Felipe Sierra · Ronald Kohanski *Editors*

Advances in Geroscience

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Foreword

In an introduction to a 2003 special issue of Science [1], my colleagues and I emphasized that "We have focused on physiological mechanisms underlying processes of aging, rather than on the large array of debilitating and costly disorders that so commonly emerge during the latter half of the life-spans of human beings." That was before the days of Geroscience, however! But what exactly *is* Geroscience? It is a term coined by my colleague and friend, Gordon Lithgow, a professor at the Buck Institute for Research on Aging who, true to his Scottish heritage, is thrifty with the use of all instruments of commerce, including terminology. Gordon used that nomenclature to summarize a new interdisciplinary research enterprise at the Buck Center; although it needs some grammatical editing, it is quite informative: "We consider that the relationship between aging and age-related disease (is) an important problem that can be tackled through an interdisciplinary approach" (http://www.geroscienceonline.org/index.php). This view emphasizes the concept that it is not only difficult to disassociate fundamental processes of aging from the numerous diseases of aging, but that joint investigations of these two domains of scholarship are essential if we are to unravel the pathogenesis of atherosclerosis, myocardial infarctions, strokes, non-ischemic heart failure, benign and malignant neoplasms, dementias of the Alzheimer type, frontal temporal dementias, Parkinson's disease and Lewy body dementias, peripheral neuropathies, cataracts and age-related macular degeneration, presbycusis, chronic obstructive pulmonary disease, type 2 diabetes mellitus, the metabolic syndrome, osteoporosis, osteoarthritis, sarcopenia, glomerulosclerosis, etc.

The editors of this volume, Felipe Sierra and Ronald Kohanski, have taken this concept to an exciting new level of implementation. As the Director of the Division of Aging Biology of the National Institute on Aging, Felipe approached his counterparts at more than twenty sister NIH institutes with narrow interests in specific diseases of aging with the following paraphrased sales pitch: "Let's have a discussion about how basic processes of aging are the major risk factor for your disease X. But first, I want to assure you that I do not want your money for my own institute! I want to start a 'Geroscience Interest Group' so that we can work together to accelerate progress towards the enhancement of healthy human

aging." The response was overwhelmingly enthusiastic and resulted in a series of productive joint conferences, including a 2013 Summit meeting at the NIH [2]. Readers are urged to learn more about this trans-NIH initiative via Felipe's excellent video on the subject: http://www.nia.nih.gov/about/links/2013/07/video-dr-felipe-sierra-discusses-trans-nih-geroscience-interest-group-and-more.

This volume, despite its 19 chapters and its stellar list of authors, can best be viewed as just a beginning step for Geroscience. Given the extent of research funding that it richly deserves – far more than the current NIH pay lines – we can anticipate major basic and translational advances in our healthspans, at which point we can go to the Food and Drug Administration and point out that the side effect of our research – increased longevity – can really be a good thing for humanity. As the late Charlie Chaplin pointed out, "we are all amateurs; we don't live long enough to become anything else" [1].

Seattle, WA, USA
June 5, 2015

George M. Martin, M.D.

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Preface

Geroscience is a new field that aims to bridge two communities: biologists focused on understanding the basic mechanisms that drive aging, and geriatricians attempting to improve the quality of life of elderly patients. Geroscience has been defined (Wikipedia) as "an interdisciplinary field that aims to understand the relationship between aging and age-related diseases." Because aging is the major risk factor for most chronic diseases, the "Geroscience Hypothesis" posits that common biological mechanisms of aging play important roles in the susceptibility of aged individuals to multiple chronic diseases.

The role of aging as a driver of chronic diseases is often downplayed under the assumption that aging is a non-modifiable risk factor. Yet we know that the rate of aging (however that is defined, as decay in function or susceptibility to disease) is modifiable by simple changes in the environment: a healthy diet, moderate exercise, and other elements of a generally healthy lifestyle will increase a person's chances of leading a longer and healthier life. In fact it is a dietary intervention, diet restriction, that provided the first handle to biologists' intent to understand the underpinnings of the aging process. That work, coupled with genetic experiments in short-lived simple organisms ranging from yeast to flies and worms, allowed scientists to unravel some of the major mechanisms involved. Furthermore, driven primarily by the Intervention Testing Program (created and supported by the National Institute on Aging), the field has moved recently to defining pharmacological interventions that expand lifespan in rodents (mainly mice). In addition to these impressive advances in terms of increasing lifespan, recently there has been a shift in focus, towards measuring healthspan as well as lifespan. Indeed, while some interventions (such as resveratrol) only increase health but not lifespan in mice, a handful of other interventions have been shown to increase both, although with the strong caveat that no manipulation has achieved that goal without having some secondary negative effects.

The enormous aging of the population worldwide, with the oldest-old being the age segment with the fastest growth, poses an urgent dilemma: if aging is indeed the largest risk factor for most chronic diseases, this increase in the proportion of elderly will necessarily pose an insurmountable challenge to the world's economic and

health-care systems. Fortunately, at the same time that this demographic change is reaching a critical stage, our understanding of aging biology is allowing scientists to consider the possibility of intervening to delay aging, and hopefully, with it all major chronic diseases. This improved knowledge has allowed the organization of concepts into six to eight hallmarks or pillars, believed to be the main drivers of the process. While some details still need further clarification, there is broad agreement within the research community about these major drivers, and differences only reflect different biases and granularity.

These advances and the emerging opportunity to modify the process of aging by pharmacological means spawned the appearance of the new field of Geroscience. The initial concept came from a group at the Buck Institute for Research on Aging which, under the leadership of Dr. Gordon Lithgow, put forward a successful proposal to the Common Fund of the National Institute of Health. This project, Interdisciplinary Research Consortium on Geroscience, was funded for 5 years between 2007 and 2012. Subsequent to that effort, the editors of this book started a trans-NIH effort following the same line of thinking and resulting in the formation of the trans-NIH GeroScience Interest Group (GSIG). The effort attracted the attention of over 20 different institutes within the NIH, as well as wide support from both the scientific community and, importantly, non-federal advocacy and support groups. With the imprimatur of so many NIH institutes, the subsequent growth of the field was impressive and culminated in the organization of a large Summit, Advances in Geroscience: Impact on Healthspan and Chronic Disease, held in the NIH Campus on October/November 2013. In turn, that effort resulted in the publication of a White Paper in November 2014 in the Journal *Cell*.

For whom is the book written? Geroscience is an interdisciplinary field attempting to address the mechanisms by which aging biology is the main risk factor for chronic diseases. As such, this book examines those mechanisms and it provides an emerging overview of the new discipline of Geroscience. Each chapter aims at connecting the clinical manifestation of specific age-related chronic diseases with the major pillars of aging biology. These pillars are suspected (or in some cases, known) to play a role in the etiology of these diseases, not just singly but in multiple diseases because aging is the major risk factor for their appearance. As such, each chapter combines features of clinical science and basic biology, and it is hoped that this approach will be informative and enlightening to both these communities: physicians will hopefully learn about the basic underpinnings of aging that might affect the outcome of chronic diseases and/or treatments, while basic scientists might profit from learning about clinical aspects of their disease of interest in the context of aging. Altogether, the editors and authors anticipate that this book will raise further awareness of the molecular mechanisms which might become targets for further investigation and, ultimately, new targets to combat multiple comorbidities at once.

This book examines the biological mechanisms and clinical consequences of aging by providing specific coverage on a wide range of chronic diseases, from arthritis and cancer to dementia and stroke among others. This book begins with an introduction of the general principles, including both a description of current

thinking in aging biology and a description of the Geroscience Hypothesis, with some background on the critical role that epidemiology has played in defining our basic understanding of age-related chronic diseases. Each of the following 16 chapters focuses on one particular disease, or group of related diseases, with an emphasis on how aging is a risk factor. This book finishes with a global discussion of pain in the elderly and a commentary on the important topic of translation into the clinic and the necessity of cross-fertilization between clinicians and basic scientists. Unfortunately, not all diseases afflicting the elderly have been covered, and this omission is simply the result of space limitations. It is hoped that this book will entice experts in those areas to think more deeply about the basis on which aging as a risk factor for their specialty disease, and perhaps publish their thoughts on this subject.

Contributors to this volume represent a large range of disciplines. An effort was made, whenever possible and appropriate, to engage in each chapter both basic scientists and clinicians; the editors are enormously thankful to all authors for the effort and sense of shared responsibility. Importantly, the editors thank all members of the GSIG executive committee for their support during the preparation of this book and the help provided on the selection of authors. Similarly, GSIG members are to be commended for the additional editorial work to complete this volume.

The editors believe that this book presents vital information and ideas that can help readers better understand how aging is a critical – but malleable – risk factor in chronic diseases of the elderly. The potential to alter the rate of aging is at the heart of Geroscience, and achieving that goal should improve lifespan and healthspan in the human population.

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