Statement of

James L. Kirkland, M.D., Ph.D.

Director, Robert and Arlene Kogod Center on Aging

Mayo Clinic

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Roundtable on Tackling Diseases of Aging: Why Research Collaboration Matters

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Chairman Nelson, Senator Collins, senators, staff of the Senate Special Committee on Aging, fellow participants and members of the public, thank you for the opportunity to appear before you today to participate in this roundtable, “Tackling Diseases of Aging: Why Research Collaboration Matters.” As the director of the Mayo Clinic Robert and Arlene Kogod Center on Aging, I commend you for your efforts to facilitate and enhance basic and clinical research on mechanisms of aging and the age-related chronic diseases. Age-related chronic diseases account for most of the morbidity, mortality and health expenditures borne by the people of the United States. Exciting, recent advances in our field are beginning to suggest that, by intervening in fundamental aging processes, we may one day be able to prevent, delay and cure multiple age-related conditions, including cancers, dementias, heart attacks, strokes, vascular disease, diabetes, kidney disease, arthritis, blindness, frailty and loss of independence, as a group, instead of one at a time.

In addition to being the director of the Kogod Center on Aging at Mayo Clinic, I am a clinical geriatrician who sees patients, as well as a basic laboratory scientist. I am investigating ways to delay chronic diseases and disabilities by designing interventions that target the fundamental aging mechanisms that predispose us to these diseases.

Mayo Clinic is the first and largest integrated, not-for-profit, medical group practice in the world. Mayo Clinic provides care for more than one million people annually from around the nation and the world at locations in 6 states. Mayo Clinic operates according to the guiding principle *the needs of the patient come first*. Mayo focuses its work within three shields, practice, research and education. Mayo conducts both laboratory-based and clinical research. A distinguishing feature of research at Mayo is an emphasis on translational research — bringing scientific findings into clinical practice. This is enabled by the organizational and physical structure of Mayo, which brings researchers into close proximity with clinicians, and an institutional philosophy of collaboration for the best interests of our patients. All patients at Mayo Clinic are treated as a whole patient, not simply a cardiology patient, a neurology patient or an endocrinology patient. This approach has allowed Mayo Clinic to successfully and cost-effectively treat patients for almost 150 years. Mayo has research complexes in Rochester, Minn., Jacksonville, Fla., and Scottsdale-Phoenix, Ariz. Mayo has a graduate school that grants Master’s and Ph.D. degrees, a medical school, extensive postgraduate training programs for scientists and clinicians, and it provides continuing medical and public education.

The Robert and Arlene Kogod Center on Aging involves all departments, both basic science and clinical, and sites of Mayo Clinic. In this respect, its structure parallels that of the Geroscience Interest Group (GSIG) that spans the National Institutes of Health. The mission of the Kogod Center is to understand, promote and extend healthspan, the portion of our lifespan during which we are healthy, independent and free of chronic pain or disability. The Center has five programs: Cellular Senescence, Healthy Aging and Independent Living; Regenerative Medicine of Aging; Aging Bone, Muscle and Joints; and Diabetes, Metabolic Syndrome and Aging. Mayo has an Alzheimer’s and Related Disorders Center headed by Dr. Ronald Petersen that is closely aligned with the Aging Center.

Investigators and clinicians in the Aging Center at Mayo Clinic publish over 15 scientific and clinical articles per month and hold over 90 major grants for aging research. In addition to basic scientists, the center includes 48 board-certified geriatricians, 9 geriatric psychiatrists, as well as over 35 physicians and surgeons whose practices are mainly focused on older patients. There are over 150 active human studies underway on aging or conditions affecting the elderly. The Center includes over 45 laboratories. It supports core laboratories that assess healthspan and functional and cognitive outcomes in aging laboratory animals and parallel outcomes in human subjects. Diagnostics to evaluate healthspan and frailty and interventions to enhance healthspan and treat frailty and age-related chronic diseases are being actively developed across the Center.

In the spirit of fostering collaboration and preventing disruptive competition, the Mayo Clinic Center on Aging has initiated and will lead the implementation of a Geroscience Network that involves 10 other leading aging centers across the nation. This network recently received financial support from the National Institute on Aging (NIA). The goal of the Geroscience Network is to enhance healthspan by coordinating areas of focus among aging centers, minimize duplication of effort, develop joint research protocols, curricula, clinical trials subject populations and clinical trials networks, and support faculty and student exchanges among centers. Links to a network of seven additional aging centers in Europe are being developed.

As previously highlighted, aging is the leading risk factor for most of the chronic diseases that account for the bulk of morbidity, mortality and health costs in modern society. Therefore, by targeting fundamental aging mechanisms it may one day be possible to prevent or treat multiple age-related diseases together, instead of one at a time. The aging field has progressed from describing changes that occur in different tissues with aging, to determining mechanisms responsible for these changes, to now designing interventions that delay them. The next step will be to translate these interventions into clinical application.

Exciting new advances in the basic biology of aging include discoveries of drugs and drug targets that extend healthspan or lifespan in mammals. Some are approaching the point of becoming the subject of clinical trials. Some are showing indications of effectiveness in not only increasing healthspan or lifespan, but also delaying or treating chronic age-related diseases in laboratory studies in experimental animals or human tissues. The pace of this work has accelerated dramatically since the demonstration that a drug, rapamycin, was effective at increasing lifespan in mice, published in 2009 by the NIA Interventions Testing Program. Importantly, 5 of the 16 drugs tested so far in this multi-institutional program have increased lifespan in mice.

At Mayo Clinic, we are conducting basic, and in some cases, early stage clinical studies, with each of these drugs. In an important separate direction, we recently found that removing senescent cells enhances healthspan in mice. We are working on the next generation of this research which includes developing new ways, including drugs and lifestyle interventions, to remove these damaging cells or reduce their negative effects on surrounding tissues. Much of this work is supported by the NIA and most involves interdisciplinary collaborations among investigators and clinicians within and outside Mayo Clinic.

Mayo Clinic is doing significant work in the field of cellular senescence. Cells undergo a limited number of divisions before they stop dividing. Once they stop dividing, these cells reach a state of limbo — called cellular senescence — where they neither die nor continue to multiply. They produce factors that damage adjacent cells and cause tissue inflammation. The immune system sweeps out these dysfunctional cells on a regular basis, but as we age, our immune system becomes less effective at "keeping house," thus allowing the accumulation of these deleterious cells. Senescent cells are associated with many age-related chronic diseases. They accumulate in the damaged blood vessels that lead to strokes, heart attacks and vascular disease, in the brain in Alzheimer's and other neurodegenerative diseases such as Parkinson's, in fat, the kidneys, the pancreas, and elsewhere in diabetes, in arthritic joints, and around cancers.

In a significant study at Mayo Clinic, mice were engineered to express a suicide gene only in senescent cells. This suicide gene makes a protein that can be activated by a drug that has no effect on normal cells. In this genetically modified mouse, healthspan can be increased by activating the engineered suicide gene product with the drug. In mice with features of accelerated aging, we found that removing senescent cells substantially delays age-related muscle weakness, improves exercise tolerance, delays age-related fat tissue dysfunction, delays cataracts, and ameliorates other age-related disabilities. This work attracted considerable public attention and was featured in over 250 newspapers worldwide, television broadcasts, and even *Saturday Night Live*. We are currently developing drugs that we hope will have similar effects in non-genetically modified experimental animals and human subjects. We are excited that considerable progress has been made. We also are testing if multiple age-related diseases and disabilities can be delayed by removing senescent cells with drugs, genetically, or through lifestyle interventions, such as exercise.

The national aging research community aspires to soon initiate human clinical studies on some of the interventions discovered to enhance healthspan and ameliorate age-related chronic diseases in experimental animals. Considerable proof of principle and pre-clinical studies need to be done, but many in the aging field are becoming increasingly, though cautiously, optimistic about translating these interventions into clinical practice. If successful, the impact of increasing healthspan and delaying age-related chronic diseases would be transformative for health care and our society. Curing individual diseases of aging, such as cancer, would add approximately four years to median life expectancy, but not impact the likely onset and consequences of other age-related conditions such as atherosclerosis or dementia. In experimental animals, we can enhance healthspan and delay death by relatively much more than this through targeting the fundamental aging processes that also appear to make a major contribution to causing most or all of these age-related diseases.

Among the work that needs to be done soon is:

- Discovery and development of even more potential interventions, so we can maintain a pipeline of emerging treatments.

- Testing effects of each potential intervention in multiple age-appropriate animal models of age-related chronic diseases as well as in normal animals just with advanced chronological aging.
- Testing across a range of species before we move to human studies.
- Understanding and minimizing potential complications.
- Testing of combinations of treatments in experimental animals to optimize outcomes and minimize side-effects.
- Conducting initial, small proof of principle trials in human subjects, and eventually full clinical trials.

Obviously, we cannot study the impact of such interventions on lifespan in humans. Also, successful interventions will need to be effective in older or at risk subjects. Drugs that have to be given in early life to have a late life effect will be difficult to study in humans.

The types of study populations we will need are also very different from those in usual clinical trials to date. We will need to test interventions in older populations with multiple co-morbidities and look for benefits using markers of more than one age-related chronic condition, rather than single outcomes. For example, these agents could be tested in trials measuring memory, physical function, vascular function and metabolic parameters in elderly subjects with a combination of atherosclerosis, insulin resistance, and early dementia, a common clinical scenario. Other scenarios might include effects of agents in improving recovery after chemotherapy or surgery in pre-frail older subjects, or local or topical use of these agents in conditions with focal dysfunction due to processes associated with chronological aging, such as senescent cell accumulation in arthritic joints.

Research in aging and clinical care for older patients is best pursued using interdisciplinary approaches. Therefore, we feel that creation of initiatives across departments within our own institution and among aging centers nationally and internationally could help to accelerate discovery and implementation of interventions to enhance healthspan and quality of life. The GSIG initiative at NIH is based on the same principles and has helped to guide the types of collaborative efforts within and among institutions that are necessary for development and implementation of interventions to enhance healthspan and delay, prevent, or treat age-related chronic diseases. Tomorrow's interdisciplinary summit in Bethesda entitled *Advances in Geroscience: Impact on Healthspan and Chronic Disease* exemplifies these efforts.

In summary, the aging field is at an exciting juncture, with recent discoveries of interventions that hold potential for increasing healthspan and lifespan and combatting major age-related chronic diseases as a group, instead of one at a time. While by no means fully certain, it appears increasingly likely that some of these interventions may soon be ready to be tested in clinical trials. There is enough promise now that a major initiative to accelerate this work is warranted.

Clinical translational research is expensive and is a new area within the aging field. It needs to be supported without cannibalizing discovery and hypothesis-driven research in the aging field. Support for these areas is already meager and must be sustained or increased to

maintain or expand the discovery pipeline, so new and better interventions can continue to be devised. We in the aging research and clinical care community are doing our best with what we currently have. We are coordinating efforts among and within our academic institutions, setting priorities to advance basic and clinical research, creating stronger links between scientists and clinicians, including not only those studying aging mechanisms, but also individual age-related diseases, and developing training programs and curricula to create the new breed of clinician-scientists in aging research who will be needed as translation progresses and clinical trials begin. More could be done, and hopefully will be, as these steps are taken and increased funding allows us to move faster in this area. We are optimistic that support might increase as the potential benefits of targeting age-related diseases as a group and enhancing healthspan are recognized by the public, governments, donors, industry, and our colleagues across scientific and clinical disciplines. Since the first wave of baby boomers started turning 65 in 2011 and 11,000 people per day will continue to reach this milestone until 2030, the potential gains for society with this approach are substantial, possibly even transformative.