THE COMMON DENOMINATOR
A Research Agenda to Slow Aging and Slow Disease

Scientists who study aging now generally agree that it is malleable and capable of being slowed. Rapid progress in recent years toward understanding and making use of this malleability has paved the way for breakthroughs and interventions that will increase human health in later life by opposing the primary risk factor for virtually every disease we face as we grow older—aging itself. Better understanding of this "common denominator" of disease could usher in a new era of preventive medicine, enabling interventions that stave off everything from dementia to cancer to osteoporosis. Poised as we are for an unprecedented aging of our population and staggering increases in chronic age-related diseases and disabilities, even modest extensions of healthy lifespan could produce outsized returns of extended productivity, reduced caregiver burdens, lessened Medicare spending, and more effective healthcare in future years. The field of aging research is poised to make transformational gains in the near future. Few, if any, areas for investing research dollars offer greater potential returns for public health.

While there has been great excitement surrounding the progress in aging research, a large gap remains between promising basic research and healthcare applications, and closing that gap will require considerable focus and investment. The field would benefit greatly from coordinated efforts within both the U.S. government and the private sector. Formalization of this coordination would both streamline funding and allow for cross-pollination of research. Additionally, an increase in both public and private funding for aging research is also urgently needed to enable scientists to capitalize on the field's recent exciting discoveries.

The payoffs from such focused attention and investment would be large and lasting. Therapies that delay aging would lessen our healthcare system's dependence on the relatively inefficient strategy of trying to redress diseases of aging one at a time, often after it is too late for meaningful benefit. They would also address the fact that while advances in lowering mortality from heart attack and stroke have dramatically increased life

expectancy, they have left us vulnerable to other age-related diseases and disorders that develop in parallel, such as Alzheimer's disease, diabetes, and frailty. Properly focused and funded research could benefit millions of people by adding active, healthy, and productive years to life. Furthermore, the research will provide insights into the causes of and strategies for reducing the periods of disability that generally occur at the end of life. As University of Michigan gerontologist Richard Miller aptly puts it, "The goal isn't to prolong the survival of someone who is old and sick, but to *postpone* the period of being old and sick. Not to produce a lot more standard-issue 100-year-olds, but to produce a brand new kind of 100-year-old person."

Key research questions within four categories—cell replacement, inflammation, stress response, and tools & models—are outlined in this Research Agenda. They were chosen by a team of leading U.S. and European scientists with the goal of identifying some of the most promising research in the field. To-date they have been endorsed by more than 65 leaders in the field. The agenda is not intended to be exhaustive, but instead identifies a range of projects that, with sufficient funding and focus, are likely to yield significant progress within 3 to 10 years. This Research Agenda and its recommendations are a modest start toward a broad strategy for primary prevention that would enhance and accelerate improvements in health and quality of life at all adult ages.

CELL REPLACEMENT

One hallmark of aging tissues is their reduced ability to regenerate and repair. Many tissues are replenished by stem cells. In some aged tissues, stem cell numbers drop. In others, the number of stem cells changes very little—but they malfunction. Little is currently known about these stem cell declines, but one suspected cause is the accumulation of "senescent" cells. Cellular senescence stops damaged or distressed cells from dividing, which protects against cancer. At advanced ages, however, the accumulation of senescent cells may limit regeneration and repair, a phenomenon that has raised many questions. Do senescent cells, for instance, alter tissue "microenvironments," such that the tissue loses its regenerative powers or paradoxically fuel the lethal proliferation of cancer cells?

A robust research initiative on these issues promises to illuminate the roots of a broad range of diseases and disabling conditions, such as osteoporosis, the loss of lean muscle mass with age, and the age-related degeneration of joints and spinal discs. The research is also essential for the development of stem cell therapies, the promise of which has generated much public excitement in recent years. This is because implanting stem cells to renew damaged tissues in older patients may not succeed without a better understanding of why such cells lose vitality with age. Importantly, research in this area would also help determine whether interventions that enhance cellular proliferative powers would pose an unacceptable cancer risk.

INFLAMMATION

Acute inflammation is necessary for protection from invading pathogens or foreign bodies and the healing of wounds, but as we age many of us experience chronic, low-level inflammation. Such insidious inflammation is thought to be a major driver of fatal diseases of aging, including cancer, heart disease, and Alzheimer's disease, as well as of osteoporosis, loss of lean muscle mass after middle age, anemia in the elderly, and cognitive decline after 70. Indeed, just about everything that goes wrong with our bodies as we age appears to have an important inflammatory component, and low-level inflammation may well be a significant contributor to the overall aging process itself. As the underlying mechanisms of age-related inflammation are better understood, researchers should be able to identify interventions that can safely curtail its deleterious effects beginning in mid-life—broadly enhancing later-life—and with negligible risk of side effects.

STRESS RESPONSE

A central theme in modern aging research—perhaps its "key" discovery—is that the mutations, diets, and drugs that extend lifespan in laboratory animals by slowing aging often increase the resistance of cells, and animals, to toxic agents and other forms of stress. These discoveries have two main implications, each of which is likely to lead to major advances in anti-aging science in the near future.

First is the suggestion that stress resistance may itself be the cause (rather than merely the companion) of the exceptional lifespan in these animal models, hinting that studies of agents that modulate resistance to stress could be a potent source of valuable clinical leverage and preventive medicines. Second is the observation that the mutations that slow aging augment resistance to multiple varieties of stress—not just oxidation, or radiation damage, or heavy metal toxins, but rather resistance to all of these at the same time.

The implication is that cells have "master switches," which like rheostats that can brighten or dim all lights in a room, can tweak a wide range of protective intracellular circuits to tune the rate of aging differently in long-lived versus short-lived individuals and species. If this is correct, research aimed at identifying these master switches, and fine-tuning them in ways that slow aging without unwanted side-effects, could be the most effective way to postpone all of the unwanted aspects of aging through manipulation of the aging rate itself. Researchers have formulated, and are beginning to pursue, new strategies to test these concepts by analysis of invertebrates, cells lines, rodents, and humans, and by comparing animals of species that age more quickly or slowly.

TOOLS & MODELS

Gerontologists' toolboxes have been greatly expanded by the same advances that have brought us bioengineered medicines and genetic tests that help oncologists select the best drugs to deploy against certain cancers. Applying the tools to study aging remains a work in progress, however, due both to the costs of new technologies and to the inevitable learning curves for mastering and harnessing them. Meanwhile, new animal models are being developed, such as the incredibly durable naked mole-rat, which promise profound insights into the aging process and how it might be altered to increase healthy life.

HARNESSING THE MOMENTUM

The science of aging is showing increasing power to address the leading public health challenges of our time. Just a few of the exciting advances recently reported include:

- Hopes that new molecular insights into the aging process—for example studies of cellular senescence and inflammation—will yield potent drugs for prevention or treatment of age-

related diseases have promoted large investments by several forward-looking pharmaceutical companies.

- The discovery that a drug called rapamycin can extend healthy life in rodents, even when administered to older ones (it is already approved for use in humans for certain diseases).
- Identification of a CETP gene variant correlated with human longevity that increases "good cholesterol" and may be protective against cognitive decline and Alzheimer's disease.

Leaders in aging science believe that it is now realistically possible to develop interventions that, by braking the aging process and addressing the common denominator of disease, greatly reduce the risk of undesirable aspects of growing older, from deadly scourges such as cancer and Alzheimer's disease to sensory impairments and osteoarthritis. Important advances have been made toward the goal of adding healthy years to life, but it can't be achieved in a timely way without significant support and prioritization of the research. This Research Agenda, created and endorsed by leading scientists, outlines just a few of the opportunities that now exist to accelerate research that promises radical improvements in health for older populations worldwide. The field of aging research is poised to make transformational gains in the near future. Few, if any, areas for investing research dollars offer greater potential returns for public health.

KEY RESEARCH QUESTIONS & THE NEED FOR NEW TOOLS & MODELS

The following research questions further identify promising opportunities that are likely to yield significant progress and should be addressed by a targeted program of research.

CELL REPLACEMENT

- How, when, and in what tissue types are cells, including stem cells, typically lost during the aging process?
- In what organs and tissues is such loss beneficial, for instance, to avert cancer? How, when, and where are such losses detrimental, and what factors distinguish beneficial from detrimental loss?
- How do tissue microenvironments change with age in different organs? Are these changes caused by an accumulation of senescent cells? Do they reduce tissue/organ function?

- Do age-related changes in microenvironments deplete tissue of resident stem cells, foil circulating stem cells from proper "homing," or prevent stem cells from functioning? Or, are there age-related systemic (circulating) factors that are detrimental to stem cell function?
- Is it possible to "wake up" stem cells within the aging body via systemically administered compounds that alter microenvironments or neutralize detrimental circulating factors?
- Do individual cells change in random ways that cause them to be out-of-step with neighboring cells and therefore fail to contribute to normal tissue/organ function? Based on single-cells assays, what are the molecular determinants of random changes, cellular responses to such changes, and their consequences for tissue/organ function?
- In animals whose longevity has been enhanced by genetic, dietary, or drug interventions, what age-related cellular losses, changes in stem-cell function, shifts in cellular microenvironments, or random changes are delayed or prevented?
- Can markers of cellular senescence, which accumulate with aging, be used as biomarkers to monitor or predict the efficacy of anti-aging therapies, the pro-aging effects of environmental or lifestyle factors, or the biological age or healthspan reserve of individuals?
- How do specific, age-related changes in stem cells or microenvironments contribute to particular diseases of aging? How can these changes be revered or neutralized?

INFLAMMATION

- Which age-related changes in inflammatory pathways are most important for the heightened risk of diseases of aging?
- How do specific, age-related changes in stem cells or microenvironments contribute to particular diseases of aging? How can these changes be reversed or neutralized?
- Which age-related changes in inflammatory pathways are most important for the heightened risk of diseases of aging?

- What role, if any, does age-related inflammation play in the loss of normal stem-cell function with age?
- Which inflammation-related sources of harm (that is, ones tightly linked to diseases of aging) are delayed or prevented by longevity-enhancing interventions, such as calorie restriction, or other interventions that enhance healthspan?
- Are age-related changes in the levels of certain inflammatory cytokines (chemical messengers secreted by immune cells) proximal causes for multiple disease of aging? Do some such cytokine changes have little or no bearing on age-related diseases, or are some even beneficial (for example, because they compensate for an age-related decline in function)?
- What are the prime causes for age-related inflammation and changes in inflammatory cytokines? Do certain environmental toxins, microbial pathogens, or dietary components stand out as leading sources of detrimental, age-related inflammation?
- Can interventions with anti-inflammatory effects broadly lower risk of multiple diseases of aging? Might this be true in humans—for example, humans treated with anti-inflammatory compounds and monitored for illnesses the compounds weren't developed to treat, suggesting that may broadly enhance healthspan and possibly longevity?

STRESS RESPONSE

- What changes in the stress response at the systemic, cellular, and molecular levels contribute to older animals' diminished stress resistance and elevated risk of serious disease?
- Are certain kinds of stress, or specific levels of different kinds of stress, usually beneficial? Are others usually harmful? Do the two—good and bad stresses—have broadly defining characteristics?
- Which aspects of cellular stress resistance are most closely tied to healthspan and longevity in animal modes?

- Are aspects of the stress response (for example, pathways switched on by oxidative stress) typically preserved or enhanced by interventions known to enhance longevity in animals?
- Can interventions beneficially induce or enhance the stress response in animals to promote healthspan and longevity?
- Are there sex-specific aspects of the stress response that contribute to male-versus-female difference in healthspan and longevity?
- Is the stress resistance of particular types of cells, such as fibroblasts in the skin, predictive of future risks of diseases of aging in humans? Can measurements of stress resistance in human cells that are readily obtainable, such as white blood cells and fibroblasts, be used to predict healthspan and longevity?
- Can interventions, such as dietary components or pharmacological agents, activate human stress responses in a way that broadly lowers risk of diseases of aging and increases healthspan?

TOOLS & MODELS

- Sequence the genomes of healthy centenarians in order to provide a better control for identifying selected disease genotypes, and to uncover what makes centenarian genotypes different from those of normal individuals.
- Expand the NIA's Interventions Testing Program in order to discover classes of compounds capable of extending the healthspan and lifespan of laboratory mice.
- Identify elements of late-life dysfunction in invertebrate models that are amenable to genetic analysis and are good proxies for age-related dysfunctions in humans—such as age-related memory deficits and cardiac function decline.
- Test novel antioxidant compounds targeted to mitochondria (sources of cell energy) in mouse models. These compounds have promise for ameliorating a common form of congestive heart failure.
- Develop novel animal models of spontaneous, age-related neurodegeneration—perhaps in certain breeds of dogs—that are most reminiscent of Alzheimer's and other human brain diseases than current animal models of such diseases.

- Investigate the mechanisms underlying resistance to diseases of aging in novel animal models, such as long-lived rodents that appear to be extraordinarily resistant to cancer.
- Assemble data on patterns of age-related diseases in marmosets—small, relatively short-lived primates that are more closely related to humans than most animals used in aging research—to facilitate their use in studies on the biology of aging, and, in the longer term, testing of candidate interventions to avert or delay age-related diseases.
- Expand "comparative gerontology" research to define the genetic basis for marked variations in healthspan and lifespan among relatively closely related species, such as chimpanzees and humans.
- Investigate candidate drugs for extending healtshpan and longevity in dogs via a broad-based initiative involving gerontologists, veterinarians, animal-health companies, nonprofit groups, and individual dog owners.
- Identify human gene variants and other prognostic factors that can be assessed in middle aged people to identify specific variants of genes and environmental factors that characterize "elite agers"—people who are likely to reach advanced ages in remarkably good health.
- Elucidate the powerful ability of some simple animals to regenerate injured tissues. Such knowledge is likely applicable to the emerging field of regenerative medicine.

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