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Translational geroscience: From invertebrate models to companion animal and human interventions

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ABSTRACT

Translational geroscience is an interdisciplinary field descended from basic gerontology that seeks to identify, validate, and clinically apply interventions to maximize healthy, disease-free lifespan. In this review, we describe a research pipeline for the identification and validation of lifespan extending interventions. Beginning in invertebrate model systems, interventions are discovered and then characterized using other invertebrate model systems (evolutionary translation), models of genetic diversity, and disease models. Vertebrate model systems, particularly mice, can then be utilized to validate interventions in mammalian systems. Collaborative, multi-site efforts, like the Interventions Testing Program (ITP), provide a key resource to assess intervention robustness in genetically diverse mice. Mouse disease models provide a tool to understand the broader utility of longevity interventions. Beyond mouse models, we advocate for studies in companion pets. The Dog Aging Project is an exciting example of translating research in dogs, both to develop a model system and to extend their healthy lifespan as a goal in itself. Finally, we discuss proposed and ongoing intervention studies in humans, unmet needs for validating interventions in humans, and speculate on how differences in survival among human populations may influence intervention efficacy.

1. Introduction

1.1. What is translational geroscience?

The hope of dramatically extending our lifespan has captivated humanity for millennia. Over the last two decades, the biology of aging has matured as a field of study and led to greater engagement and investment in aging as a biological problem that can be understood at the molecular level [1–3]. In addition to the functional decline and loss of vigor associated with age, a generalized increase in disease susceptibility is now regarded as a consequence of biological aging [4,5]. Numerous chronic diseases manifest during aging. In fact, of the ten leading causes of mortality in high income countries (as of 2016, the last year with available data), eight have advanced age as their greatest predisposing factor [6]. Developing interventions that target the molecular mechanisms of aging (or "hallmarks of aging", as they're commonly referred) should not only add vigorous years to our lives, but also reduce overall human disease burden. Translational geroscience is an emerging, interdisciplinary field descended from basic gerontology that seeks to identify, validate, and clinically apply interventions to maximize healthy, disease-free lifespan [7–9].

1.2. Why drug aging?

In some ways, the secrets of healthy aging are not enigmatic. Proper diet with care to include necessary micronutrients, exercise, adequate sleep, and effective management of stress are all well-known and intuitive ways to add to our healthy years. An important question to address in light of this is why we should focus on developing interventions if lifestyle management alone is sufficient to extend healthy lifespan? One answer is that many people do not have the resources (either in terms of money, time, or both) to proactively invest in maintaining their health. For some, making sure there is enough to eat is a priority over eating healthy. Instead of exercise after a long day of work, many instead prioritize family time and relaxation. This situation is common, even in economically-thriving countries. Those people, whose limited

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resources keep them focused on day-to-day survival, are as equally deserving of living long, disease-free, lives as those with resources to invest in their long-term health. All of this is not to say that lifestyle choices should not be pursued, or even prioritized, as healthy aging strategies, only that pharmacological interventions that increase healthy lifespan are an option to address an important inequity that exists in human health.

Another reason to consider pharmacological intervention to maintain our health as we age comes from early successes in preclinical geroscience to identify compounds that can impressively extend lifespan in model systems. Several compounds are now known to extend lifespan across broad evolutionary distances [10–14]. For example, rapamycin, among the most promising current interventions, can extend lifespan in yeast, worms, flies, and multiple mouse models [15–20]. While the magnitude of effect varies between organisms and genetic backgrounds, experiments in genetically heterogeneous mice show average lifespan extension between 10 and 25% [19]. Applied to human populations, a 15% increase in average life expectancy at birth in the US would change from 78.8 (as of 2015, the last year with available data) to 90.6 years [21]. This would be a dramatic improvement in human survival. In addition to improving lifespan in wild type model systems, rapamycin also promotes extended lifespan in multiple mouse disease models [22,23], including heart disease [24] and cancer models [25–28]. This bolsters the hypothesis that there are broad clinical applications for rapamycin and other mTOR inhibitors. In a first of its kind test, short-term rapamycin administration improved measures of cardiac function in pet dogs [29]. While no lifespan data are available for humans, the short-term treatment with mTOR inhibitors appear to broadly improve immune function in the elderly [30,31].

In addition to rapamycin, multiple other compounds show promise as healthspan and lifespan extending interventions. Metformin, typically used to treat type II diabetes, extends lifespan in worms and mice [32,33]. In humans, numerous meta analyses suggest an association between metformin use and lowered cancer incidence [34–42]. Further tests in non-diabetic individuals, like the proposed Targeting Aging with Metformin (TAME) study, will better establish metformin's potential to broadly reduce cancer and other age-related disease incidence in humans [10]. Nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) are NAD (+) precursors that improve several features of aging, including muscle and cognitive function and vascular aging, and treatment with NR beginning at midlife is reported to increase lifespan in mice [43–45]. Senolytics, compounds that specifically target senescent cells for destruction, are important therapies that could increase lifespan and reduce age-related disease burden, particularly cancer and diseases driven by chronic inflammation [46–48]. Other compounds commonly used by humans, including caffeine, aspirin, and ibuprofen have successfully extended lifespan in model systems [12,14,49–51]. This raises the question: what other commonly consumed and FDA-regulated compounds alter physiology in such a way as to promote longevity?

1.3. How do we identify and validate lifespan promoting compounds?

What other molecules extend healthspan and lifespan? What combinations of molecules can be designed such that they target multiple pathways associated with aging and increased disease risk? Most importantly, how does individual genetic variation influence success of these interventions? We are only beginning to explore this “intervention space” and understand what is possible with regards to healthspan and lifespan intervention. In addition to broader options with regard to mTOR inhibition, compounds that target other pathways known to regulate aging, or stated more precisely, other nodes in the “aging network”, are critical to develop and validate. Breakthroughs in interventions that extend healthy longevity can lead the way to a precision medicine like approach to maximize individual health by utilizing combinatorial treatment strategies coupled with individualized dosing based on genotype. In what follows, we describe a translational geroscientific workflow to identify and validate lifespan-extending interventions. We envision this as a translational pyramid with identification of compounds in invertebrate systems, like yeast, forming the base of our translational research pipeline and leading to experiments in other invertebrate systems, in models of genetic diversity, into wild type and genetically diverse vertebrate systems, then finally, in companion pets and humans (Fig. 1).

2. Invertebrate systems

For basic biology, single-celled yeast and invertebrate systems (referred to hereafter simply as “invertebrates”) boast unrivaled benefits. These organisms are inexpensive to culture in large populations and have a variety of phenotypes and disease models that can be analyzed using multiple techniques. There are also well-developed genetic tools, models of genetic diversity, and cost-effective genome sequencing methods that are broadly utilized. Taken together, invertebrate systems are optimal for discovery-driven research. For biology of aging in particular, most invertebrates are short-lived, which allows experiments to be conducted in a reasonable time frame. Using multiple invertebrate models to identify and validate interventions provides assessment of evolutionary translatability that is important to consider when developing mammalian interventions [52]. Beyond these general characteristics, each of the three major invertebrate genetic model systems (yeast, worms, and flies) have unique strengths and weaknesses.

2.1. Wild type (WT) lab models

The term wild type (WT) originally described the collective traits of organisms isolated from the wild, namely flies [53]. Today, the term is more commonly used to denote the genetic background

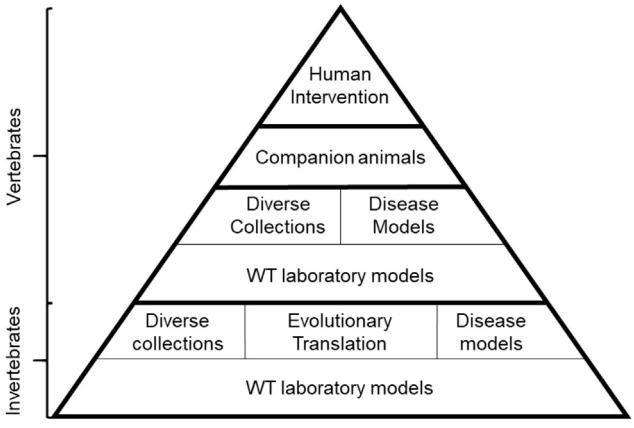

Fig. 1. A translational pyramid for longevity intervention from invertebrates to companion animals and humans. Interventions are first screened using common laboratory models (either invertebrate or vertebrate) in wild type (WT) laboratory genetic backgrounds. Successful interventions can then be studied for their efficacy among genetically-diverse collections. Disease models and other short-lived backgrounds can also be utilized to identify particular translational opportunities for interventions. Studies in genetically-diverse companion animals can validate interventions that are then tested in humans.