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METHODS PAPER

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Abstract The AGE Presents Introduction to Geroscience video lecture series is a collection of high-quality didactic video lectures and associated teaching materials focused on foundational topics in aging biology. The videos are made freely available on YouTube and are targeted toward an audience familiar with concepts learned in the first year of a college undergraduate biology/biomedical major. Members of the American Aging Association also receive the original lecture slides and lecture notes, with additional course materials to be developed in the future. We expect that these lectures will enhance understanding of geroscience among the general public while also providing tools that educators can use in the classroom for high school, undergraduate, and graduate level curricula.

Keywords Hallmarks of aging · Education · Gerontology · Longevity · Online

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The term geroscience refers to the field of scientific discovery that connects the biological mechanisms of aging with age-related functional declines and disease [1, 2]. Geroscience can be considered as a focused sub-field of gerontology, which broadly encompasses social, cultural, psychological, cognitive, and biological aspects of aging with a particular emphasis on challenges faced by older adults. The impact and relevance of geroscience is growing rapidly, as policymakers, regulators, and scientists in both academia and industry increasingly recognize the central role that aging biology plays in nearly every major cause of death and disability in developed nations [3].

As the profile of geroscience expands, there is a growing need for accessible, high-quality educational tools that impart foundational knowledge in the field, as well as contemporary concepts, theoretical frameworks, and cutting-edge advances in research. It is also essential that such a collection of resources come from a respected, authoritative source that is deeply connected with the science of aging, as there is an abundance of misinformation about aging biology already in the public domain. To address this need, the American Aging Association (AGE), with support of the Nathan Shock Centers of Excellence in the Basic Biology of Aging at the University of Washington and The Jackson Laboratory, has created a video lecture series and associated materials called "AGE Presents." AGE Presents serves to provide trustworthy and informative outreach to the general public and as a resource for educators who wish to develop geroscience-related curricula.

The initial series in the AGE Presents collection is called "Introduction to Geroscience." This series consists of ten didactic video lectures on foundational and current topics in geroscience. Each lecture is given by a scientist with specific expertise in the topic. The lecture topics are loosely based around the Hallmarks of Aging framework [4], which provides a structured, modular approach suitable for both classroom teaching and public viewing. Lecturers were instructed to make the content accessible to viewers with a basic understanding of biological principles expected for a typical freshman or sophomore undergraduate student majoring in biology or a closely related field. Although later episodes in the series are enhanced by prior episodes, each video is intentionally structured so as to be accessible on its own. This provides flexibility to educators who wish to incorporate a subset of lectures or individual lectures into a pre-existing or new curriculum.

Each video lecture was recorded between December 2020 and March 2021 using Zoom. Videos are made available on the AGE YouTube Channel (https://www.youtube.com/c/AmericanAgingAssociation), roughly once per week beginning in May 2021 and running through the 2021 AGE Annual Meeting in July 2021. AGE Members also receive access to the instructional content used in each lecture as a Microsoft PowerPoint slide deck and are free to use or modify individual slides so long as attribution is given to AGE Presents. We anticipate the creation of additional lecture notes, suggested readings, and quizzes for AGE Members to support easy integration into educational curricula.

The AGE Presents "Introduction to Geroscience" lectures consist of the following episodes:

Lecture 1: "Targeting Biological Aging: A New Paradigm for 21st Century Medicine." This lecture is presented by Dr. Matt Kaeberlein, Professor of Laboratory Medicine and Pathology at the University of Washington. Dr. Kaeberlein begins by introducing the concept of geroscience and illustrating the much greater impact on human health that can be achieved by targeting the biology of aging compared with traditional approaches of targeting individual diseases one-at-a-time [5]. He introduces the Hallmarks of Aging as a framework for understanding biological processes that become dysregulated during aging and discusses how the cross-talk between individual hallmarks represents a complex underlying network of interactions. Dr. Kaeberlein then discusses the drug rapamycin as a specific example of a potential 21st Century Medicine intervention, which appears to delay or reverse biological aging in studies of diverse laboratory model organisms [6].

Lecture 2: "Genome Instability and Aging." This lecture is presented by Dr. Laura Niedernhofer, Professor of Biochemistry, Molecular Biology & Biophysics at the University of Minnesota. Genome instability encompasses the myriad of different alterations to DNA induced by normal cellular processes and genotoxic stresses, including spontaneous chemical changes to nucleotide bases and single-base mutations, DNA strand breaks, epigenetic changes, and multiple types of telomeric instability [7]. Dr. Niedernhofer describes the DNA repair pathways that surveil and correct particular types of genome instability and explains how studies of progeroid syndromes, which are disorders characterized by accelerated aging phenotypes in certain tissues, have led the way toward defining the importance of DNA damage in age-related phenotypes. Using a mouse model defective for one DNA repair pathway as an example, Dr. Niedernhofer describes how age-associated DNA damage promotes increased cellular senescence, another Hallmark of Aging [4].

Lecture 3: "Telomeres and Aging." This lecture is presented by Dr. Nausica Arnoult, Assistant Professor at the University of Colorado, Boulder. Dr. Arnoult introduces telomers via the "Hayflick limit" discovery describing the finite replicative lifespan of human fibroblasts [8], which turned out to be due to telomere shortening with each cell division. She describes important functions of telomeres in bypassing the end-replication and end-protection problems and discusses telomeric structural components, including the T-loop and the shelterin complex. From this point, she describes the importance of telomeres as a tumor suppressor mechanism, pointing out that cells in the germline and pluripotent stem cells are not subjected to the "mitotic clock" due to the expression of telomerase. Dr. Arnoult then proceeds to describe the involvement of telomeric dysfunction in the development of cancer and in "accelerated aging" diseases such as dyskeratosis congenita, Hoyeraal-

Hreidarsson syndrome, aplastic anemia, and Werner syndrome [9]. Finally, she concludes with a brief mention of the correlation between telomere length and lifestyle interventions.

Lecture 4: "Epigenetic Alterations and Aging". This lecture is presented by Dr. Morgan Levine, Assistant Professor at Yale University. Epigenetic modification, particularly methylation of CG rich DNA regions, regulates gene expression and cellular differentiation by establishing active (euchromatin) and inactive (heterochromatin) regions of the genome [10]. Along with these concepts, Dr. Levine introduces an important distinction between chronological and biological age. She describes the development of epigenetic "aging clocks" which identify patterns of epigenetic changes that are associated with chronological age and have been proposed as useful tools for measuring biological aging [11, 12]. These epigenetic "aging clocks" represent an exciting new research paradigm to understand healthy aging, develop new insights regarding age-associated disease, and may, when combined with epigenetic reprogramming, lead to breakthroughs in regenerative medicine.

Lecture 5: "Proteostasis and Aging". This lecture is presented by Dr. Malene Hansen, Professor at the Buck Institute for Research on Aging. Dr. Hansen begins by introducing cellular defects observed during advanced age, particularly focusing on the proteostasis network. She then provides a detailed description of cellular events involved in maintaining proteostasis including regulation of protein synthesis, refolding of proteins by chaperones, protein repair mechanisms, and degradation of proteins in both the cytosol and within organelles. Specifically, in the cytosol removal of damaged proteins by the ubiquitin proteasome system, chaperone-mediated autophagy and sequestration and degradation of large aggregates by macroautophagy are critical.

Lecture 6: "Nutrient Signaling and Longevity". This lecture is presented by Dr. Leena Bharath, Assistant Professor in the Department of Public Health and Nutrition at Merrimack College. Dr. Bharath's talk is framed around the interaction of nutrition and aging, with an emphasis on intracellular sensing of nutrient supply and the effects of nutrient demand on healthspan and lifespan. She also highlights how aging promotes altered nutrient signaling which can lead to the onset of metabolic, neoplastic and neurodegenerative diseases. Dr. Bharath introduces how nutrient sensing regulates the cell's ability to recognize and respond to fuel substrates and then describes the network of factors that respond to nutrient status. Finally, she expounds on three factors that are studied extensively for their role in modulating aging in response to nutrient sensing: insulin/ insulin-like growth factor 1 signaling, the mechanistic target of rapamycin (mTOR), and AMP-activated protein kinase (AMPK).

Lecture 7: "Mitochondria, Oxidative Stress, and Aging." The lecture is presented by Dr. Holly Van Remmen, Professor and Chair of the Aging and Metabolism Research Program at the Oklahoma Medical Research Foundation. Dr. Van Remmen begins by distinguishing between "programmed" and "damage" theories of aging, with particular emphasis on Denham Harman's Free Radical Theory of Aging [13]. She then proceeds to describe free radicals and mitochondria as their main source, as well as non-mitochondrial sources of free radicals. After pointing out the multiple functions of mitochondria in biology, she proceeds to describe the nature of the oxidative damage caused by reactive oxygen species (ROS), specific markers of such damage, and the intricate cellular network of antioxidant response pathways and the redox network underlying it. Dr. Van Remmen then introduces landmark experiments in transgenic mice testing these theories, including mouse strains lacking or overexpressing antioxidant enzymes, strains with altered polymerase gamma activity, and strains with mitochondrial targeted catalase [14]. Finally, she introduces the naked mole rat as a long-lived model organism with exceptional antioxidant capacity.

Lecture 8: "Cellular Senescence and Aging". This lecture is presented by Dr. Darren Baker, Associate Professor at the Mayo Clinic. Dr. Baker begins with a general introduction of aging biology, including active areas of research and theories of aging with a focus on cellular senescence as a driver of aging phenotypes. He then proceeds to introduce the "Hayflick limit" [8], how it came

to be regarded as the driver of organismal aging, and the discovery of telomere shortening as the mechanism behind the phenomenon. He proceeds to describe the signaling pathways of the senescence program and the markers associated with senescent cells. Particular emphasis is given to the Senescence-Associated Secretory Phenotype [15]. Dr. Baker describes the serendipitous use of the *BubR1*$^{H/H}$ mouse model to discover the effects of the senescence program on accelerated aging phenotypes [16]. He recapitulates both positive and negative effects of cellular senescence on tissue homeostasis, and the development of the INK-ATTAC model to selectively remove senescent cells [17]. Using this approach, several causal relations between cellular senescence and age-related pathologies can be established. Finally, he concludes with a brief description of senolytics and senomorphic drugs and their therapeutic potential.

Lecture 9: "Stem Cell Exhaustion." This lecture is presented by Dr. Ashley Webb, Assistant Professor at Brown University. Dr. Webb begins with an introduction to stem cells. Stem cells reside within tissues and have the ability to replicate and give rise to terminally differentiated functional cells throughout the body. Stem cells, while prevalent and active during early development, are rare in adult tissues and typically found in a quiescent, or dormant, state [18]. As Dr. Webb describes, several age-related changes impair stem cell function, including reduced proliferative ability, skewed differentiation of progenitor cells, decreased ability to activate cells, and an overall reduced number of resident stem cells in aged tissues. These changes ultimately limit tissue repair and renewal, leading to age-related functional decline [19]. Promisingly, several lines of evidence suggest that stem cell exhaustion may be a reversible feature of aging. Heterochronic parabiosis (a surgical procedure where two mice of different ages share a circulatory system) reveals that circulating factors are capable of restoring stem cell function. Using a cocktail of different transcription factors, induced pluripotent stem (iPS) cells show epigenetic and metabolic reprogramming to a younger state. Well-known healthy aging dietary and pharmacological interventions, like caloric restriction, rapamycin, and NAD + supplementation, for example, also rejuvenate aspects of stem cell function [20–22].

Lecture 10: "Intercellular communication." This lecture is presented by Dr. Scott Leiser, Assistant Professor of Molecular and Integrative Physiology and Internal Medicine at the University of Michigan. Dr. Leiser reintroduces key concepts of aging and geroscience, the four main model organisms in aging research (yeast, worms, flies, and mice), and conserved longevity pathways. Dr. Leiser points to biological stressors and stress response mechanisms as common denominators underlying these longevity pathways and introduces the concept of hormesis as a cellular and organismal response that is associated with longevity [23]. Perception of stress, Dr. Leiser remarks, is an example of a conserved intercellular signaling network with profound implications in aging biology. He proposes that, by mapping the underlying communication networks, we may be able to uncouple the benefits of hormetic responses from the drawbacks of the stress itself. Using the Insulin/IGF-1 signaling axis and dietary restriction as examples, Dr. Leiser provides examples of how organisms sense these longevity cues in specific tissues, often neuronal in nature, which elicit longevity responses in different tissues [24]. He then describes proof of concept studies in worms that genetically or pharmacologically tampering with these cell non-autonomous pathways can modulate longevity independently of the initial stressor. Finally, Dr. Leiser concludes with outstanding questions the field is currently investigating, including the ability to translate pharmacological targeting of cell non-autonomous networks to human longevity.

The AGE Presents Introduction to Geroscience series consists of ten publicly available video lectures on the AGE YouTube channel and associated course-development materials provided to AGE members. These lectures are designed to be used together to comprise an introductory course on geroscience and aging biology or can be used individually, as desired, for didactic training in select topics of interest. We anticipate addition of several more foundational lectures to the AGE Presents collection as well as lectures on advanced topics in the field. It is our hope that the AGE Presents collection will prove valuable to AGE Members while simultaneously having a positive impact on outreach for the field to the general public.

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