Executive Session
Trans-NIH GeroScience Interest Group Summit

November 1, 2013

Rationale

The goal of biomedical research is to increase the quality of human life.

Chronic diseases of the elderly are the main limitation to achieving that goal.

Aging biology is the major risk factor for most of these diseases.

Session Goals

- Generate a new vision of collaborative interactions that will advance understanding of how the molecular, cellular and systemic degenerative processes of aging affect the etiologies of chronic disease.

- Identify strategic scientific areas of overlap among divergent chronic diseases and suggest new research interactions or directions to address those areas that will promote health.

I. Defining Aging and Aging Research

Healthy aging optimizes biological processes and delays onset of chronic diseases. It compresses morbidity and increases lifespan and healthspan.

> "How do we translate aging? Imagine you have an anti-aging drug. What would we define that as? Does it extend maximum lifespan? Median lifespan? Healthspan? Does it target multiple chronic diseases, but not aging? Target stem cells? How do we really picture this?"

However, aging is a complex, multi-system process, not easily defined. Identifying the underlying principles of aging—what keeps you healthy, instead of what makes you sick—requires an integration of science across multiple disciplines. How do we describe aging at a biological level versus a developmental time point? And what are the goals of aging research? Should they focus on treatment, prevention, healthspan, or all of these?

Achieving a unifying and compelling conception of aging and a "big vision" for aging research can help to:

- Educate the public, beyond the "elite class."
- Galvanize public support.
- Interest aging and chronic disease scientists in multidisciplinary collaborations to integrate discoveries and solve vexing problems.
- Attract research funding.

II. Insights From Summit Sessions

The seven summit sessions demonstrate three important aspects of aging-related research. First, ***cause and effect are incompletely understood***, and even widespread assumptions are open to reinterpretation. "Do we really know what we think we know?" asked one participant. For example, does rapamycin slow the appearance of aging phenotypes or does it increase lifespan independent of those phenotypes? And even though macromolecular damage correlates strongly with disease, said another participant, "We're not sure after all these studies how important damage is in aging itself." Nor is there an integrated understanding of how repair systems work to reverse damage or why there is not always a correlation among various types of damage. One could cite many other examples.

> "When we make slides . . . arrows imply causality, but we don't understand causality in the aging field at all."

Second is the ***systemic effect of physiologic changes and, therefore, substantial overlap among research areas***. Inflammation, for example, is not an endpoint in and of itself. Danger signals (e.g., senescent cells or macromolecular damage) trigger immune sensors, which, in turn, activate inflammatory mediators and effectors, such as interferon or interleukin 6 (IL-6). Through the systemic plasma, these substances trigger other responses; IL-6 can affect stroma, and stroma can affect cancer cells.

Similarly, stress transduces exposome inputs (e.g., psychological perception of danger or physical adversity) into a broad range of systemic changes impacting homeostasis, macromolecular damage, epigenetic profiles and other physiologic pathways. Macromolecular damage, in turn, plays an important role in cell senescence.

"We ought to consider an engineering systems approach, a co-investigator program. . . . . The effects of stress are managed through proteins. In our own boats we're not going to address that. We need to bring together investigators who don't normally play in the same boat."

The interdisciplinary nature of aging research requires collaboration among basic and applied scientists and among multiple scientific fields, encompassing physiology, psychology and biology. As one participant said, "I'm suggesting that basic scientists with elite knowledge about cells and signaling pathways have interventional or observational human analog studies." Another participant averred, "We need to organize in teams with different expertise and communicate."

The third important lesson from the geroscience summit is the ***vast opportunity to build on current knowledge to slow aging and to prevent or alleviate diseases of aging***. "The fact that we can more or less agree on six things that drive aging is profound," said one participant. "The fact that we can slow aging in animals is profound."

Over the last decade, the field of aging has become "more respectable and exciting," attracting the interest of researchers in other fields. Moreover, new technologies offer new opportunities; for example, perhaps enabling identification of "easier/better" signatures of aging for different cell types.

Ultimately, researchers agree that aging processes are malleable. The prospect of extending lifespan and compressing morbidity should be attractive to researchers, funders, policy makers and individuals worldwide.

III. Research Ideas

A. Research Models

Single Model vs. Multiple Models

A uniform, common model of aging can provide a focus for a broad range of scientific expertise, resulting in a "road map" or "blueprint." For example, understanding "every single detail" about aging in mice would expand our understanding of integrative physiology and enable researchers to predict outcomes, using systems network analysis. The resulting blueprint could then be applied to humans.

Alternatively, identifying commonalities across models offers statistical power. For example, researchers can collect livers or blood across mouse models or treatments and examine epigenetic changes, such as DNA methylation signatures. They might also examine proteomic, metabolomic, stem cell or other changes. What happens when epigenetic drugs are applied within the context of different aging models?

Is it even necessary to reconcile all models? If a model leads to a treatment, is it at least good enough to be used as a model, since treatments alone will advance the field?

Mini-Longitudinal Study

Perhaps there is benefit in examining a small number of people intensively across disciplines in a mini-longitudinal study, looking at everything from brain to gut to skin to understand what's going on.

"To capture complexity, either you cut in pieces and reassemble or you measure lots of things and make a model. What do we have in mind with *model*?"

Standardization

Regardless of the aging model or models in use, it is beneficial to employ common definitions of healthy aging phenotypes; that is, to define a "healthy" range of variability across a common set of physiologic markers that change with age in healthy tissues. Such standardization will enable comparison across studies.

Animal Models vs. Human Models

"As soon as we focus on the mouse, we have to translate to humans."

Basic models of animal studies are necessary to inform drug development, to identify physiologic mechanisms and to inform small molecule research, including chemical genetics.

However, animal models tend to be highly specific and contrived. A high fat diet, for example, changes physiological dynamics. A high fat diet plus stress changes things more, and that is the context in which most people live their lives, but not the context in which most animal studies occur.

Human studies, however, can only show associations, such as factors linked to compression of morbidity or the slowing or speeding of aging.

One approach is to test interventions in human cells first and then move to animal models (using older animals) to elucidate mechanisms. Alternatively, one participant suggested using worms and mice as "training wheels" to "understand more before we get to human studies."

To address the problem of ingrained mouse strains (and differential intervention outcomes in different strains), there was a suggestion to take eight founder strains, breed them to create 300 new genetic admixtures, and inbreed the new strains to enable replicative experiments in each strain. Ideally, researchers would do genetic sequencing and epigenetic and metabolomic profiling of all the strains. Findings across the genetically mixed strains, including consistent pathways of response, may be more applicable to humans.

> "If we find the same general principles in worms, flies and mice, that already gives you more robustness than you usually find in disease models."

Hierarchical Model

Rather than focus on single organs or tissues or cells, it may be fruitful to examine normal aging or specific interventions at three levels of complexity: the whole organism (animal or human), tissue(s) and molecular.

B. Disease-focused Approaches

Integrating Aging and Chronic Disease Research

Geroscience attempts to recapitulate biology, physiology and psychology—active areas of research in their own right. However, scientists in these discrete disciplines generally do not consider aging a component of their work.

From a geroscience perspective, there are several problems with chronic disease research as currently performed. First is the modeling of diseases in young animals, a popular approach because it is fast and cheap. However, ignoring the aging component likely distorts animal models of disease, since all diseases share aging as backdrop. For example, comorbidity is a signature of aging that is generally absent from animal models. Perhaps the best way to convince chronic disease researchers to address aging is to demonstrate the dramatic effect it may have on their models: Parkinson's disease, for example, likely manifests differently in an older animal than in a younger animal.

> "We need to shift people to realize, maybe they're studying the wrong model entirely. The [geroscience] community has to decide what the right models are and then provide the tools and reagents to look at right models of aging. Then introduce your disease. Otherwise, there is an explosion of useless data."

A second problem with chronic disease research is the exclusion of individuals at risk for comorbidities in clinical trials. And a third is a tendency not to examine confounding factors.

Perhaps one fruitful approach is to examine conditions such as frailty and functional pain disorders—both of which are incompletely understood, but accelerate aging—across multiple research areas, including those addressed in the geroscience summit (inflammation, stress, epigenetics, metabolism, macromolecular damage, proteostasis and stem cells).

The same integrated approach could be used for beneficial interventions, such as exercise or caloric restriction, and for drugs, such as rapamycin or new epigenetic drugs. As one participant averred, "Many conditions deserve to be studied in this integrated way."

> "We need a different type of grant system to take people out of their immediate comfort zones. People have to come together."

At the very least, chronic disease researchers will be interested in knowing the effects of lifelong disease treatment. For example, how do diabetes drugs work in the elderly? Interventions need to be tested in the context of aging to inform long-term treatment strategies.

Responders vs. Non-responders

Metabolomics is most effective with carefully chosen phenotypes that are maximally contrasted. Perhaps the best model of contrast for aging, and a good basis for a systems approach, is to use an intervention shown to be efficacious for slowing

aging and contrast treatment responders with non-responders, characterizing the reasons for the response or lack thereof. This type of research is the "Holy Grail for personalized medicine" and does not depend upon a consensus about biological drivers of aging or a single, unified model. One intervention that is not universally effective is influenza vaccination, for example. Moreover, it may be possible to develop epigenetic drugs specifically to slow aging or chronic diseases of aging. Already, there are exciting efforts ongoing to develop epigenetic drugs (EZH2, BETs) for cancer treatment.

C. Physiologic Approaches

Cause and Effect

Take potential aging drivers and divide them into "prime causes" and "prime effectors." In other words, figure out "what's upstream and what's downstream." Another participant phrased this as identifying "the most proximal factor that drives/influences aging biology metabolism," whether it is the microbiome, stem cell deterioration, epigenetic changes and/or clock mechanisms.

Caveats: It's easy to affect aging in animals, but more difficult to determine why aging is effected. For example, the mTOR enzyme complex impacts all seven physiologic systems highlighted in the geroscience summit. Which ones are most important? Inflammation is both cause and effect. Blocking inflammation in animal models can prevent insulin resistance, but so can blocking other pathways. Each manipulation has its own aging effect.

Super Centenarians

Start with basic hypotheses and examine a broad range of epigenetic markers to identify commonalities and trends among individuals aged 100+. Is there evidence that physiological pathways are altered consistently? Can we describe characteristics of disease resilience in this population?

Caveat: Everything changes with aging.

Pathway-specific Studies

Individual physiologic pathways may provide valuable information on aging across tissues and models. Participants

"Whatever the microbiome is doing chemically can be exaggerated with aging as the gut becomes more porous."

mentioned many possible pathway-specific research foci:

- How senescent cells contribute to chronic illness.
- Whether stem cells have intrinsic anti-aging mechanisms that promote stability in DNA and in proteostasis and transcriptional networks.
- How stem cells differ from differentiated cells in terms of epigenetic changes of aging.
- Whether epigenetic changes are a reliable signature of aging and health/disease trajectories. Whether those changes vary across cell types. And whether they constitute a "common node" to alter health trajectories. (Note: Epigenetic enzymes and posttranslational modification "readers" are "eminently druggable targets.")
- How DNA methylation functions as a predictor of physiological aging.
- Human and mechanistic analysis of the microbiome, including aged versus young microbiomes.
- Human and mechanistic analysis of circadian clocks.
- Association between reduced macromolecular damage and lifespan.
- How obesity-related and aging-related metabolic dysfunction are similar and/or distinct.
- Whether (and how) futile cycles regulate the aging process.
- The role of central regulation, including control of circadian rhythm in aging biology.
- Whether chromatin accessibility (which requires specific histone chaperones) is affected by aging and how.

Caveat: When you impact one pathway, you impact others.

D. "Big Data" Approaches

Large Cohort Studies

Currently, human cohort studies seldom assess aging biomarkers, making these studies less relevant to human models of aging. Piggybacking multiple lines of research on one large cohort study offers economies of scale, enabling funders to be efficient with scarce resources. Multiple grants could be used to support one large study, cutting across research institutes and diseases. Alternatively, aging trials can be opened up for chronic disease research studies.

To take best advantage of cohort studies, geroscience researchers need to think creatively about what to measure in humans.

"We need remote sampling and large numbers of people and lots of data and behavioral studies in place of limited clinical trials. We need to push for an idea of the best measure in people, cells, tissues."

For example, researchers can study mitotic and non-mitotic cells in a subset of subjects. Large longitudinal studies would also enable researchers to explore behavioral and basic biological mechanisms of aging before disease develops.

Two large NIH studies are now underway: (1) the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which aims to elucidate interactions among individual cells and complex neural circuits in time and space, and (2) the Human Connectome Project, which is amassing a large quantity of neural data and developing an interface to graphically navigate the data. As part of the connectome project, clinicians are doing MRIs on young adults ages 18 to 22 to generate anatomical and functional maps of brain connectivity. Once the proof of concept is complete and methodologies developed, younger and older individuals will be included in pilot studies.

Exploiting Data Troves

Clinical and public health entities collect enormous amounts of data on individuals and populations, in electronic health records, disease registries, etc. In comparison to costly observational studies and clinical trials, electronic data stores offer a relatively inexpensive means to study aspects of aging in humans. The challenge is to acquire the statistical and mathematical tools to integrate and analyze the information, much of which is fragmented across data sources.

Caveat: Only superficial clinical phenotypes can be gleaned from this data. Researchers will need to identity areas needing "deep phenotypes" versus areas that can be cost-effectively addressed using electronic health data.

IV. White Paper

A general outline for a white paper was proposed to crystallize messaging for audiences ranging from research funders to the general public.

1. Explain *geroscience*. What is it? Why is it important? What is its value? Why does it offer greater efficiency than disease-focused research?

2. Why did conference planners choose the seven session topics (inflammation, stress, epigenetics, metabolism, macromolecular damage, proteostasis and stem cells) as a focus for the summit? That is, why is each important?

3. Have session chairs answer the following questions about their session topic:

   (a) What do we now know and how does it relate to diseases of aging?
   (b) What do we still need to explore?

(c) What resources do we need to answer outstanding questions?