Drug Discovery

Anti-aging Drugs

From Basic Research to Clinical Practice

Edited by Alexander M. Vaiserman

ROYAL SOCIETY OF CHEMISTRY

Anti-aging Drugs
From Basic Research to Clinical Practice

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Foreword

In 1970, the world's largest learned society focused on aging underwent a schism that persists to this day. Denham Harman, one of the foremost American gerontologists of that era, had become so incensed at the flight from translational work—or even, to judge from public pronouncements, translational aspirations—of nearly all his colleagues that he felt it necessary to found the American Aging Association in direct competition with the Gerontological Society of America, which had overseen the field for the previous quarter-century.

Was that a good move? This excellent volume provides a fitting affirmative answer. The American Aging Association languished in genuine obscurity and neglect for over 20 years, but by 2000 it had risen to a much greater degree of respect, and it has since become arguably the most prestigious society in the field worldwide, without ever losing sight of its intervention-focused roots. It has done so because of real progress in the laboratory: progress that has shifted other communities to a more translation-friendly stance rather than the other way around.

The pharmacological approach that dominates the following chapters is by no means the only option available to the biomedical gerontologist; in particular, my own work and that of SENS Research Foundation is focused mainly on stem cell and gene therapies. But it remains apparent that pharmacological interventions, simply by virtue of being so much easier to administer, are of immense value even if they only provide much lesser benefit to the average older person than more exotic alternatives, not only because even modest benefit is better than nothing, but also because the latter will not be available for a while and the former can act as a bridge to them.

The first and last sections of this book are no less important. Biogerontology runs the same risk as any science, of becoming an echo-chamber immune to the need for interaction with wider society. Biologists of aging

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are perhaps even more duty-bound than any scientists, in consequence of the humanitarian importance of their field, to avoid falling into such a trap. It is therefore laudable that Vaiserman has chosen to invite chapters covering the pros and cons of both the feasibility and the desirability of significant, near-term success in the age-old quest to extend our youth. As one who has dedicated his life to that mission, I can attest that the best way to further it is to discuss it.

Enjoy these chapters as much as I have. They jointly constitute a comprehensive and invaluable primer in the current state of pharmacological anti-aging medicine.

Aubrey de Grey

Preface

Over the last few years, anti-aging medicine has received increasing attention in both public and scientific communities. Public interest in this area of research is largely driven by media attention related to recent developments in regenerative medicine and genome modification technologies. Probably the most famous example of that is the case of Elizabeth Parrish, the CEO of Seattle-based biotech firm BioViva, who claims that she had managed to reverse her own aging process with CRISPR gene editing technology by receiving a treatment targeting two gene loci, one a gene controlling telomere length and the other to protect against loss of muscle mass with age. Even though no confirmation has been received so far on whether or not this technology successfully changed her genome, many safety, ethical and regulatory issues are raised from this case. First of all, this concern is related to possible side effects associated with the use of this technology, primarily cancer. In this respect, using the more conventional pharmacologically based approach seems a reasonable alternative, particularly since many natural and synthetic agents have shown great potential for promoting health and longevity in numerous animal models. Among them, the most attention is currently drawn to rapamycin, resveratrol and the antidiabetic drug metformin. The last one was recently approved by the FDA to be examined in the Targeting Aging with Metformin (TAME) clinical trial to establish whether it may reduce the risk for aging-associated pathologies, such as cognitive impairments, cardiovascular disease and cancer, in non-diabetic persons. If successful, the TAME study would be the first demonstration that a particular drug can prevent or delay the onset of aging-associated chronic human disorders. It might provide a novel regulatory pathway for further clinical trials of pharmaceuticals specifically designed to slow the aging process.

The present volume is the first one devoted entirely to the pharmacological aspects of anti-aging medicine. It provides a comprehensive overview

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of current research aimed to search for natural and synthetic compounds that can potentially be developed as drugs for treating aging-related chronic pathologies and, ultimately, for healthy life extension. In the first section of the book, the basic conceptual and methodological aspects of modern anti-aging medicine are described. The next sections are concerned with the main classes of lifespan-promoting agents, such as antioxidants, calorie restriction mimetics, epigenome-targeted drugs and phytochemicals with health-promoting properties. In the subsequent sections, the strategies for translation of research findings in the field of anti-aging medicine into clinical and healthcare practice as well as opportunities and challenges related to the implementation of such approaches are discussed. This volume constitutes a comprehensive collection of chapters written by leading experts in the field. It will be a relevant and useful resource not only for professional scientists and clinicians, but also for scientifically interested amateurs wishing to know more about the current research in anti-aging pharmacology.

Finally, I would like to acknowledge Dr Oksana Zabuga for the helpful assistance in preparing the manuscript of this volume, as well as the editorial staff at the Royal Society of Chemistry, especially Harriet Manning and Rowan Frame, with whom I had the good fortune to work on this project, for their patience and encouragement.

Alexander M. Vaiserman

Contents

Section I: Overview

RSC Drug Discovery Series No. 57
Anti-aging Drugs: From Basic Research to Clinical Practice
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Published by the Royal Society of Chemistry, www.rsc.org

Section III: Antioxidants

Section IV: Mimicking Caloric Restriction

Section V: Other Pharmacological Approaches

Section VI: Social Context

Section I

Overview

CHAPTER 1

Anti-Aging Drugs: Where are We and Where are We Going?

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1.1 Introduction

Human longevity dramatically increased during the last century when implementation of vaccinations, disinfectants and antibiotics led to a substantial reduction of infectious diseases as a leading cause of death.[1] The decline in mortality among the elderly has continued over the past few decades. It is most probably owing to preventative factors, such as improved diets, as well as exercise and reduction in smoking.[2] If current demographic trends continue then 20% percent of the global population of 9 billion will be over the age of 60 by 2050.[3] As a consequence, most modern nations are undergoing rapid population aging. Although the life expectancy has enhanced dramatically in modern generations, this process has, nevertheless, not been accompanied by an equivalent increase in healthy life expectancy.[4] Since aging is a primary risk factor in most chronic disorders, the prevalence of age-associated disorders, such as type 2 diabetes, neurodegenerative disease, cardiovascular disease, osteoporosis and cancer, rises considerably with the increasing average age in populations of developed countries, representing a

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great socio-economic challenge. It is estimated that there will be more than 30 million people over the age of 80 will be in the U.S. by 2050; about half of them will suffer from different forms of dementia, and at least 3 million of all adults will be diagnosed with Parkinson's disease.[5] The expected prevalence of age-associated conditions will have substantial consequences for future society, including increased financial and psychological burdens for families and greater pressure on government health care programs and entitlement budgets.[6,7] The demographic trend consisting of an increasing proportion of aged people in the populations of developed countries likely explains the dramatic increase in the interest of the lay public and country leaders in research in the field of biogerontology.[8]

1.2 Human Life Extension: Concerns and Considerations

Investigations aimed at human life extension have traditionally raised concerns that it can lead to the growth of the older population segment and, consequently, to the high prevalence of ageing-associated chronic pathologies. Numerous experimental studies have, however, demonstrated that life extension is usually accompanied by delayed or reduced morbidity, including cardiovascular disease, neurodegeneration, and tumors.[9] There is also increasing evidence from epidemiological studies, which is consistent with the findings from animal models. For example, centenarians, in particular those who live in so-called 'Blue Zones' (five regions in Europe, Latin America, Asia and the US with unusually high concentrations of centenarians), have been not only shown to exhibit exceptional longevity but also often remain free from disability and chronic diseases until very advanced age.[10]

The compression of morbidity has been the primary strategy in gerontology and geriatric research during the last few decades. This strategy claims that we may limit morbidity to a shorter period closer to the natural ending of life, thus reducing the burden of illness and disability by delaying the age at onset of major age-associated chronic disorders.[11] Geroscience, a novel branch of geriatric medicine, is centered on healthspan extension.[12] Extension of healthspan is a crucial component of achieving 'optimal longevity', defined as living long, but with good health and quality of life, including improved functioning, productivity and independence.[11] Attempts to increase healthspan are currently focused on slowing the basic biological processes accompanying aging, such as mitochondrial dysfunction, cellular senescence, age-related decline of stress resistance, dysregulated cellular energy sensing and growth pathways, impaired proteostasis, deteriorated stem cell function/bioavailability, as well as oxidative and inflammation stress.[13,14] All these processes interfere with the normal physiological cellular signaling pathways, demanding compensatory adjustments with aging to maintain homeostasis. At a certain age, however, these compensatory mechanisms become exhausted and different aspects of aging are manifested,

thereby increasing the risk for functional decline and the onset and progression of chronic diseases.[15] Therapeutic strategies to combat aging and age-related diseases are a part of an investigation field commonly referred to as 'anti-aging medicine'. Anti-aging medicine has emerged as a new specialization in medical practice at the beginning of the 1990s. Over the past few years, it has become an increasingly discussed and debated topic.[16] Its main purpose is to prolong both healthspan and lifespan by specific regimes of exercise and dieting, as well as by advanced biomedical interventions aimed at slowing, stopping or reversing the aging process.[17,18]

Traditionally, the process of aging is believed to be 'natural' and therefore inevitable. However, in the view of many authors, the idea that aging is an indefeasible part of human nature is quite questionable.[19] In accordance with many modern evolutionary theories, aging has emerged as a by-product of evolutionary processes and does not have a specific function.[20] If aging is really not an intrinsic, irrevocable component of life, then it could be manipulated similarly to other processes that are generally deemed to be unnatural or pathological. The major assumption underlying anti-aging research is that age-associated senescence may be regarded as a pathophysiological phenomenon that might be prevented or even reversed.[21] Modern anti-aging medicine promotes biomedical technologies and approaches that have the potential to delay or postpone aging processes.[2] The success obtained in this research field is greatly attributed to the increasingly broad application of omics-based approaches, such as genomics, transcriptomics, proteomics and metabolomics.[22] Through the implementation of these technologies, a better understanding has been achieved regarding the key molecular and cellular pathways involved in the aging process, including inflammation, proteostasis, autophagy, mitochondrial efficiency and nutrient signaling, and regarding the most effective interventions to counteract age-related senescence.[23,24] The impetuous progress in highlighting the mechanisms underlying aging and longevity and first successful pharmacological interventions to extend healthy lifespan in different model organisms indicate that the aging process is malleable.

1.3 Anti-Aging Pharmacology: Promises and Pitfalls

The development of pharmacological agents targeting aging-related functional declines and pathological manifestations ('anti-aging drugs') is now in the spotlight in geroscience. An exponential growth of research in the field of geriatric pharmacology, including the study of prospective anti-aging drugs, has been observed over the past 20 years.[25] The first step in the process of drug development is known to involve the selection of druggable targets.[26] The situation when gene targets are determined by the study of genetic variations linked to either gain-of-function or loss-of-function phenotypes is especially useful because these targets can be considered as those that have been reliably validated.[27] Over the last two decades, a number of genetic pathways have been identified that play an unequivocal role in control of the aging

process and longevity;[28–30] all these genes represent attractive drug targets. Currently, many pharmacological agents targeting the putative mechanisms of aging are under development.

Taking into account the extraordinary complexity of the mechanistic pathways underlying the aging process, the recognition of these pathways and development of anti-aging interventions seems a challenging task. Significant progress has, however, been achieved in the last few years in this research field. A number of pharmacological agents with the potential to target particular aging-associated pathways and to produce protective responses against age-related pathologies are currently under investigation. In recent years, several classes of bioactive chemical agents and nutraceuticals have been shown to have potential therapeutic efficacy in anti-aging medicine.[3,31] In experimental studies, many substances have been identified as having life-extending properties. Among them are calorie restriction mimetics, such as resveratrol, rapamycin and metformin,[32,33] antioxidants (vitamins A, C and E, quercetin, melatonin, coenzyme Q10, *etc.*),[34] autophagy inductors, such as spermidine,[35,36] senolytics,[37] phytochemicals, *e.g.*, curcumin, genistein, catechins and epigallocatechin gallate (EGCG),[38] and several other natural and chemical compounds. In recent years, modern biotechnological approaches have been used for developing novel anti-aging pharmaceutical applications. For example, the coupling of curcumin-based nanoparticles with the Tet-1 peptide, which has affinity for neurons and possess retrograde transportation properties,[39] as well as mitochondria-targeted antioxidant SkQ1,[40] have been recently explored as promising therapeutic applications for the treatment of Alzheimer's disease. Over the last decade, consistent evidence has also been reported for the role of epigenetic factors, including DNA methylation, histone modifications and microRNA regulation, in the aging process as well as in the pathogenesis and progression of age-related diseases.[41,42] A lot of hope is being pinned, therefore, on pharmacological agents targeted to the epigenetic regulation of gene activity, such as inhibitors of DNA methyltransferases and histone deacetylases, including sodium butyrate, trichostatin A, sodium 4-phenylbutyrate and suberoylanilide hydroxamic acid.[43]

It should, however, be noted that all agents that can be classified as potent anti-aging therapeutic compounds are multi-functional and targeted at multiple signaling pathways mediating aging. Moreover, the evidence remains limited regarding the overall health benefits of these substances, including epidemiological studies exploring the consequences of their long-term intake for human health. Furthermore, there is evidence that uncontrolled intake of some anti-aging agents can be useless or even harmful. For example, the consumption of antioxidants is considered as quite reasonable by many researchers, especially in the cardiovascular research area.[44] The appropriateness of antioxidant intake, however, still remains a matter of debate. Meta-analysis of observational studies and randomized controlled trials conducted in well-nourished and healthy populations demonstrated that antioxidant supplementation may be associated with undesirable consequences for health and all-cause mortality.[45] Another example is the fact that supplementation with several promising pro-healthspan compounds can

in some cases trigger insulin resistance. This applies to substances such as rapamycin[46] and statins.[47] Therefore, people should use them with caution and only with careful medical monitoring.

Another method of anti-aging drug discovery is evaluating the pharmacological agents already approved by the FDA and other regulatory agencies for treatment of particular conditions associated with aging, such as statins, metformin, beta-blockers, renin-angiotensin-aldosterone system inhibitors, thiazolidinediones, and anti-inflammatory medications.[48] These classes of drugs are commonly used in the treatment of patients with various chronic medical conditions and their efficacy and safety have been proven in many clinical trials. They have also been shown to improve health, physiological functioning and well-being in middle to old age patients with chronic disorders.[49] Such agents are presently not used in the treatment of age-associated physiological dysfunctions in the absence of clinical manifestation of disease. However, these medications might theoretically be redirected to treating or preventing conditions or syndromes typically associated with aging.

Le Couteur *et al.*[50] noted in their review that 'despite the potential profits and the extraordinary capacity of drug discovery technology, there is a paucity of new drugs in the development pipeline, particularly for those medications that are likely to be highly profitable because they are used long term and by a large proportion of the population.' The longevity dividend, *i.e.* an idea that extending healthy life by slowing aging is the most efficient way to combat the fatal and disabling pathologies that plague us today,[51] may provide an opportunity to revitalize the drug development pipeline. Indeed, by delaying the aging process *per se*, it likely would be possible to prevent or delay all age-associated pathologies rather than to overcome them one by one, which is the current approach of the disease-based paradigm in drug development. Furthermore, prevention of a particular age-related chronic disorder, *e.g.*, cardiovascular disease, will apparently have only a modest effect on the population life expectancy because comorbidity, *e.g.*, cancer, will to a great extent substitute the reduction in mortality risk caused by preventing the targeted pathology. The main idea of geroscience is that preventing the clinical manifestations of all age-related diseases as a group by inhibiting the basic aging mechanisms can be far more effective than preventing the individual chronic disorders.[11,49] A recent analysis conducted by Goldman *et al.*[52] demonstrated that substantial socio-economic benefits might be derived from this approach in comparison with current public health strategy targeted to prevention of particular disorders. According to this analysis, the economic impact of delaying aging and increasing healthspan in the US is estimated at ~7 trillion dollars over the next fifty years. Hence, it is obvious that discovery of new drug targets based on biogerontological research represents an incredible opportunity for the pharmaceutical and healthcare industries.[53] Currently, the consensus among physicians and health professionals that the optimization of physiological and mental functioning throughout the life course should be a major emphasis of any contemporaneous biomedical policy addressing global aging. A healthy lifestyle comprising proper

nutrition and physical activity represents the first-line function-preserving strategy. Pharmacological compounds, both existing and potential, can serve as a prospective complementary approach.[48]

1.4 Concluding Remarks and Future Directions

To summarize, it can be assumed that targeting aging *per se* can be a more effective approach to postponing or preventing age-related disorders than treatments targeted to specific pathological conditions. Because of the aging population, such a therapeutic strategy is undoubtedly an area of increasing relevance for the pharmaceutical industry and public health organizations. As has been recently emphasized by Longo *et al.*,[54] 'the time has come not only to consider several therapeutic options for the treatment of age-related comorbidities, but to initiate clinical trials with the ultimate goal of increasing the healthspan (and perhaps longevity) of human populations, while respecting the guiding principle of physicians *primum non nocere*.' In modern pharmacy, anti-aging is likely one of the most prospective markets because the target group can potentially include each person. Several supplements, such as resveratrol, are already advertised in the pharmaceutical market as "anti-aging pills".[55] Very promising in this regard is rapamycin (also known as sirolimus), which is already approved by the FDA as an antibiotic and immunosuppressant drug. Current marketing research demonstrates that most people are willing to pay for long-term pharmacological therapy to prevent or delay the aging-related decline in physical and mental functions.[50] Recent sociological surveys show a great desire for extended life and health in the US and worldwide. In most of the surveys conducted until now, the cautious attitude to life extension was a consequence of an erroneous equation of extended life with a prolonged period of age-related functional decline and frailty. When continued health was stipulated in the questionnaire design, responses significantly favored longer life. In the survey by Donner *et al.*,[56] 20% of respondents wished to die at the age of 85, whereas 42% wanted to have an unlimited lifespan. Despite the widespread misconception that implementation of anti-aging medicine would increase the proportion of chronic patients in modern societies, it in fact would lead to reducing the ratio of unhealthy to healthy population since it would result in delaying the onset of age-related pathological conditions. In other words, it may lead to a decrease of biological age (*i.e.*, old individuals will become biologically younger) and to an increase of the age of disability, thereby increasing the retirement age and enhancing revenues without enhancing taxes.[57] Optimistic predictions of the feasibility of health- and life-extending interventions, however, should certainly be critically discussed in terms of their ethical, economic and social implications. Only after in-depth examination and following comprehensive debates will the implementation of such approaches in clinical practice be possible.

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CHAPTER 2

Aging: Natural or Disease? A View from Medical Textbooks

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2.1 Introduction

Whether a given condition is labelled as a disease or not can depend on a number of factors—including linguistics. For example, in one survey people were asked of 60 different conditions whether they considered them to be a disease or not.[1] The study found that alcoholism was seen as a disease, but smoking not. In some ways this is an odd finding since both—broadly speaking—elicit dependence symptoms, involve substance abuse and are detrimental to health in the long-term. Plausibly, this quirk reflects the choice of words employed in the survey. Perhaps if the terms used had instead been *drinking* and *nicotine addiction*, the classification would have come out the other way around.

Difficulties of classification also affect *aging*. For example, if one went to the doctor and asked for a prescription for anti-aging drugs, their response would likely be surprise, amusement or perhaps mild irritation. This is because aging, in the medical field, is not regarded as a disease.

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The question of what exactly is meant by "anti-aging drugs" is complicated by several factors. First, linguistics, and the problem that the word "aging" has more than one meaning. Second, the question of whether aging is a disease. Thirdly, problems relating to what counts as an anti-aging intervention. These issues will be reviewed here briefly and a serving definition of the meaning of *anti-aging* suggested. This builds on previous work that attempts to define anti-aging interventions.[2–10] We will then present an attempt at a broad and general description of the biological basis of aging, to offer the beginnings of an etiological basis for the understanding of senescence as a disease syndrome. Then, in the main part of this chapter, we examine how the aging *vs.* disease question is presented in general medical textbooks.

2.1.1 What Does "Aging" Mean?

The word *aging* acts as a stumbling block in discussion because it has multiple meanings that are sometimes conflated. The main, distinct meanings are:

- The passage of time (*calendar aging*).
- Time-dependent alterations, usually in adult living organisms, but also inert objects (*age changes*).
- Cumulative deteriorative changes in adult organisms leading to pathology and death (*senescence*).[11–13] Senescence is one type of age change.

An unfortunate additional source of confusion is that the word senescence also has a second meaning, as introduced by Leonard Hayflick, that of *cellular senescence*. This refers to a specific type of cellular change where the proliferative capacity of cells is lost and a pathogenic hypertrophic phenotype appears. Confusion between these two meanings can, in some contexts, be avoided by use of the term *organismal senescence* to contrast with cellular senescence. However, it seems likely that the two meanings of senescence will continue to generate confusion. Replacement of *cellular senescence* with another term would solve this problem.

Thus, the English language is a hindrance in that the multiple meanings of aging impede understanding. Not all languages have this problem; for example the Russian *stareniye* (старение) means, essentially, senescence. For people, age changes include maturational changes, such as the attainment of wisdom, and character development. In this sense, an anti-aging drug would be highly undesirable; clearly, the interest is in anti-senescence (or geroprotectant) drugs, where senescence is meant in its original sense, not the sense of cellular senescence.

2.1.2 Is Aging a Disease?

Human senescence manifests as a wide range of deteriorative changes, including some that are debilitating and sometimes fatal (*e.g.* cardiovascular disease, cancer and dementia) and some that are not (*e.g.* greying of hair

and wrinkling of skin). In medicine, a conceptual division is made between the former, as diseases for which aging is a risk factor, and the latter, which are not pathological but rather manifestations of *normal* aging.[14–16] Here, aging itself is viewed as a natural and non-pathological process. However, this division and the notion of normal aging is problematic in a number of respects. For example, the designation of particular senescent changes as normal or pathological has been controversial, as illustrated by the transfer of late-onset Alzheimer's disease and osteoporosis from the former to the latter category.[5] Moreover, from a biological perspective, senescence, a biological process whose defining characteristic is deterioration, is a fundamentally pathological process, identifiable as damage accumulation, degeneration, loss of function, and emergence of numerous disease states that can cause suffering and death. At present there exists some division between perspectives on aging in the medical and scientific domain. In the former the concept of normal aging is more prevalent, whereas in the latter there are more doubts about the existence (or meaning) of "non-pathological senescence".

As a contribution to this debate, we present here an attempt at a disease definition of aging. Ideally, a disease definition will include a full description of the disease etiology. In the case of aging this is not possible since the biological mechanisms that cause senescence are only partly understood. This definition does not pretend to encompass the views of all biogerontologists, and it surely will not do so. We hope that its faults will incite others to develop better definitions.

2.1.2.1 An Attempt at a Broad Account of the Etiology of Senescence

Organismal senescence manifests as diverse pathologies, including neurodegenerative diseases, cardiovascular disease and cancer, as well as minor pathologies such as skin wrinkling, and encompasses the etiologies of these conditions. There is no single etiology of organismal senescence, but rather multiple causes that generate a number of syndromes and unitary diseases. Thus, aging is a disease super-syndrome. These etiologies are predominantly the result of inherited predisposition, but environmental factors that promote damage and injury also play an important role, often through effects on the expression of predispositions (*e.g.* mechanical injury to joints can contribute to osteoarthritis).

Insofar as it is genetically determined, organismal senescence is a form of genetic disease, but of a special kind, as follows. According to contemporary medical understanding, a genetic disease is the result of a mutation in a gene that disrupts its evolved function, changing the gene from wild type to mutant, thereby disrupting biological function and causing pathology. By contrast, the inherited predisposition to organismal senescence is largely specified by wild-type genes. This seemingly paradoxical claim makes sense in the light of the evolution of aging.

Until the middle of the last century, aging was viewed as an adaptation that benefited the species by removing worn out, old individuals. This view is still