efficacy modifier takes on a different meaning and also a different value. However, there exist relations between the two ways of defining efficacy and efficacy modifier, as indicated in Table 1. Ehlert’s efficacy parameters are in fact reflective of the four geometric asymptotes in functional response curves; that is, they correspond to the fractional activity of four active receptor states (R*, AR*, R*B, and AR*). Importantly, however, the lack of efficacy cooperativity in Ehlert’s model may lead to difficulties in data analysis when strongly positive or negative allosteric modulators display a distinct asymptote that cannot be adequately described by $x_{2,0}/(x_2 + x_{0})$, except for $\beta_1/(1 + \beta_2 x)$ in OM or OM-concordant ATSM.

In summary, we have identified ‘ligand cooperativity’ exclusion or inclusion, respectively, as the differing mechanistic assumption underlying Ehlert’s receptor states and population model or OM and OM-concordant ATSM. We have bridged both approaches to receptor agonism and allosterism parameterization by relating model-dependent parameters, while noting both equivalence and key non-equivalence. Given the caveat of Ehlert’s model in lacking ligand cooperativity, functional receptor allosterism data analysis may encounter difficulties when strongly positive or negative allosterism is in play.

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References

Science & Society
Longevity-Promoting Pharmaceuticals: Is it a Time for Implementation?
Alexander M. Vaiserman1,∗ and Francesco Marotta2

Recent experimental studies demonstrate that medications targeting aging (antioxidants, calorie restriction mimetics, autophagy inducers, etc.) can substantially promote health and extend lifespan. Pharmacologically targeting aging appears to be more effective in preventing age-related pathology compared with treatments targeted to particular pathologies. The development of new antiaging drugs represents a great opportunity for the pharmaceutical and healthcare industries.

Population Aging as a Global Challenge
Human longevity dramatically increased over the past century, when implementation of vaccination, disinfectants, and antibiotics led to a substantial reduction in infectious diseases as a leading cause of death. As a consequence, most modern nations are undergoing rapid population aging. If current demographic trends continue, then 20% of the global population of 9 billion will be over the age of 60 by 2050 [1]. Although life expectancy has increased dramatically in modern generations, the process has not been accompanied by an equivalent increase in healthy life expectancy [2]. Since aging is a primary risk factor in most chronic disorders, the prevalence of age-associated disorders, such as type 2 diabetes mellitus (T2DM), neurodegenerative disease, cardiovascular disease, osteoporosis, and cancer, rises considerably with the increasing average age in populations of developed countries, representing a significant socioeconomic challenge. This could explain the increasing interest in gerontological research from the public and health professionals alike.

Healthspan Extension: Life to Years not Years to Life
The investigations aimed at human life extension have traditionally raised concerns that it could lead to growth of the older population and, consequently, to the increased prevalence of aging-associated chronic pathologies. However, numerous experimental studies have demonstrated that life extension is usually accompanied by delayed or reduced morbidity, including cardiovascular disease, neurodegeneration, and tumors [3]. There is also increasing epidemiological evidence that centenarians, in particular those who live in so-called ‘Blue Zones’ (five regions in Europe, Latin America, Asia, and the USA with unusually high concentrations of centenarians), not only exhibit exceptional longevity, but also often remain free from disability and chronic diseases until very advanced age [4].

For the past few decades, the primary strategy in gerontology was the compression of morbidity. Geroscience, a novel branch of geriatric medicine, is centered on healthspan extension [5]. The attempts to increase healthspan are currently focused on slowing the basic biological processes accompanying aging, such as oxidative damage, mitochondrial dysfunction, altered proteostasis, cellular senescence, and telomere shortening [1,5]. All these processes interfere with normal physiological cellular signaling pathways, demanding compensatory adjustments with aging to maintain homeostasis.

Antigliaging Pharmacology: Promises and Achievements
Traditionally, the process of aging is believed to be ‘natural’ and, therefore, inevitable. However, many authors question the idea that aging is an undefeatable
part of human nature. In accordance with many modern evolutionary theories, aging has emerged as a by-product of evolutionary processes and does not have a specific function [6]. 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 antiaging research is that age-associated senescence may be regarded as a pathophysiological phenomenon that might be prevented or even reversed [5]. The development of pharmacological agents targeting aging-related functional declines and pathological manifestations (“antiaging drugs”) is now in the spotlight in geroscience. Exponential growth in research in the field of geriatric pharmacology, including the study of prospective antiaging drugs, has occurred over the past 20 years [7].

The first step in the process of drug development is the selection of druggable targets. Determining gene targets by the study of genetic variations linked to either gain- or loss-of-function phenotypes is especially useful because these targets are considered as having been reliably validated [8]. Over the past two decades, several genetic pathways have been identified that have an unequivocal role in the control of the aging process and longevity; thus, all of the genes in those pathways represent attractive drug targets. Currently, many pharmacological agents targeting the mechanisms of aging are under development. Several classes of bioactive chemical agents and nutraceuticals have been shown to have potential therapeutic efficacy in antiaging medicine [9]. These include: calorie-restriction mimetics, such as resveratrol, rapamycin, and metformin; antioxidants (vitamins A, C, and E; quercetin, melatonin, coenzyme Q10, fermented papaya preparation, etc.); autophagy inducers, such as spermidine; phytochemicals [e.g., curcumin, genistein, catechins, epigallocatechin gallate (EGCG) etc.]; putative enhancers of cell regeneration; and several other natural and chemical compounds. Consistent evidence has also been reported for the role of epigenetic factors, including DNA methylation, histone modifications, and miRNA regulation, in the aging process as well as in the pathogenesis and progression of age-related diseases. Therefore, much hope is being pinned 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. In experimental studies, many of these substances have been identified as having life-extending properties. Table 1 details the lifespan-promoting effects of the most promising antiaging substances observed in the most widely used model organisms (nematodes, fruit flies, and mice). The maximum values for life-extending effects reported in the literature are shown in Table 1 as percentages of the mean lifespan changes.

However, all agents that can be classified as potent antiaging therapeutic compounds are multifunctional and target multiple signaling pathways underlying 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 on human health. Furthermore, there is evidence that uncontrolled intake of some antiaging drugs (e.g., antioxidants) can be useless or even harmful. 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 [10]. However, the consumption of antioxidants is considered as reasonable by many researchers, especially in the cardiovascular field [11].

### Table 1. Lifespan-Extending Effects of Topical Antiaging Compounds\(^a,b\)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Mechanism of Action</th>
<th>18%</th>
<th>19%</th>
<th>28%</th>
<th>31%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Antioxidant activity</td>
<td>20%</td>
<td></td>
<td>15%</td>
<td>40%</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Regulation of circadian rhythm</td>
<td>N.D.</td>
<td></td>
<td>28%</td>
<td>17%</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Mimicry of calorie restriction</td>
<td>18%</td>
<td>29%</td>
<td>26%</td>
<td>17%</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>Mimicry of calorie restriction</td>
<td>19%</td>
<td>26%</td>
<td>26%</td>
<td>17%</td>
</tr>
<tr>
<td>Metformin</td>
<td>Mimicry of calorie restriction</td>
<td>36%</td>
<td>N.D.</td>
<td>38%</td>
<td>N.D.</td>
</tr>
<tr>
<td>Spermidine</td>
<td>Induction of autophagy</td>
<td>15%</td>
<td>30%</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

\(^a\)Percentages are mean increase in lifespan, except where noted.

\(^b\)Abbreviations: HCD, high-calorie diet; N.D., not determined.
Should Aging be Treated as a Disease? Scientific and Social Perspectives

Currently, the US Food and Drug Administration (FDA) does not recognize aging as a medical condition. However, such a viewpoint seems rather contradictory. Indeed, the aging process is normally accompanied by many health problems that are commonly recognized as medical issues, including: atherosclerosis causing hypertension, heart attacks and strokes; muscle loss resulting in sarcopenia; decrease in bone density leading to osteoporosis; and atrophy of brain tissues causing dementia. All these states commonly occur in humans, are classified as diseases, and require medical intervention. This has various consequences: for example, more than a quarter of total Medicare spending in the USA occurs during the last year of life of older people without any improvement in their quality of life. Thus, a growing debate has emerged over the past few years regarding the issue of whether aging could be classified as a disease. One recent example of such discussion is a research topic in the journal Frontiers in Genetics: “Should we treat aging as a disease? Academic, pharmaceutical, healthcare policy and pension fund perspectives’ (http://journal.frontiersin.org/researchtopic/3133/).

Recently, the FDA policy on the matter became less rigorous. In particular, examination of the potential of the antidiabetic drug metformin in reducing the risk for aging-associated pathologies, such as cognitive impairments, cardiovascular disease, and cancer in non-diabetic people, has been approved [12]. This agent was chosen for clinical evaluation since it has been previously shown to influence many molecular and cellular pathways involved in aging processes, such as oxidative damage, cellular senescence, inflammation, autophagy, and apoptosis. In addition, monotherapy with metformin was recently shown to reduce the mortality of patients with T2DM compared with matched, nondiabetic controls [13]. The goal of the Targeting Aging with Metformin (TAME) clinical trial is to treat 3000 volunteers aged 70–80 years for 5–7 years and to see whether the development of age-related conditions is delayed. If successful, the TAME study would be the first demonstration that a particular drug may delay the onset of various aging-associated human diseases. This decision by the FDA could be indicative of a shift in its position on antiaging pharmacology from the regulations for cosmetic products to updated regulations for the prevention and treatment of age-related chronic disorders [14]. It might provide a possible regulatory pathway for further clinical trials of pharmacological agents designed to slow the aging process. Recognizing aging as a disease would inspire donors and research funding agencies to channel more resources into biogerontological research and, in particular, into the development of pharmaceutical agents targeting aging.

Targeting Aging: A Better Way to ‘Healthspan’

In summary, we have argued here that targeting aging per se can be a more effective approach to postponing or preventing age-related disorders compared with treatments targeted to specific pathological conditions. A recent analysis conducted by Goldman et al. [15] demonstrated that substantial socioeconomic benefits might be derived from this approach compared with current public health strategies targeted to the prevention of particular diseases. According to this analysis, the economic impact of delaying aging and increasing healthspan in the USA was estimated to be ~US$7 trillion dollars over a further 50 years. Hence, it seems obvious that the discovery of new drug targets based on biogerontological research represents an incredible opportunity for the pharmaceutical and healthcare industries.

References


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http://dx.doi.org/10.1016/j.tips.2016.02.003