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Speaking the Same Language: Team Science Approaches in Aging Research for Integrating Basic and Translational Science With Clinical Practice

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Abstract

Research on aging is at an important inflection point, where the insights accumulated over the last 2 decades in the basic biology of aging are poised to be translated into new interventions to promote health span and improve longevity. Progress in the basic science of aging is increasingly influencing medical practice, and the application and translation of geroscience require seamless integration of basic, translational, and clinical researchers. This includes the identification of new biomarkers, novel molecular targets as potential therapeutic agents, and translational in vivo studies to assess the potential efficacy of new interventions. To facilitate the required dialog between basic, translational, and clinical investigators, a multidisciplinary approach is essential and requires the collaborative expertise of investigators spanning molecular and cellular biology, neuroscience, physiology, animal models, physiologic and metabolic processes, pharmacology, genetics, and high-throughput drug screening approaches. In an effort to better enable the cross-talk of investigators across the broad spectrum of aging-related research disciplines, a goal of our University of Pittsburgh Claude D. Pepper Older Americans Independence Center has been to reduce the barriers to collaborative interactions by promoting a common language through team science. The culmination of these efforts will ultimately accelerate the ability to conduct first-in-human clinical trials of novel agents to extend health span and life span.

Keywords: Animal models, Geroscience, Therapeutic interventions, Translation

Translational Significance: Progress in aging research has now advanced to a phase in which studies of interventions in animal models are providing essential data to inform the potential for improving human health span and life span. Given the critical differences between humans and animals, it is important to have an integrated team of basic, translational, and clinical researchers, that are working in parallel to ensure the data generated in the animal models will be translational. This article provides a framework for integrating these diverse research teams, with the ultimate goal to improve translational studies and more efficiently advance interventions that will benefit human longevity.

From Bench to Bedside: Bridging the Translational Gap in Aging Research

Aging research employing *Caenorhabditis elegans*, Drosophila, and mice has elucidated well-conserved pathways that regulate the life span and health span of these species (1–3). Similarly, these model systems have provided a platform to test compounds that might improve health span. In this context, agents such as metformin and rapamycin appear to extend the life span of a wide range of species, suggesting these U.S. Food and Drug Administration (FDA)-approved agents might also be beneficial for humans (3,4). These are a few examples of a growing number of biologically based, rational approaches to modify the aging process (5) as well as nonpharmacological interventions aimed at improving mobility and frailty including exercise (6–8). To this end, a critical component of translational studies is in vivo experiments that capture the biological construct of aging and analogous aging-related endophenotypes. Identifying an intervention that extends chronological age in an animal model does not prove that it will be similarly effective in improving either chronological age or health span in humans. To benefit human health, the intervention must show improvement in measures of aging-related

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impairments relevant to humans, including physiological, physical (eg, mobility, frailty), and neurological (eg, memory, attention) functions. In addition, although fundamental basic biological studies can be conducted in invertebrate species, translational studies are most appropriately conducted in vivo in mammals. This requires identifying robust and reliable aging-dependent outcome measures that have translational validity in an appropriate model system that best recapitulates the features of biological aging. In this respect, identical or analogous endpoints in animal models should be prioritized as a means that would best enable a clinical trial design. Given the inherent limitations of animal models, inclusive of the lack of typical comorbidities and spectrum of aging-related features that present in older adults which are not fully recapitulated in any individual animal model, these translational studies would be strengthened with the inclusion of a biomarker that is conserved across species from animal to human (eg, blood-based biomarker, oxygen consumption).

Team Science in Aging: Building the Translational Science Workforce

A framework of team science is most successful when it is initiated during the early phases of an investigator's training. To accomplish the integration of this framework, the University of Pittsburgh Claude D. Pepper Older Americans Independence Center's Research and Education Core (REC) uses a wide range of learning strategies for trainees (9). The REC integrates training in basic and clinical research, creates a structured but flexible and rich learning environment, and provides core competencies, self-assessment tools, research project support, and access to a talented source of senior investigators from multiple disciplines who are dedicated to aging research and mentoring. The training program includes coursework and seminars to introduce content from basic and/or clinical research and didactic workshops aimed at "speaking the same language" with the goal to better connect basic researchers with clinical researchers. The ultimate goal is to facilitate translational research, bridging the gap between basic and clinical research, and accelerating the pace of approval for a successful intervention.

As part of these activities, we developed an exercise that involved pairing a basic science researcher with a clinical researcher, with the goal of designing a hypothetical translational study using preclinical model systems and best matching to a proposed clinical trial design.

Key elements of this workshop involved discussions of the optimal clinical study population (eg, age, sex, predisposing conditions), the primary and secondary endpoints, and biomarkers to correlate functional outcomes. Discussions then focused on the most appropriate animal model (eg, age, sex, predisposing conditions), the analogous primary and secondary endpoints, and a biomarker to correlate the functional outcomes that were identical across species (Table 1).

Although the exercise was hypothetical, putting into practice this conceptual framework including establishing collaborations between clinical researchers and basic scientists with expertise in executing preclinical in vivo studies, will ultimately facilitate the pace of identifying potential interventions. When this is not done as a coordinated effort, but rather in siloed labs of basic scientists separately from clinical investigators, it risks failure to translate or rather minimizes the ability of the translational studies to serve as a predictor of a potential clinical outcome and ultimately wastes resources.

As a starting point for collaborative discussions, we created a rubric and provided an example of a hypothetical study design involving a nonpharmacological intervention. In this example case, the clinical study aimed to improve balance and mobility in older adults (age 65+) through an intervention of gait training on a treadmill. The research question was to evaluate whether gait training on a treadmill decreases gait variability and improves gait efficiency and physical activity versus over-ground walking. As presented in Table 1, the rubric provided a means to design both clinical and preclinical studies in parallel with the intention of the animal study to provide insight into the potential of the intervention to have beneficial effects in aging mice.

Rubric for Designing a Translational Study

Defining the Study Population

To enable the best match of a translational study to that of a proposed clinical trial, an understanding of the intended clinical population is an important element. For example, if the study is focused on patients with a diagnosis of Alzheimer's disease (AD), then a mouse model genetically engineered to recapitulate aspects of AD may include those with an analogous genetic mutation (eg, ApoE4, PSEN1) and/or with similar pathological features (eg, amyloid plaque deposition in brain) would be a relevant animal model. If the study population is focused on older adults, then an animal model with similar aging phenotypes to that of the clinical population may be suitable. More specifically, if older adults with progressive walking difficulty due to aging and not due to a traumatic event or specific disease are being studied, then normal aging mice may be appropriate and with no intended genetic or induced perturbation (Table 1). The key to a translational study for aging is to ensure that the biological construct of aging is part of the study design; although one should be cautious of not simply using literature references to guide an equivalent animal to human age based on a mathematical algorithm (11,12). In this respect, identifying the age-dependent phenotype at a chronological age in the animal model that also incorporates analogous aging-related changes (eg, physiological, metabolic, physical) would be a more appropriate model than young, experimental animal, and this phenotype should be confirmed within the researcher's own laboratory prior to embarking on an extensive intervention study. For example, if the intervention is targeting age-related hearing loss, a highly prevalent problem with aging, then the selection of an appropriate animal model with documented age-related hearing loss (eg, C57BL/6J mice at >12 months) would be a better model than a young mouse at 12 weeks of age with intact hearing or other strains such as DBA/2J with early adulthood hearing loss (13). Other important elements may include a priori inclusion and exclusion criteria (eg, impaired hearing, comorbidities, genetic predisposition). For the example clinical trial aimed at older adults >65 years of age, we identified aged C57BL/6J mice >24 months of age which has been suggested to be analogous to human age of >65 (11,12). We chose the C57BL/6J mouse strain specifically given its well-documented aging-related impairments in gait at 24 months, and devoid of the exclusion criteria proposed in the clinical study (eg, no progressive neuromuscular disorders,

Table 1. Translational Study Design Rubric

	Clinical Study	Animal Study
Study population	Older adults >65 Males and females	Aged mice >24 months* Males and females
Inclusion/exclusion criteria	Progressive neuromuscular disorders Severe pain that inhibits walking Inability to participate in the intervention Unstable heart disease Poor vision/hearing	Perturbation (no genetic or induced-disease/impairment) Baseline assessments to rule out significant impairment (eg, inability to perform, blindness, deafness) and counterbalanced across low and high performance to minimize bias †
Intervention ‡ and frequency	Training 2× per week for 12 wk – Either walking on the treadmill versus around the track over ground Frequency – Goal = 30–45 min of continuous walking per session	Training 2× per week for 12 wk – Training on a fixed-speed rotarod (10 RPM) Frequency – Goal = 10-min cumulative rotarod performance per session
Expected effect and outcome measures (3)	Interventions result in improvement from baseline Primary: Gait efficiency – Oxygen consumption at usual walking speed Secondary: Gait variability Activity and participation (LLFDI and physical activity)	Interventions result in improvement from baseline and *rotarod intervention hypothesized as improved v sham* Primary: Gait efficiency – Oxygen consumption at usual walking speed Secondary: Gait performance (% failure, gait variability) Frailty, sociability, spontaneous activity (wheel running), motivation

Notes: The rubric provides a means to design parallel human and in vivo studies with analogous outcome measures that may help to provide a go/no-go decision point for a proposed clinical trial based on expected outcomes, or de-risking if side effects are observed (see Figure 1 for additional details and assay descriptions). LLFDI = Late Life Function and Disability Instrument scale.
*Animal studies should be powered to detect a statistically significant effect; mouse aging studies typically require n = 8–12 per sex per treatment versus sex-matched young control (see [10]).
†High levels of variability are often observed in animals which can be related to caging effects among other variables; therefore, baseline data can be used to stratify high and low performers randomized across treatment groups to minimize bias (see [10]).
‡See Figure 1.

no severe pain phenotype that inhibits walking, ability to participate in the intervention; Table 1) (14). Our basic scientist with expertise in aging C57BL/6J mice and with their ability to perform treadmill tasks was also knowledgeable of the challenges of aging mice and suggested that a baseline assessment be conducted that could be used to exclude subjects that failed to perform the task but also stratify high and low responders into balanced cohorts so as not to unknowingly bias the study (Table 1; Figure 1).

Outcome Measures

A well-designed translational study should incorporate outcome measures in the experimental design that are most analogous, if not identical to, the intended clinical outcome measures. Although there are critical differences between humans and animals (eg, bipedal gait in humans versus quadrupedal gait in rodents), an experimental design that is cognizant of such challenges without overinterpreting the data is still beneficial (Figure 1). These translational studies may not only have predictive value for the potential efficacy of an intervention, but also provide an opportunity to evaluate which outcome measure may be most robust, to select and prioritize across a number of potential interventions which should be advanced for clinical trials, or more importantly, to de-risk an intervention when an adverse event is noted in the translational study prior to moving into a clinical trial.

In this example case, where the intervention was aimed at evaluating whether gait training in aging humans on a treadmill decreases variability and increases efficiency and activity relative to over-ground walking, the proposed outcome measures included gait efficiency as the primary endpoint with gait variability, activity and participation using the Late Life Function and Disability Instrument scale (LLFDI) (15–17) as the secondary measures. For the study design in mice, the first discussion was about which instruments would be best suited to capture the analogous measures while also being quantitative. Although gait variability including width, length, and step sequences can be quantified using treadmills in mice, because they are fixed to a treadmill speed optimized to encourage the mice to walk without stopping, then an additional instrument such as quantifiable running wheels could also be included to evaluate speed. Interestingly, running wheel activity in aged mice has also been demonstrated to show aging-related changes in speed which added an additional quantifiable measure to the proposed study (10). To capture an analogous measure of Activity and Participation to LLFDI, a frailty index in mice (10,18) was suggested to best capture changes across a spectrum of functional characteristics in the aging mice from baseline (pre-intervention vs post-intervention; Table 1) which has analogs of the LLFDI.

Testing an Intervention: From Mouse to Man

Once the outcome measures were identified, the next step in the study design was the intervention component. In the example clinical study, treadmill training was proposed 2× per week for 12 weeks with an "over-ground walking" control group that was required to walk around a track for a similar time (30 minutes) of the proposed treadmill

intervention. This presented a unique challenge for the translational study in the mice because living within the confines of a cage is not analogous to over-ground walking in the control clinical cohort. However, access to a running wheel within the homecage would be able to provide insight into spontaneous over-ground walking in addition to capturing measures of speed and motivation. With respect to defining the training intervention in the mice, the requirement of 30 minutes of continuous walking on a treadmill would need an additional motivating factor for the mice to maintain compliance. Typical motivational elements used in treadmill exercise in mice such as shock or food reward would then be presented variably across the experimental cohort depending on performance and these additional variable stressors could lead to a misinterpretation of the outcome (Figure 1). Therefore, the team discussed that in lieu of treadmill training 2× a week for 12 weeks, mice would be trained on a fixed speed rotarod versus non-rotarod trained cohort; with the expected outcome that this intervention would lead to improvement from baseline in treadmill gait measures and spontaneous wheel running activity (Table 1). It was also important to recognize that although the intervention frequency in humans was proposed as a 12-week training regimen (calculated as ~0.003% of the average human life span); a 12-week intervention in mice was a much more significant intervention (~10% of the average 29.5-month life span of a C57BL/6J mouse). However, it was noted that if the 12-week intervention met the outcome measures in the mice, a follow-up study could readily be conducted to evaluate the minimal intervention frequency sufficient to produce similar outcomes. The most important element of the translational study as discussed among the basic and clinical teams was the inclusion of a biomarker that was identical across species. With respect to the clinical study (Table 1), oxygen consumption could be easily quantified in humans by open circuit spirometry and analysis of expired gases during normal walking and then used to calculate the energy cost of walking (19). The energy cost of walking is used as an indicator of gait efficiency. This identical measure could also be quantified in mice using a similar approach (20,21). Based on the translational nature of these measures, the team decided that these would serve as the best primary outcomes with the analogous human-to-mouse outcomes (eg, gait speed) serving as secondary measures.

Concluding Remarks

As the field of geroscience continues to evolve and potential therapeutic interventions are being proposed, translational studies that bridge the gap from bench to bedside are increasingly needed. Relatedly, there is also a continuing need for more comprehensive comparative studies of aging to better enable more precise translational research. Critically, it is important to recognize that translational challenges are not unexpected and all animal models have limitations. Researchers need to have rational expectations of the translatability of preclinical findings and be careful so as to not misinterpret or over-interpret results. A cautionary tale can be found from findings in preclinical studies of cognitive measures where despite myriads of positive findings in rodent models, there has been a significant translational failure in human studies and often those data have been over-interpreted (22,23). In this respect, the establishment of Team Science initiatives that facilitate close collaborations between basic scientists and clinical researchers will ultimately enable more efficient translational studies. These important studies will not only allow for determining if resources are warranted to advance the intervention in a clinical population, but also potentially prioritizing 1 intervention over another based on the success or failure of a translational study, or de-risking interventions that may lead to adverse events.

Supplementary Material

Supplementary data are available at *Innovation in Aging* online.

System	Clinical Intervention	Outcome Measure	Analogous Mouse Intervention	Challenges ...
Cardiopulmonary 	• Aerobic conditioning	• 6 Minute walk test • 400 m walk test	• Forced Treadmill • Ladder climbing	• Use of noxious stressful stimuli (food restriction, shock probe) negatively influences CNS function and individual variability to stimulus is problematic
Musculoskeletal 	• Strengthening and Stretching	• Grip strength, lower extremity strength, power, repeated chair stand, sit and reach test	• Swim exercise • Grip Strength	• Adaption to "immobile posture" results in floating; swim stress negatively influences CNS (e.g. alterations in corticosterone) • Technician related variability (force); confounded by body weight
Nervous system 	• Task-oriented motor learning • Timing and coordination exercise	• Figure 8 walk test • Gait variability • Smoothness of walking	• Rotarod motor (learning) performance • Treadmill gait	• Ceiling effects (rotarod); quadrupedal gait in rodents versus bipedal in huams • Failure to perform at set speed

Figure 1. Challenges of designing analogous outcome measures in translational studies with animal models for evaluating non-pharmacological interventions to improve mobility.

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Conflict of Interest

T.F. is a founder and stockholder in Generian Pharmaceuticals and Coloma Therapeutics. S.J.S.R, S.L.G., N.M.R., and J.S.B. have no conflicts to report.

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