dietary restriction is examined in genetically heterogeneous backgrounds, its effectiveness varies widely ([15]). To mimic genetic heterogeneity, the NIA recently initiated the *C elegans* ITP with the goal of identifying candidate compounds that extend life span in multiple strains of *C elegans* and other *Caenorhabditis* species. The hope is that the *C elegans* ITP will accelerate the rate of discovery of broadly effective therapies and identify new classes of compounds for ITP testing.

The ITP has also tried late intervention studies. These protocols are faster, more reflective of what could be achieved in humans, and have identified several efficacious compounds (including rapamycin, acarbose, and 17 α-estradiol) ([3],[16]). But, is there a way to reduce further the time it takes to perform life-span extension studies in mice? One possibility is to use progeroid mouse models in preclinical efficacy trials. Many of these models have short life spans and develop age-related diseases somewhat analogous to those observed in humans ([17–19]). In these systems, compounds could be screened within a few months, rather than several years. Although interventional responses have yet to be compared between a panel of progeroid models and nonmutant aging mice, recent results suggest that at least some drugs have similar effects in both models ([20]).

The use of genetically engineered mice also may get around another caveat to current mouse studies: The spectrum of age-related diseases in mice is distinct from humans. For example, aged mice do not naturally develop atherosclerosis, diabetes, Alzheimer's disease,

or epithelial tumors. Therefore, simple measurements of life span fail to accurately assess each individual potential improvement in health span, many of which could be of great relevance for our aging population. Some studies have circumvented this issue by using a high fat diet to induce age-related human phenotypes (21). Others have tested whether interventions affect the resilience of old animals. Such resilience measures are meant to mimic recovery from acute insults, such as surgery or chemotherapy (see the article about resilience in this series). The recent availability of sophisticated instrumentation that enables murine frailty and resilience measurements akin to those currently performed in the clinic has greatly aided these efforts. For example, metabolic as well as endocrine endpoints, including bone density, adiposity, and lean mass, as well as gait, balance, cerebral atrophy, memory, and cognition, can all be measured now in preclinical studies.

Compounds that increase health or life span effectively in preclinical model systems may not have attractive chemical properties for use as human therapeutics. Some interventions targeting fundamental aging mechanisms in experimental animals might need to be administered early in life or chronically to healthy individuals to elicit benefits in late life. Such interventions would be difficult or impossible to study, validate, and implement in humans, especially if there were notable side effects in asymptomatic younger people decades before benefits occur. However, basic laboratory studies of the mechanisms through which such interventions act might lead to development of new but related interventions that can be implemented in later life.

The first application for therapies that target fundamental aging processes will likely be for individuals with age-related symptoms where a degree of toxicity or risk is acceptable. For example, an agent that clears senescent cells could first be used for a potentially fatal condition, such as idiopathic pulmonary fibrosis, or to reduce the side effects of high dose chemotherapy (22). Alternatively, therapies that target fundamental aging processes might be used acutely in resilience studies in older asymptomatic individuals to improve outcomes of a pending stress such as elective surgery, chemotherapy, transplantation, or hospitalization.

In cases where use of interventions that target fundamental aging processes is contemplated in asymptomatic patients, safety considerations will be of paramount importance. A drug that appears initially safe may elicit severe side effects in response to changes in diet, disease state, and age or in response to drugs that may be administered for other conditions. This will be a particular issue for interventions that require lifelong administration in order to slow development of age-related dysfunction. Therefore, it will be critical to address drug safety early in development, ensuring that proposed interventions exhibit minimal toxicity. In addition, the drug-like properties of candidate therapeutics should be evaluated early by employing in silico, in vitro, and in *vivo* models. Another consideration for these studies will be the pervasive nature of polypharmacy in older patients. A new mouse model in which five commonly prescribed medications (ie, acetaminophen, citalopram, metoprolol, omeprazole, and simvastatin) are coadministered at therapeutic doses may be useful in testing for preclinical drug interactions (23). Finally, lead compounds should undergo rigorous drug metabolism and pharmacokinetic studies to ensure that their adsorption, distribution, metabolism, and excretion are optimized for *in vivo* efficacy. Of note, these drug metabolism and pharmacokinetic studies may need to be performed in old animals, which have altered metabolism and liver and renal function. To conduct these types of analyses will require collaboration with experienced pharmacologists and medicinal chemists who can generate derivatives to overcome any encountered toxicity or stability issues.

Translational Preclinical Biomarkers

The NIA launched an extensive effort between 1988 and 1998 to identify biomarkers of human aging (24). When these endeavors did not produce a measure uniformly predictive of life span, many dubbed the investment a failure. Yet, many new insights into the basic mechanisms of aging were discovered through these studies and multiple preclinical life span correlates were identified (eg, cellular stress tolerance and proliferative capacity (25), patterns of circulating growth hormone and insulin-like growth factor-I [IGF-1] levels (26), mitogen activated protein kinase activity in the cerebral cortex (27), motor ability, and behavioral measures of learning (28)). Conclusion of the NIA's Biomarkers Initiative did not put a stop to biomarker research. Indeed, some of the most promising preclinical aging biomarkers identified to date (eg, p16[INK4a], or secreted proteins associated with the senescence-associated secretory phenotype) were identified more recently (29–33).

We do not know whether biomarkers that predict life span in model organisms also predict human morbidity and mortality. This knowledge gap complicates the transition from preclinical to clinical studies and represents a barrier in the development of therapeutics designed to target fundamental aging mechanisms. Moving forward, an arsenal of translatable biomarkers will be needed to take aging interventions from bench to bedside. Moreover, use of a composite outcome strategy, in which multiple aging measures are combined into one variable, may better capture the diversity of successful interventional responses. Although some of these are already available, other essential measures will take years to develop. The following sections describe the possible utility and current developmental stages of four subtypes of biomarkers potentially useful for translational aging studies: dosing/ pharmacokinetic biomarkers, pharmacodynamic biomarkers, biomarkers to test if basic aging mechanisms are actually targeted by the drug, and surrogate endpoint biomarkers.

Dosing and pharmacokinetics of biomarkers

For each drug candidate, methods to measure concentrations in body fluids (blood, urine, or saliva) or tissues (hair, skin biopsies, other) need to be developed to monitor compliance during clinical trials, as well as efforts to establish doses, dose intervals, and drug clearance. This can be challenging and time consuming, because the assays need to meet registration standards if the drug is to receive regulatory approval. In general, the path toward developing these types of biomarkers is not likely to differ much for drugs targeting basic aging mechanisms compared with other drug classes. Once available, these assays could be used in clinical trials to adjust doses and dosing intervals in the general overall target population as well as subpopulations, such as people with liver or kidney dysfunction, variation in body composition, different ages, and men compared with women.

Pharmacodynamic biomarkers

Pharmacodynamic biomarkers are sometimes relatively straightforward to translate from bench to bedside. They provide direct evidence that a drug is eliciting a specific pharmacologic effect. For example, the inhibition of mTOR activity after administration of rapamycin, a known mTOR inhibitor, can be measured by the phosphorylation status of ribosomal protein S6 kinase 1 (S6K1) or EIF4E binding protein (4EBP-1). Decreases in phospho-4EBP1 or phospho-S6K1 have been used as pharmacodynamic biomarkers in both preclinical mammalian models and human clinical trials.

However, pharmacodynamic biomarkers are more challenging when drugs are identified in high-throughput screens or in models where the molecular target is not always clear. In these situations, biomarker development and validation can require considerable resources. Moreover, there is no guarantee that a biomarker developed in mice, for example, will translate to humans. For this reason, the selection of preliminary pharmacodynamic biomarkers should take into account species conservation—focusing on targets with the highest probability of human translation. A second challenge relates to the development of pharmacodynamic biomarkers for preclinical compounds with complex molecular targets. The Geroscience hypothesis proposes that inhibiting general aging processes will alleviate many age-related diseases. If correct, the best compounds to target aging mechanisms may hit multiple pathways. The extent to which each target is hit may be an important determinant of efficacy versus toxicity (34). A good example of this phenomenon was recently described in the cancer field, where Cagan and others have hypothesized that the overall effects of a drug must be "balanced" such that cells respond in a desirable fashion (34). How the pharmacodynamics of such compounds could be measured both preclinically and during human trials is not clear. In this case, a more precise understanding of the molecular circuitry of aging would aid in the development of universal pharmacodynamic mechanism-based biomarkers.

Mechanism biomarkers

Mechanism-based biomarkers can be used to test if fundamental aging mechanisms are actually targeted by candidate drugs during clinical trials. Although this is not currently required for drug registration with regulatory agencies, testing these markers could indicate to the basic biomedical research and clinical communities that the agent may really work by affecting fundamental aging processes. One day, studies using such biomarkers could become a requirement for labeling if claims are to be made that the candidate drug targets aging processes themselves.

Dozens of predictive molecular (eg, $p16^{INK4a}$, IL-6, telomere length), behavioral (eg, rotarod performance, maze learning), and phenotypic (eg, changes in T-cell subsets, pharyngeal pumping in *C elegans*) biomarkers of aging processes have been developed in animal models. However, data about these types of measures from human clinical trials are limited. Take, for example, $p16^{INK4a}$. More than 10 years ago, a correlation between $p16^{INK4a}$ and chronological age was first established in mice (29,35). Since then, the use of $p16^{INK4a}$ as a mechanism biomarker in preclinical studies has grown exponentially, but there have been limited human studies. Liu and colleagues reported a correlation between $p16^{INK4a}$ levels in peripheral blood T lymphocytes and chronological age and showed that $p16^{INK4a}$ is lower in individuals who exercise and higher in those who smoke (30). These data suggested that $p16^{INK4a}$ levels in peripheral blood T lymphocytes are predictive of biological, rather than chronological aging, but did not prove that $p16^{INK4a}$ can be used as a proxy for longevity. However, $p16^{INK4a}$ expression has been used to inform about the gerontogenic effects of chemotherapy (36), bone marrow transplantation (37), and HIV infection (38) and is predictive of transplant outcome for certain organ types (39–42). Other age-associated molecular biomarkers (eg, IL-6, C-reactive protein, telomere length) may have similar utility in human studies, yet no FDA-approved clinical test has been developed for any of these markers.

A different problem exists for preclinical functional or behavioral biomarkers of aging. Many assumptions have been made regarding the equivalency of such measures between model organisms and humans, which may or may not hold true. For example, how does a rotarod performance test equate to common geriatric physical assessments? What about pharyngeal pumping in *C elegans*? Comparative studies are still needed to determine the best preclinical studies to predict functional decline and reflect whether drug candidates act by targeting aging processes themselves in humans.

Surrogate endpoint biomarkers

Surrogate endpoint biomarkers are those that accurately predict individual's outcomes. Examples include lowered blood pressure in patients at risk for stroke, decreased viral load in HIV positive patients, and sustained cognitive function in those with neurodegenerative syndromes. In the preclinical development of therapeutics that target fundamental aging mechanisms, a single endpoint measure is the mainstay and gold standard—maximum (or near-maximum) life span, as opposed to average life span. Although both life span and regenerative capacity have been linked to a multitude of aging biomarkers and genetic alterations, a cumulative measure predictive of maximum life span has yet to be identified. Exemplifying this, although $p16^{INK4a}$ levels accumulate with age in mice, they are not predictive of mortality (43). Interestingly, quantitative modeling in humans indicates that $p16^{INK4a}$ expression rises exponentially with chronological age, but plateaus in older individuals (44). These models suggest that attrition of biologically older individuals, who exhibit elevated $p16^{INK4a}$ levels, does occur in the human population. However, to establish $p16^{INK4a}$ as an endpoint biomarker predictive of health span or maximum life span would require a large longitudinal study. Furthermore, it would be necessary to demonstrate that interventions that lower $p16^{INK4a}$ almost always increase health span or maximum life span in humans before $p16^{INK4a}$ would be viewed as an acceptable primary endpoint of clinical trials by the medical community and regulators.

One could argue that human endpoint biomarkers are unlikely to work in preclinical models. For example, major causes of human mortality (ie, ischemic heart disease, stroke, chronic obstructive pulmonary disease, respiratory infections, and epithelial tumors) are rare in mice (45–47). Therefore, to address the lack of translational endpoint biomarkers, several approaches could be taken. First, the field might decide to develop a standardized suite of preclinical aging biomarkers by "reverse translating" a suite of established clinical measures of age-related disease. This process would not be simple, as it would require a concerted effort between geriatricians and basic scientists to not only identify potential aging biomarkers but also to validate them in a variety of clinical and preclinical contexts. However, given the presumed preference of the public for interventions that increase health span over maximum life span, the assessment of multiple age-related morbidities may be better than a single measure predictive of mortality. Lumping these measures into a composite outcome score could be useful in assessing interventions that may affect multiple age-related phenotypes. For instance, improvements in cognitive and immune function might be seen in one patient, whereas another exhibits decreased frailty. Both would be considered successful outcomes of an intervention targeting basic aging mechanisms, however, efficacy based upon a single one of these endpoints would be reduced when compared with a composite-type assessment. A second approach to developing aging biomarkers would be to institute mandatory blood and tissue banking from all trials of age-related therapeutics, creating an incredible resource for testing hypotheses about potential future biomarkers. To this end, several large collections of samples already exist that might be exploited in the context of aging (eg, biomarkers from the

Framingham Heart Study and the Baltimore Longitudinal Study of Aging).

The discovery, development, and validation of translational biomarkers capable of measuring general aging processes will not be easy or cheap. Unlike most preclinical model systems, the aging human population is incredibly complex and heterogeneous. Factors like comorbidities, polypharmacy, and frailty may decrease the utility of some aging biomarkers in the elderly people. As a result, the validation of biomarkers will require significant investments of time and money on both sides of development—clinical and preclinical. In the preclinical setting, it may be necessary to test biomarkers in multiple model systems, representative not only of genetic diversity but also of common human comorbidities. The use of a recently described mouse model of polypharmacy would provide a means for assessing the efficacy of therapeutics aimed at slowing development of aging phenotypes in the context of other medicines that are commonly prescribed in geriatric populations (23). From the clinical perspective, larger cohorts will be needed to statistically validate the use of biomarkers in elderly individuals. Exactly who would conduct and/or pay for these trials is unclear. The selection of biomarkers will also require forethought. Successful biomarkers of aging must be practical in both preclinical and clinical settings, require a minimal amount of time and specialized equipment or expertise, and be noninvasive. Furthermore, it would be necessary to show that multiple interventions that extend life span in humans also affect the biomarker and that changes in the biomarker caused by the interventions reliably predict effects of the intervention on health span or longevity. Of course, it would take decades to complete these studies in humans. Development of dosing/pharmacokinetic, pharmacodynamic, and mechanism-based biomarkers for use in clinical studies of agents that target fundamental aging processes appears feasible. However, developing surrogate endpoint biomarkers that would be acceptable to regulators as a shortcut to make claims about effects of a candidate drug on life span in humans will not be achievable any time soon.

Integration of Researchers and Clinicians

The Geroscience approach for developing therapeutics to target fundamental aging mechanisms and promote health span is relatively new and challenges conventional methods for treating disease. As recently discussed by Nikolich-Zugich and colleagues (48), it is incumbent upon basic aging researchers, pharmacologists, gerontologists, geriatricians, and health economists to work together to find ways to facilitate the translation of basic science discoveries. The aging research community needs to engage other fields, educating them about the Geroscience approach and our need to change the one disease/one therapy mentality adopted by the pharmaceutical industry, NIH, and FDA. Such a movement is occurring both within the NIH through the Trans-NIH Geroscience Initiative, which provides a compelling example for the academic community. The challenges and potential benefits of targeting fundamental aging processes must also be conveyed to politicians and lay public, in particular the baby-boomers who stand to be the first beneficiaries of translational aging research.

Conclusion

Recent, fundamental advances in our understanding of aging biology have brought the prospects of therapeutic interventions to extend health span and treat age-related diseases and disabilities as a group closer to reality. Despite the growing numbers of promising genetic

and pharmaceutical interventions, significant work and financial investment are still needed in order to translate these basic science discoveries into the clinic. To this end, clinical trial strategies relevant to human frailty and resilience must first be established in validated invertebrate and vertebrate models. In addition, standardized preclinical drug development pathways are desperately needed. Some barriers to the clinical translation of therapies that target fundamental aging processes can be overcome by developing new preclinical testing approaches and clinical trials strategies, as well as and funding impediments unique to aging interventions. These goals will only be achieved through the concerted efforts of basic biologists, clinicians, industry, the NIH, and the FDA. Together, we must engage in dialog and establish a framework to facilitate the translation of candidate compounds into effective drugs that promote health span and target age-related disorders in humans.

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