Creating the Next Generation of Translational Geroscientists

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See related editorial by Thomas Gill

Advances in understanding fundamental processes of aging have led to a variety of investigational therapies to delay or prevent age-related diseases and conditions. These geroscience therapeutics hold the promise of revolutionizing medical care of older adults by treating the complex syndromes of aging and preserving health and independence. A crucial bottleneck is the study of geroscience therapeutics in early-stage, first-in-human, or proof-of-concept clinical trials. There is a limited pool of clinical investigators with the combination of knowledge and skills at the interface of clinical research, care of older adults, and aging biology needed to successfully design, fund, and implement geroscience trials. Current training pipelines are insufficient to meet the need. The sixth retreat of the National Institute on Aging R24 Geroscience Network brought together basic scientists, gerontologists, clinicians, and clinical researchers from the United States and Europe to discuss how to identify, recruit, and train investigators who can perform early-stage clinical trials in geroscience. We present herein the group’s consensus on necessary subject domains and competencies, identification of candidate learners, credentialing learners, and the efficient and rapid implementation of training programs. Foundations and funding agencies have crucial roles to play in catalyzing the development of these programs. Geriatrician investigators are indispensable but cannot meet the need alone. Translational geroscience training programs can create a cadre of groundbreaking investigators from a variety of backgrounds and foster institutional cultures supportive of multidisciplinary translational aging research to turn innovative ideas into transformative therapeutics that can improve the health and independence of older adults. J Am Geriatr Soc 67:1934-1939, 2019.

In July 2017, a multidisciplinary group of clinicians and researchers who focus on the care and study of older adults or on the fundamental mechanisms of aging (Supplementary Table S1) met at a retreat in San Francisco, CA, to create a roadmap for developing a biomedical workforce capable of efficiently translating recent advances in geroscience through early-stage clinical trials to improve the health and care of older adults. This retreat was the final of a series of six retreats funded by the National Institute on Aging (NIA) R24 Geroscience Network: a consortium of 18 centers across the United States that seeks to accelerate the translation of advances in the basic science of aging toward improving the care of older adults.

“Geroscience” describes the application of biological mechanisms of aging to improve human health and treat disease.¹ The novelty of geroscience as a translational discipline, and the source of its clinical promise, is that the same mechanism(s) of aging contribute to many chronic conditions. A geroscience intervention might have greater, even transformative, clinical impact compared to treating several conditions individually. Multimorbidity, for example, is seen not as a coincidence of independent diseases but rather as a multisystem manifestation of aging that can be targeted by therapies—a perspective familiar to geriatric medicine practitioners. The geroscience hypothesis is that therapies targeting fundamental aging processes might improve human health span by delaying, preventing, alleviating, or reversing
a wide range of chronic diseases and conditions for which age is the primary nonmodifiable risk factor.2

The Geroscience Network retreats2 created strategies for developing geroscience interventions and testing the geroscience hypothesis (Figure 1). The first three retreats defined specific needs in drug screening and development,3 preclinical animal models,4 and clinical trials.5 The fourth retreat helped to develop the protocol for the Targeting Aging With Metformin study, a proposed randomized controlled trial testing whether metformin can delay multimorbidity.6 The fifth retreat described three frameworks for designing early-stage clinical trials of geroscience interventions, targeting geriatric syndromes, age-related diseases, and resilience.7

Together, these retreats identified early-stage, proof-of-concept clinical trials as the key bottleneck in the development of geroscience interventions. Many discoveries remain “stuck” at the laboratory bench. One of the most critical barriers to translation is the scarcity of investigators with the combined training and expertise in clinical research, care of older adults, and aging biology necessary to lead these trials. The retreats concluded that neither geroscience clinical trials nor the investigators to carry them out will emerge spontaneously at any scale from existing programs. The need for new infrastructure to support geroscience clinical trials was discussed in a separate white paper.7 This final retreat described the unmet need for geroscience investigators and discussed four major topics related to training this workforce: subject domains and competencies, identification of candidate learners, credentialing, and program implementation.

Investigators for Early-Stage Geroscience Clinical Trials: An Unmet Need

Geroscience clinical trials, as envisaged by the Geroscience Network retreats, would target integrative, multisystem phenotypes of aging, such as geriatric syndromes,8 multimorbidity, or resilience to acute health stressors.9 The pathophysiology being targeted is aging, not a particular disease. Although aging occurs throughout the lifespan, these phenotypes that are representative of aging are best characterized and most feasible to study in older adults. They also comprise the core of geriatric medicine as a clinical specialty. Apart from the biological mechanisms of the interventions, geroscience trials that target geriatric syndromes, multimorbidity, or resilience in older adults will be familiar to any geriatric-oriented investigator. Many geroscience interventions, such as those targeting senescent cells or proteostasis, have pleotropic effects on multiple systems. Therefore, they may be similar in concept to the pleotropic and multicomponent interventions that are the well-studied standard of care for geriatric syndromes.8,10 Geroscience clinical trials will emphasize, rather than exclude, older adults with multiple comorbidities.11 They will often occur in coordination with care programs specialized for older adults, such as inpatient geriatric services, rehabilitation, and prehabilitation. They will involve multidomain and functional outcomes.12 The field of geroscience can also be advanced through testing interventions in more traditional single-disease clinical trials with a disease-specific primary outcome if these trials incorporate elements like aging biomarkers and multidomain or functional secondary outcomes.

While there was a strong consensus that the interrelationship between geroscience and geriatric medicine makes translational investigators drawn from a geriatric medicine background indispensable to the progress of both areas, the workgroup also recognized that most investigators will come from other fields. Geriatric medicine is a small field with few clinical trialists and even fewer bench or T1 translational researchers. “Geriatricized” investigators from other fields have been critical to advancing many areas of aging research and are already doing the same in the nascent field of geroscience. Joan Mannick and Nir Barzilai, two of the most prominent champions of geroscience, who are leading major studies targeting syndromes of aging with drugs modulating mechanisms of aging,6,13 were originally trained in infectious disease and endocrinology, respectively. Training programs must be sufficiently flexible to enroll candidate investigators from a variety of backgrounds to

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**Figure 1.** What is translational geroscience? A deep understanding of fundamental mechanisms of aging leads to the development of therapeutic interventions. These aging-targeting interventions are then tested for efficacy in clinical trials using outcomes that broadly represent aging, including geriatric syndromes, chronic diseases of aging and multimorbidity, or decreased physical resilience. The first generation of such geroscience clinical trials is currently underway or completed. Mechanisms of aging are adapted from the “Pillars of Aging”,1 and clinical trial frameworks are from an earlier report of the Geroscience Network.7
serve a variety of roles on multidisciplinary geroscience teams.

Training Domains and Topics

The competencies required for a geroscience team to perform early-stage clinical trials fall into four broad domains (Figure 2): (1) elements standard to clinical research, (2) elements of geriatric medicine, (3) elements specific to geriatrics clinical research, and (4) elements unique to geroscience. The ideal investigator leading a multidisciplinary team will possess deep expertise in all four areas. More often, investigators will acquire sufficient expertise in several areas to work effectively with teammates who have complementary expertise to run geroscience clinical trials or to incorporate geroscience elements into their clinical trial.

The first domain consists of the standard competencies needed to perform human subject research and clinical trials. These define the curriculum of most clinical research training programs such as those supported by CTSA. Examples of knowledge and skill elements include study designs, statistics, developing aims, writing trial protocols and Institutional Review Board applications, and team leadership.

The second domain includes competencies in geriatric medicine that are not only essential to clinical care but also to the design of research studies involving older adults. These topics include geriatric syndromes, frailty, multimorbidity, polypharmacy, aging physiology, functional measures, and cognitive testing. Many of these represent the targeted conditions or key outcome measures of geroscience trials.

The third domain includes clinical research competencies specific to research with older adults. Examples include recruitment of older patients, research in regulated care settings, ethical conduct of research in vulnerable populations, functional and cognitive assessment research tools, multidomain outcomes, and the management of incidental findings.

Many investigators already possess expertise in the first three domains, which essentially comprise an older-adult clinical research training curriculum. Outstanding programs exist to provide this expertise to investigators from other fields, including the NIA’s Grants for Early Medical/Surgical Specialists’ Transition to Aging Research (GEMS$STAR) and Butler-Williams Scholars Programs.

The fourth domain includes new competencies unique to geroscience, which few clinical investigators from any field currently possess. For investigators across the translational spectrum, this must include a working understanding of the biological mechanisms of aging that geroscience interventions are developed from and target, to inform study design, biomarkers, and outcome measures. Clinical investigators must understand the strengths, weaknesses, translational opportunities, and relevance of the preclinical models in which interventions are tested. Meanwhile, basic scientists require an understanding of how multimorbidity or geriatric syndromes can be modeled in preclinical systems, as well as of age-relevant pharmacokineti-c and toxicology testing in old animals. Geriatric pharmacology—how aging physiology affects drug metabolism, interactions, excretion, and efficacy—is core to both preclinical and clinical study of interventions. Finally, this is a new field with no clear regulatory template and limited industry involvement, so the first generation of investigators must be able to navigate US Food and Drug Administration Investigational New Drug (IND) applications and phase 1 trials, and be able to work collaboratively with regulatory agencies on new drug approval indications, such as multimorbidity or frailty.

Across these four domains, the group identified six core competency areas: Biology of Aging, Geriatric Medicine, Clinical Research and Trials, Statistics and Epidemiology, Geriatric Pharmacology, and Regulatory/Compliance. The group is currently working to define a curriculum with specific competencies, learning objectives, learning activities, and assessment activities.

Candidates

Candidates for translational geroscience training would be drawn from diverse backgrounds and career stages, and they would be trained with varying intensity to fill different roles in the research ecosystem.

The workgroup determined that a key priority must be to identify and cultivate a core group of specialist translational geroscientists who will have expertise in all four content domains: clinical research, geriatric clinical research, geriatric medicine, and geroscience. Identification of candidates in medical or graduate school, or early in training, would allow the greatest use of existing training programs.
and funding mechanisms, reduce opportunity costs, and provide time for the deepest development of specialized expertise. Further along, established researchers might move laterally into geroscience research from geriatric clinical research, from translational research in other fields of medicine, or from basic science. Geriatricians interested in clinical research can be identified during or immediately after clinical fellowship and recruited to adopt a translational geroscience focus for their clinical research efforts. Clinical researchers in neurology, oncology, cardiology, orthopedic surgery, or many other fields, who are interested in studies of geriatric conditions in older adults, might be similarly recruited to adopt a primary geroscience focus and become champions of translational geroscience. Whatever their field of origin, this group would receive intensive training in all four content domains and would be competent to lead geroscience clinical trials as envisaged.

A larger group of researchers would receive focused training in specific areas to function as part of a multidisciplinary geroscience translational team. A cardiologist, for example, might receive training in geroscience biology, then partner with others to run a heart failure trial of a geroscience intervention with geroscience secondary outcomes. Such training would not be as intensive or comprehensive as the full four-domain curriculum envisaged above, but it could be efficiently provided from the same infrastructure to a much larger pool of researchers.

An even broader pool of candidates would receive sufficient training to participate in a translation-competent research chain spanning basic research through drug development to clinical trials and practice implementation. The basic scientists, clinical researchers, and clinicians in a translation-competent chain share a core common knowledge base, have a familiarity with the systems on the adjacent links in the chain, and can interpret literature from adjacent links. Basic scientists with successful laboratories may not be able to make the leap to clinical research, but they would still play a critical role in the translational research chain. Basic and clinical researchers might share a common understanding of frailty and how frailty can be measured in animal models and in the clinic, and they might help adapt each other’s tools and studies to facilitate translational collaborations.

**Credentialing**

The workgroup concluded that a formal national accreditation for geroscience training would be unnecessary and counterproductive from the standpoint of creating flexible and efficient training programs. Geroscience training must also be distinct from geriatric medicine training to accommodate diverse candidate backgrounds, although curriculum elements should be shared. In time, principles of geroscience that are necessary for practice should be integrated into accreditation requirements for geriatric medicine clinical fellowship. Some form of credential or certificate for geroscience training might still be useful to early career investigators by helping to establish credibility, demonstrating competence for a grant application, and serving as a formal milestone in career development plans. Many training programs at CTSA hubs offer some form of credential or degree. Credentialing for geroscience research should be similarly locally defined and flexible.

**Recommendations for Implementation**

The workgroup suggested two core principles for implementation of geroscience training at local institutions, considering the novelty and size of the field, and the diversity of training candidates: (1) existing training programs should be leveraged wherever possible, focusing new efforts on those elements that are unique to geroscience; and (2) programs should be developed and implemented through interinstitutional collaborations. These and additional recommendations for implementation of training programs are described herein.

The ideal program for training in geroscience research would assemble as many elements as possible from existing programs and add new elements only where necessary. For example, an institution might assemble general training in clinical research from CTSA courses, training in geriatric medicine and aging physiology from programs aimed at geriatric medicine fellows or interprofessional trainees, biology of aging courses from a Nathan Shock Center, and training in clinical research in older adults from existing programs at Veterans Health Administration Geriatric Research Education and Clinical Centers (GRECCs), National Institutes of Health (NIH) Claude D. Pepper Older Americans Independence Centers (OAICs), or the European Research Institute for the Biology of Aging.

Unique geroscience elements could be developed by a consortium of institutions and centers, shared, and flexibly implemented locally. Common curricular elements can be developed at a single center and distributed for local use. Online courses hosted at one institution could be open to others. Larger centers might implement intensive short courses for visiting scholars. An institution could mix and match elements to create a program for its trainees (Supplementary Figure S1). Helping to develop specialized new geroscience curricular elements would likely fit the missions of GRECCs, OAICs, Nathan Shock Centers, and similar centers. Foundations that currently fund geriatric medicine training, aging workforce development, or aging biology should view the development of a translational geroscience workforce as critical to their missions. Given the priority of the need, the NIH could specifically fund geroscience curricular development through a targeted funding opportunity or Common Fund initiative.

Ideally, training programs in this new field would be developed in concert with active clinical trials to provide practical examples from which trainees can learn and follow. Writing a draft IND application for an actual compound or a trial protocol for an actual proposed study under appropriate mentorship provides an ideal learning experience for a trainee, and materially advances the clinical study. Translational research targeting geriatric conditions must ultimately involve geriatricians. The workgroup recognized that this is a difficult and long-term problem embedded in larger challenges for the field of geriatric medicine. The pipeline of emerging geriatric fellowship-trained bench scientists may be as small as one per year in the United States. This, in part, reflects the “geriatrician gap” and
relative scarcity of geriatrician-investigators in general, but also the false impression that geriatric conditions and the field of geriatrics are unsuited to T1 translational investigation. Existing programs have been successful in encouraging researchers from other fields to study older adults, but they have not expanded the pool of geriatrics-trained clinical or translational investigators. The new field of translational geroscience requires at least a core group of geriatrician-geroscientists and a larger number of geriatrician clinical researchers who can function well in a multidisciplinary translational team. Integrating geroscience into medical school and fellowship curricula, exposing students and trainees to geriatrician physician-scientists, and promoting translational or bench research in the Medical Student Training in Aging Research program could help stimulate interest in geriatrics in general as well as cultivate geroscience candidates. The workgroup debated the potential impact on research training pipelines of lengthening the standard geriatric medicine clinical fellowship from 1 to 2 years. A longer fellowship would provide more time for trainees to master the increasing body of clinical expertise needed for geriatrics, allow greater exposure to geroscience and other translational areas relevant to geriatrics, and provide more intensive exposure to research in general. Altogether, this might help attract research-oriented trainees into geriatrics but also may discourage nonresearchers or nontraditional candidates from entering geriatrics. The workgroup did not reach a consensus. Regardless, many geriatric medicine fellowship programs have mechanisms to support further intensive research training that can be readily applied to translational research training.

Existing NIH funding mechanisms, such as the GEMSSTAR program and Paul B. Beeson career development awards, are natural fits to fund trainees in geroscience and should be expanded with dedicated support for awards to candidates pursuing a geroscience career path. Although Beeson and GEMSSTAR currently focus on early career investigators, it will be crucial to also support midcareer changes in focus toward geroscience to quickly leaven the field of geroscience with experienced investigators ready to act as mentors. The R38 Stimulating Access to Research in Residency program could also be tuned to specifically support programs for translational geroscientist development.

Finally, these deeply collaborative programs require host organizations to act as hubs. A barrier to translational science in aging has historically been the division of researchers across societies with different professional constituencies and areas of emphasis, such as the Gerontological Society of America, American Geriatrics Society, and American Aging Association. The NIA’s Division of Aging Biology and Division of Geriatrics and Clinical Gerontology provide a laudable model in their collaborative funding programs that bridge shared interests. The new national Research Centers Coordinating Network and Clinician-Scientists Transdisciplinary Aging Research Coordinating Center might provide a virtual or physical hub for geroscience training. The American Federation for Aging Research also provides models for coordinating transdisciplinary basic and clinical research in aging. Any new organization should be strongly grounded in these existing communities and supported by a broad range of member institutions to maximize cooperation.

CONCLUSIONS

The final Geroscience Network retreat provided a strong consensus that new approaches are needed to identify and train translational researchers who can bring geroscience advances through early-stage clinical trials and, ultimately, into the clinic to change the care of older adults. A cadre of geriatric-focused translational researchers from a variety of backgrounds should be identified early, mentored, and brought through an integrated training program that includes core curricular elements in clinical research, geriatric medicine, geriatrics research, and geroscience. Broader, modular programs will help strengthen the geroscience competence of the entire translational research chain. National guidance and facilitation will encourage the spread of such programs, but implementation will be local, flexible, and customizable. Wherever possible, programs will adapt existing local training programs and share geroscience resources through a network and core sites. New or adapted infrastructure and funding mechanisms are needed to support these common national efforts and to support trainees and mentors. The retreat generated strong enthusiasm and consensus for taking advantage of the current moment of opportunity to forge a new field of translational research with promise to transform clinical care for millions of older adults.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article.

**Supplementary Figure S1.** Sample multiyear modular curriculum outline using flexible local and shared elements. A trainee might acquire general clinical research training through existing Clinical and Translational Sciences Institute (CTSI) coursework. An existing interprofessional training program provides coursework in principles of geriatric medicine. A geroscience course is available online from another center. A geriatric research course is implemented locally using shared materials developed at another center. Materials from a local geropharmacology course are adapted for online learning and shared with other centers. The curriculum includes a site visit to the US Food and Drug Administration (FDA) to learn about regulatory issues and is capped with an intensive visiting scholar course at another institution on writing Investigational New Drug (IND) applications and designing a phase 1 clinical trial.

**Supplementary Table S1.** Retreat participants.