

Review

The Business of Anti-Aging Science

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Age-related conditions are the leading causes of death and health-care costs. Reducing the rate of aging would have enormous medical and financial benefits. Myriad genes and pathways are known to regulate aging in model organisms, fostering a new crop of anti-aging companies. Approaches range from drug discovery efforts to big-data methods and direct-to-consumer (DTC) strategies. Challenges and pitfalls of commercialization include reliance on findings from short-lived model organisms, poor biological understanding of aging, and hurdles in performing clinical trials for aging. A large number of potential aging-associated interventions and targets exist, but given the long validation times only a small fraction can be explored for clinical applications. If even one company succeeds, however, the impact will be huge.

Treating Multiple Age-Related Diseases by Retarding the Aging Process

The dream of fending off old age is as old as human civilization. Given the global aging of the population, developing interventions that preserve health in old age and postpone the onset of age-related diseases is more important than ever. In addition, we now know that it is possible to retard aging in animal models. Various genetic, dietary, and pharmacological interventions have been shown to increase lifespan, in some cases dramatically (tenfold is the current record), in short-lived model organisms like yeast, worms, flies, killifish, mice, and rats [1–3]. Importantly, life-extending interventions not only increase longevity but can retard the onset of age-related diseases, resulting in the extension of healthspan (i.e., the length of time one lives in good health). These breakthroughs in the biology of aging and its impact on health and disease, referred to by some as ‘geroscience’, have led to the promise that we will be able to delay or slow human aging, resulting in unprecedented health benefits [4].

Leading causes of death worldwide, and notably in industrialized countries, are age-related diseases like cardiovascular diseases, cancer, and neurodegenerative diseases (Figure 1). Because of the strong relationship between the aging process and age-related diseases [5,6], the benefits emerging from anti-aging science have enormous potential. Using a model of future health and spending in the USA, the effect of delayed aging resulting in 2.2 years additional life expectancy would yield US\$7 trillion in savings over 50 years; whereas addressing single pathologies such as cancer and heart disease would yield less, mostly due to competing risks [7].

Aging can be defined as a progressive deterioration of physiological function accompanied by an increase in vulnerability and mortality with age [8]. Here, anti-aging based therapies are defined as those that delay the onset of multiple pathologies via core biological processes associated with age-related functional decline. While some therapies may be branded as single pathology for funding, business, or regulatory reasons, we include them nonetheless if they target aging-related processes or longevity-determining pathways and genes.

Trends

It is increasingly being recognized that directly targeting the aging process, as opposed to individual aging-related diseases or symptoms, is a viable strategy. This is leading to R&D with the ultimate aim of commercializing therapies directed at slowing aging itself.

Some therapeutic approaches – direct-to-consumer nutraceuticals and trial-tested scientific diets – do not require FDA approval, which can significantly reduce their time to market.

To slow the aging process, nonstandard therapies such as blood-based therapies are also being tried.

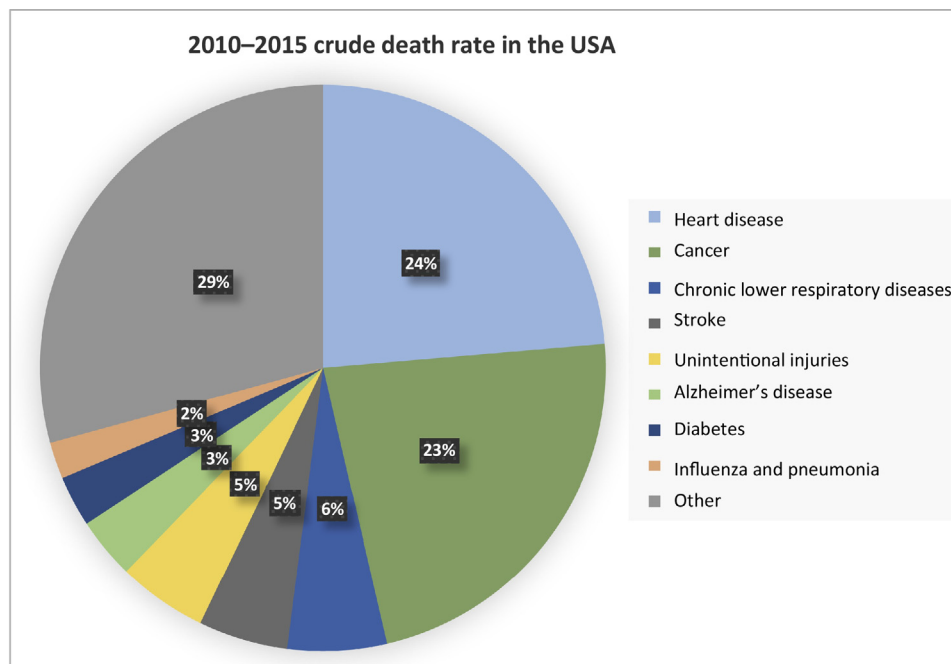
Big-data approaches are being harnessed in an attempt to build models of healthy aging.

Approaches are increasingly coming directly from aging results in model organisms.

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Trends in Biotechnology

Figure 1. Leading Causes of Death in the USA. Between the years 2010 and 2015 in the USA, an average of 2 577 202 deaths per annum from an average yearly population size of 315 109 368 were recorded (0.818%). The chart shows the top eight broad causes of death, with the major contributors being age-related and chronic diseases such as cancer, diseases of the heart, stroke, and Alzheimer's disease. The categories in the pie chart were grouped based on ICD codes as follows: heart disease (I00–I09, I11, I13, I20–I51); cancer (C00–C97); chronic lower respiratory diseases (J40–J47); stroke (I60–I69); unintentional injuries (V01–X59, Y85–Y86); Alzheimer's disease (G30); diabetes (E10–E14); and influenza and pneumonia (J09–J18). Data from the Centers for Disease Control and Prevention (CDC) Wide-Ranging ONline Data for Epidemiologic Research (CDC WONDER) (<https://wonder.cdc.gov/ucd-icd10.html>).

Given its huge potential financial benefits, anti-aging science has tremendous commercial opportunities. The anti-aging industry has struggled in the past in terms of reputation [9], but driven by more recent scientific breakthroughs it has been growing substantially with several young companies supported by world-leading brands like Google [10]. Here we first review companies and approaches in anti-aging biotech (Table 1). We then discuss some of the challenges and pitfalls in business development based on anti-aging science and lastly provide a vision for how the field may progress in the future.

Anti-Aging Biotech Companies and Approaches

Pharmacological Targeting of Aging

As with most diseases, traditional pharmacological approaches are the most straightforward and widely explored way to target aging. This topic has been reviewed [1,4,11,12] and therefore is only briefly discussed here (Box 1).

Box 1. A Plethora of Potential Drug Targets

The multitude of genes, processes, and pathways modulating aging in short-lived model organisms provide a plethora of potential targets for drug discovery [1]. Hundreds of genes modulating aging and/or longevity have been identified in model organisms [2], most of which can be grouped into common pathways and processes like insulin/insulin-like signaling, autophagy, oxidative phosphorylation, and TOR signaling [6]. There is also evidence that life-extending pathways tend to be evolutionarily conserved [62]. For instance, disruption of the insulin–IGF1 pathway has been shown to extend lifespan in yeast, worms, flies, and mice and *IGF1R* mutations have been associated with human longevity [3]. Thus, evolutionarily conserved life-extending genes and pathways are important targets for drug discovery [1].

Table 1. Anti-Aging Biotech Companies (Also See <http://whoswho.senescence.info/companies.php>)

Name	Funding/capital/size	Founded	URL	Therapeutic approach
Pharmacological targeting				
Antoxis	US\$2.5 million	2005	antoxis.com	Antioxidants
Androcyte		2011	supercentenarianstudy.com	Genetic study of supercentenarians
Sierra Science	Research LLC, marketing partner Defytime	1999	sierrasci.com ; defytime.jp	Telomerase-activating compounds
Prana Biotechnology	US\$20 million, public 2002	1997	pranabio.com	Neurodegenerative disease therapies; PBT2 in Phase IIb trials
Biotie	US\$152 million, acquired by Acorda Therapeutics 2016	1998	biotie.com	Neurodegenerative disease therapies; SYN-115 in Phase III trials
Navitor Pharmaceuticals	US\$57 million	2014	navitorpharma.com	Rapalogs
Cohbar	US\$9.2 million, public 2015	2009	cohbar.com	Mitochondria-based therapies; planned clinical trial for MOTS-c analog
Telocyte	Angels	2015	telocyte.com	Telomerase activation for Alzheimer's
Unity	US\$116 million	2009	unitybiotechnology.com	Senolytic agents
Oisin Bio	<US\$5 million, development/preclinical	2014	oisinbio.com	Gene therapy-based senescent cell clearance
Everon Biosciences		2009	everonbio.com	SAMolytic agents
Siwa Therapeutics			siwatherapeutics.com	Senescent cell antibodies
Proteostasis Therapeutics	US\$108 million, public 2016	2007	proteostasis.com	Drug-based control of protein homeostasis
Retrotope	US\$15 million	2006	retrotope.com	Drug-based mitochondrial restoration; RT001 in Phase I/II trials for Friedreich's ataxia
Mount Tam Biotechnologies	Preclinical, public 2015	2014	mounttambiotech.com	Rapalogs; TAM-01 in preclinical trials for systemic lupus erythematosus
resTORbio	US\$15 million, clinical subsidiary of Puretech Health	2017	restorbio.com	Develop immunosenescence drugs; mTORC1 inhibitor RTB101 in Phase II trial
Big data				
Calico		2013	calicolabs.com	Develop drugs based on the biology that controls lifespan
HLI	US\$300 million	2013	humanlongevity.com	Integrate large omics data sets to find patterns in age-related diseases
Insilico Medicine	VC-funded C-corp startup	2014	insilicomedicine.com	Identify existing drugs affecting age-related gene pathways
Chronos Therapeutics	US\$12 million	2009	chronos therapeutics.com	Repurpose drugs for neurodegenerative disease; patented use of fujimycin
Gero	US\$6 million, research		gero.com	Gene network analysis to identify anti-aging targets, worm study in progress; also has activity-based wellness-predictor phone app
DTC				
Elysium Health	US\$20 million	2014	elysiumhealth.com	Nutraceuticals; trial-tested NAD ⁺ precursor Basis
Juvenon		1999	juvenon.com	Rat-tested oxidative stress reducer Juvenon
L-Nutra	US\$10 million round B	2009	l-nutra.com	Trial-tested fasting-mimetic diet ProLon
Genescient	US\$500 000	2006	genescient.com	Nutraceuticals based on genetic analysis of long-lived flies
Young blood				
Alkahest	US\$54 million	2014	alkahest.com	Working with Grifols to develop plasma-based therapies
Ambrosia			ambrosiaplasm.com	For-profit clinical trial to study blood-based therapy

Table 1. (continued)

Name	Funding/capital/size	Founded	URL	Therapeutic approach
Stem cell/regenerative				
BioTime	US\$76 million, public 1992		biotimeinc.com	Develop cell therapies
Centagen			centagen.com	Develop activators of adult stem cells
RepliCel Life Sciences	US\$3 million, development	2006	replicel.com	Develop regeneration-based therapies; Phase I clinical trials for Achilles tendinosis and age-related skin damage
BioViva	Crowdfunded	2015	bioviva-science.com	Gene therapy to induce telomerase
Biomarkers				
Genox – subsidiary of NIKKEN SEIL		1991	genox.com	
Interleukin Genetics	US\$65 million, public 2003	1997	ilgenetics.com	

Notable examples of anti-aging drug discovery efforts include pharmacological manipulations of sirtuins, sirtuin 1 (*SIRT1*) in particular (targeted by resveratrol), and *TOR* (targeted by rapamycin), which are currently being explored [1]. *TOR* inhibition by rapamycin results in increased lifespan from yeast to mammals [1,13]. In a small but groundbreaking clinical trial by Novartis, rapamycin improved immune function in elderly volunteers [14]. Because rapamycin has various side effects, companies and laboratories are trying to develop safer analogs, known as ‘rapalogs’. One company focusing on the *TOR* pathway is Navitor Pharmaceuticals, which aims to treat diseases of aging through selective regulation of the mTOR pathway. Another similar company focused on rapalogs, Mount Tam Biotechnologies, has worldwide licensing rights to the Buck Institute’s research assets related to autoimmune disease including the rapalog TAM-01 (<http://www.buckinstitute.org/buck-news/buck-mt-tam-biosciences-target-lupus>).

Research on resveratrol and sirtuins was high profile in 2008 when GlaxoSmithKline (GSK) purchased the sirtuin-focused biotech company Sirtris (based on work at Harvard Medical School) for US\$720 million. Enthusiasm for resveratrol and sirtuins as anti-aging compounds has arguably declined in more recent years. Briefly, results have been largely disappointing since then [1], with resveratrol failing to extend lifespan in studies in mice [15] among other controversies [16]. GSK has closed Sirtris, although research on sirtuins and on new chemical entities that are thought to activate sirtuins [17] is still reportedly ongoing at GSK (<http://blogs.nature.com/news/2013/03/gsk-absorbs-controversial-longevity-company.html>). While Sirtris demonstrated that anti-aging biotech companies could rapidly grow in value and become a financial success for founders and early investors, its more recent problems might have hurt subsequent anti-aging science-based enterprises by discouraging investors and entrepreneurs.

Antioxidants have been historically a major focus of the field. However, currently the idea that antioxidant pathways play a major role in aging is being challenged [8,18,19], and epidemiological studies have largely failed to support the supposed benefits of antioxidants [20]. While many dietary supplements still focus on antioxidants, few companies in the field maintain such a focus. One exception is Antoxis, founded in 2005, which designs and synthesizes therapeutic antioxidants.

Telomeres, the protein-bound structures at the ends of chromosomes, shorten with cell division and, at least in some tissues, with age [8,21]. Although genetic manipulations of telomerase in mice have yielded conflicting results [8,21,22], one study found that

overexpression of telomerase in adult mice led to a 24% increase in median lifespan while not increasing the incidence of cancer [23,24]. Therefore, the idea of activating telomerase as anti-aging remains a powerful one, even resulting in one self-experiment using gene therapy by BioViva [25]. One notable company working on telomerase activation, Sierra Science, claims to have screened 250 000 compounds. Other companies focus on particular age-related diseases, such as Telocyte, which is working on telomerase activation for Alzheimer's disease.

Telomere shortening, as well as various stressors, can cause proliferating cells to stop dividing and enter a proinflammatory senescent state. There is evidence that senescent cells accumulate with age, at least in some tissues [8,26]. In a landmark study, drug-induced clearance of p16^{Ink4a}-positive cells (a marker of senescence) once per week from age 1 year extended the median lifespan in two normal strains of mice by 24–27%, although maximum lifespan was (slightly) increased in only one strain. Tumorigenesis and age-related deterioration of heart and kidney were delayed or slowed [27]. As a consequence, Unity Biotechnology, a company founded by researchers at the Mayo Clinic involved in the abovementioned work as well as the Buck Institute, has raised US\$116 million from investors including Amazon founder Jeff Bezos to develop senolytic (i.e., an agent that destroys senescent cells) treatments. Continuing research by the cofounders has focused on senolytic agents, including the killing of senescent fibroblasts with piperlongumine and ABT-263 [28]. Interestingly, they have also acquired a patent related to a senescent cell antibody for imaging and delivery of therapeutic agents [29].

Other companies focusing on senolytics include Oisin Biotechnologies, although, according to their website, they seem to be developing a genetically targeted intervention to clear senescent cells, suggesting a different approach than Unity. Moreover, Everon Biosciences has shown that a significant portion of cells with p16^{Ink4a} expression may be a subclass of macrophage termed senescent associated macrophages (SAMs) [30]. Following this discovery Everon has announced that they will focus on these SAMolytic agents. Last, Siwa Therapeutics' focuses on developing antibodies against senescent cell markers capable of identifying and removing senescent cells.

Given the multiple genes, processes, and pathways associated with aging, there are many opportunities to develop pharmacological approaches against one's favorite target (Box 1). For example, the idea that protein homeostasis is important during aging has led to the creation of Proteostasis Therapeutics, which aims to develop drugs that control the body's protein homeostasis, which in turn could lead to therapies against genetic and degenerative disorders including several age-related diseases. Also, Retrotope focuses on drug development for restoration of mitochondrial health. Their first product candidate, RT001, is being clinically tested in Friedreich's ataxia. Meanwhile, Cohbar has plans for Phase I trials in 2018 for an analog of the mitochondrial MOTS-c peptide, which was shown to prevent age-dependent insulin resistance in mice [31]. Last, while most efforts mentioned thus far are based on discoveries in model organisms, drugs targeting human longevity-associated genes are also promising [1]. For example, Androcyte focuses on supercentenarians – individuals over 110 years of age – in the hope of identifying unique determinants of these human longevity outliers that may then be targeted pharmacologically.

Basic Biology and Big Data

With a decidedly Silicon Valley-based confidence inspired by the successes of the high-tech industry spanning four decades, venture-capital funded big-data approaches are being pursued in aging and longevity science. High-profile players include Calico and Human Longevity Incorporated (HLI).

Started as one of Google's moonshot projects in 2013, Calico is attempting to harness big data to improve understanding of the basic biology that controls lifespan. Not much is known about how this will look in practice; however, they have formed an up-to-US\$1.5 billion partnership with AbbVie to develop drugs targeting diseases related to old age (<https://news.abbvie.com/news/abbvie-and-calico-announce-novel-collaboration-to-accelerate-discovery-development-and-commercialization-new-therapies.htm>).

Another high-profile player is HLI by Craig Venter. HLI is focused more directly on data than Calico and aims to create the largest database of integrated high-throughput assays – genotype, transcript, and microbiome data – along with deep phenotypic data on patients to fully map genotype to phenotype to inform health care in general. Published efforts have focused on deep sequencing of human genomes [32].

Other companies are using big-data techniques to find new uses for already approved drugs [12]. This is an attractive approach as pharmaceutical companies incur US\$1.8 billion in capitalized costs to develop and obtain approval for drugs from scratch, while the safety of approved drugs is already known [33]. While many companies do this, it forms a key component of some companies in longevity science. For one project Insilico Medicine uses deep learning on multiple 'omics' data types to find new relationships between existing drugs and gene regulatory pathways effected in, or otherwise related to, aging-related diseases. Chronos Therapeutics, by contrast, focuses on neurodegeneration-specific age-related diseases. They patented the use of fujimycin, an already FDA-approved immunosuppressive drug for the treatment of eczema and organ transplantation, to treat disorders related to cellular lifespan, which include many age-related diseases such as cardiovascular diseases, type 2 diabetes, Alzheimer's, and osteoporosis, by increasing cell lifespan through disruption of OBD1, a sirtuin inhibitor [34]. While these approaches remain unproved in terms of translation, it is interesting to note that a network pharmacology approach was recently shown to be able to predict new life-extending compounds in worms [35].

DTC Approaches

In addition to reasons for spending on basic research in general, anti-aging science has unusual potential to benefit from market forces due to particularly favorable demographics. The median wealth of US families aged 62 years or older is over US\$200 000, compared with US\$100 000 and US\$14 000 for middle-aged and young families, respectively. This may in part be responsible for the increase in investment in even non-traditional therapies and DTC products and services aimed at extending healthy lifespan.

One high-profile DTC company is Elysium Health, which sells its Basis pill directly to consumers. Basis contains an NAD⁺ precursor, nicotinamide riboside, that declines with age and is required for sirtuin activity; it also contains pterostilbene, which is similar to resveratrol. The systemic decline of NAD⁺ with age is a possible cause of age-associated changes in sirtuin activity in both the nucleus and mitochondria, with resulting age-associated dysfunction and pathologies [36]. In addition to its role in redox reactions, NAD⁺ is an important substrate of several enzymes: sirtuins, ADP-ribose transferases, PARPs, and CD38/CD157 (cADPR synthases) [37].

Elysium has already concluded a preregistered, 2-month randomized, double-blind Phase I trial for Basis using 120 healthy 60–80-year-olds. While results have yet to be published, a company press release claims that participant's blood NAD⁺ levels were increased by 40% for the duration of the second month. However, the release did not mention the results for health measures such as lipid profile, physiological performance, or sleep quality (<https://www.elysiumhealth.com/clinical-trial-press-release>).

Box 2. Intermittent Fasting Is Less Restrictive Than Caloric Restriction

IF – where, for example, calories are reduced by 40% on 2 days per week – has been argued by some experts to have the same range of benefits as chronic CR [63]. In a further refinement, a low-calorie/low-protein diet eaten for 4 days every 2 weeks, without effecting total long-term caloric intake, appears to have similar effects. Middle-aged mice showed improvements in a broad set of age-related phenotypes including reduced visceral fat, lower incidence of some cancers, fewer tissues with inflammation, reduced immunosenescence, improvement of some types of memory, and an 11% increase in median lifespan [40]. A similar diet taken 5 days per month for 3 months resulted in reduced fasting glucose, lower circulating IGF1 level, fat loss, and reduced CRP in those with elevated cardiovascular disease risk in a 38-person preregistered pilot trial [40]. Subsequently, a similar pilot trial of 100 healthy participants reported a reduction in markers for aging, diabetes, cancer, and cardiovascular disease [64].

Another notable product, Juvenon, by Juvenon, uses α -lipoic acid and acetyl-L-carnitine as main ingredients. Feeding rats acetyl-L-carnitine and α -lipoic acid leads to a decline in oxidative stress and DNA damage as well improved movement and memory [38,39].

Caloric restriction (CR) is the most studied and most consistent intervention that increases both health- and lifespan. While a CR diet is too harsh for most people, intermittent fasting (IF) has been proposed as a less-restrictive alternative (Box 2). Based on this premise, L-Nutra was created to develop and market proprietary fasting-mimetic meals designed to provide the beneficial effects of IF. Their first formulation, ProLon, comprises 5 days of meals to be taken every 1–6 months. In a registered, randomized 38-person clinical trial, ProLon was shown to reduce weight and abdominal fat and maintain healthy levels of blood glucose, C-reactive protein (CRP), and insulin-like growth factor 1 (IGF1) [40].

Using long-lived ‘Methuselah’ flies, Genescent uses genetic and gene expression network analysis to discover the genetic determinants of this long-lived strain. Their goal is to translate these findings into human targets by developing nutrigenomics-based therapies for chronic age-related diseases. Their proprietary combination of four herbal extracts had mixed results in extending lifespan in flies, with greater effect on stressed flies [41].

Young Blood

Perhaps most uniquely surprising, therapies are now being tested based on research into the effects of parabiosis (Box 3). A Stanford University spinout, Alkahest, with some of the main parabiosis researchers on board, was formed to take advantage of this research and test the effect of young plasma as a treatment for Alzheimer’s. Grifols, the largest plasma-based manufacturer worldwide, has invested US\$38 million in Alkahest with an additional US\$13 million to develop and sell Alkahest’s plasma-based products (<http://www.grifols.com/en/web/international/view-news/-/new/grifols-to-make-a-major-equity-investment-in-alkahest>). Additionally, young human blood has been shown to revitalize brain function in old mice [42].

One further company, Ambrosia, was established to run a clinical trial on the anti-aging benefits of young blood in relatively healthy people [25,43]. Controversially, however, the company is

Box 3. Anti-Aging Effects of Young Blood

In biology, parabiosis is the joining of two animals’ circulatory systems. Historically it was noticed that connected healthy animals could extend the lifespan of treated animals [65], although such effects have not been subsequently validated. In a series of studies starting in the 1950, it was observed that the older of the pair exhibited better longevity and tissue function [65] whereas young mice exposed to old plasma showed a decrease [66]. Further, aged mice given young plasma showed improvement in age-related decline in hippocampus-dependent learning and memory [67]. However, 10–12-month-old CBA/Ca female mice (a strain with normal longevity) injected weekly with young plasma did not show increased lifespan [68]. Most recently, using a blood-exchange device to exchange blood between young and old mice once, old mice exhibited improved hepatogenesis and response to muscle injury while young animals showed no difference in injury response and worsened hepatogenesis. For every other test – including physical performance and hippocampal neurogenesis – while young mice worsened, old mice showed no difference [69].

planning to charge participants US\$8000, making this a pay-to-participate trial that has raised ethical concerns [43].

Stem Cells and Regenerative Medicine

Several companies have also been focusing on stem cells and regenerative medicine. Given the multiple uses of stem cells, the applications in regenerative medicine extend far beyond aging conditions and diseases. Nonetheless, a few companies have focused in particular on age-related conditions. Examples include: BioTime, which aims to develop embryonic/iPS stem cell therapies and regenerative medicine; Centagen, which aims to activate adult stem cells; and RepliCel Life Sciences, which focuses on regenerative medicine to treat injured tendons, pattern baldness, and skin damaged by sun and age.

Challenges in Developing Human Anti-Aging Therapies

A growing number of companies are now focusing on anti-aging science (Table 1). In a way this is surprising, given that the first high-profile anti-aging company, Sirtris, while a success as an early investment has thus far failed to live up to its anti-aging expectations. Modern advances, abundant aging-related targets and an aging population can arguably be driving the current crop of anti-aging biotechs, but how realistic is it that these will succeed? In a sense there are few assumptions of which we can be confident. At present we can state that: (i) aging is a complex process; (ii) although there are numerous theories of aging with vocal advocates, there is no consensus among scientists regarding the underlying causes of aging; and (iii) aging can be manipulated in short-lived model systems by genetic, dietary, and pharmacological intervention. However, that leaves many open questions, so the uncertainty concerning human anti-aging approaches remains very high.

Humans Are Not Huge Worms or Big Mice

Although findings from short-lived model organisms, particularly in terms of the plasticity of aging, have been a major breakthrough in the field, the degree to which they are relevant to humans is unknown. Human homologs of genes associated with aging in model organisms have been associated with human longevity in some cases, but these are rare (Figure 2) and thus our understanding of the genetic basis of human longevity remains largely unknown [44]. For example, one recent large-scale study found only two loci significantly associated with human longevity and failed to validate previous findings like the association of *IGF1R* with longevity [45]. Therefore, it is plausible that most findings from short-lived model organisms will not be relevant to human beings [44]. Briefly, not only may the pathways necessary to extend lifespan in model systems be often irrelevant to the comparatively long-lived human species,

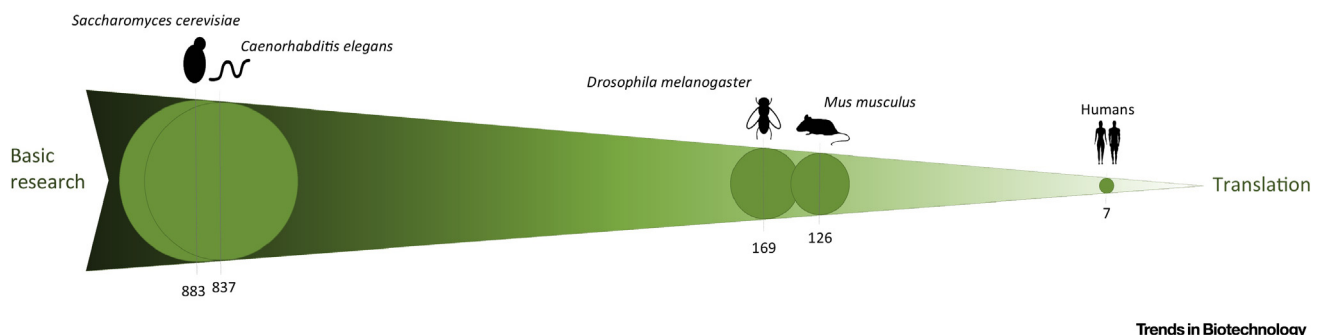


Figure 2. Genetics of Aging from Model Organisms to Humans. The numbers below each organism represent the number of aging- and/or longevity-associated genes for each organism in build 18 of the GenAge database [2]; for humans, only genes directly associated with human aging and/or longevity according to GenAge are included. The area of each circle is proportional to the number of genes.

but, to make matters worse, studies in model systems are mostly performed on genetically homogeneous laboratory strains that may not be representative of human populations [44]. Besides, our understanding of aging manipulations in short-lived models like yeast and worms is far superior to that in rodents [1,2,46] due to the ease of performing large-scale screens (Figure 2).

Given the above concerns, a major open question is how effective anti-aging interventions can be in humans. Even if they have benefits, how do these compare with mundane lifestyle choices like going to the gym? Likewise, while some anti-aging therapies might have benefits, they may not be beneficial for everyone. On the bright side, there are various efforts to develop alternative model systems, including dogs [47] and primates [48], although of course the limitation is that studies in such animals take much longer and are more expensive than in rodents.

So Many Targets, So Little Time

According to the GenAge database, we now know of >2000 genes that modulate longevity in model organisms [2], and the DrugAge database lists >400 compounds that can increase longevity in model organisms [46]. Most aging-related genes and pathways have not yet been targeted pharmacologically [46]. Given the volumes of data generated in the life sciences, various approaches in computational and systems biology have been developed to help identify and rank new candidates, identify regulatory genes, and gather biological insights [35,49–51], as reviewed in [52]. Such approaches are imperative, as is the integration of differing expertise in developing and prioritizing targets, drugs, and therapies for testing. Despite these advances, our capacity to identify interventions that will succeed in clinical trials remains poor.

One crucial limitation in biotech is the long time it takes for clinical validation and to obtain regulatory approval [53]. Taking several years, clinical trials are long, expensive operations. In aging this is even more of an issue because aging is, compared with traditional diseases, a relatively long process and we still lack accepted aging biomarkers that can be used as end points. In addition, the field of life sciences remains immature in that our knowledge of human biology is still very incomplete [54]. Thus, while the number of targets has increased dramatically thanks to advances in technologies like genomics, our capacity to validate those targets in a clinical setting has not substantially improved [53]. In other words, the success rates of clinical trials remain very low [55], and pharmaceutical R&D efficiency has even declined [56], despite what is generally agreed as substantial technological progress in recent decades. Therefore, biotech is a risky business that requires long-term involvement, and anti-aging biotech even more so.

Clinical Trials for Aging and Rejuvenation

Because of the time it takes for aging to develop, clinical trials for aging *per se* are not realistic at present. One effort, however, is trying to perform the first clinical trial for aging, using metformin, which would be an important proof of principle [57]. Even if this is successful, there are many practical challenges in performing clinical trials for aging, including how long it will take and how much it will cost [1,58,59]. As mentioned above, we also still lack suitable biomarkers of aging, which is a major impediment [12]. Recent advances in the development of epigenetic biomarkers of aging – an ‘epigenetic clock’ – offer promise [60] but it remains unclear whether these are suitable for clinical trials.

An additional concern in anti-aging interventions is whether these are suitable for old and frail individuals and/or long-term administration. Drugs like metformin already in clinical use may be particularly suitable for targeting aging, and recent discussions have explored how to develop a preclinical drug development pipeline in anti-aging [58,59]. In addition, while commercialization of medical interventions is dominated by small-molecule pharmaceuticals, investments

stemming from advances in anti-aging science now include young blood therapies, senescent cell ablation, and DTC diets and nutraceuticals (Table 1).

One important development in anti-aging therapies focuses on rejuvenation. Some anti-aging interventions like resveratrol and many longevity drugs promise to slow aging, which for clinical testing entails a variety of problems as described above. However, interventions like senolytic drugs and young blood promise rejuvenation, which is less challenging from a validation perspective and therefore much more attractive for commercial exploitation. Therefore, developing interventions that reverse at least some aspect of aging is a more powerful translational path than trying to slow aging.

Concluding Remarks and Future Prospects

Of the 4000 private and 600 public biotech companies worldwide, only a few percent have shown increasing profitability. Historically, only one in 5000 discovery-stage drug candidates obtain approval and only a third of those recoup their R&D costs [61]. Besides, as mentioned above, the success rate of clinical trials is not improving, although we have more information, data, and potential targets than ever before (see Outstanding Questions). Given the various constraints on the study of aging, including the reliance on short-lived model organisms, long validation times, and poor biological understanding, it would be surprising if most of the companies described here are active a mere 5–10 years from now. Likewise, most companies in the anti-aging biotech sector are startups, and thus riskier. From an investor's perspective this means that investors in anti-aging biotech are expecting to lose money but hoping to win big.

Omics approaches are imperative, as is a multidisciplinary outlook, but while these have augmented the search space, attrition rates remain very high. Perhaps surprisingly, despite the so-far failure of Sirtris, which would be expected to hurt the industry, anti-aging biotech is more vibrant than ever. Clearly even such high-profile failure has not dissuaded investors, including many tech billionaires. No doubt new technologies will be developed and new targets discovered in the coming years and decades, possibly opening new avenues for the commercialization of aging in other directions. The promise of fending off old age remains more powerful than ever and the financial gains for any company delivering on that promise will continue to be extremely attractive. Anti-aging biotech can then be seen as an extreme reflection of the biotech sector: risky and most likely to fail, but if one company is successful the outcomes are monumental.

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Outstanding Questions

How applicable to human aging is any given result in a model organism?

Are gaps in our understanding of the basic biology of aging in model organisms as well as in humans impeding the development of new approaches?

Which innovative methods may reduce the long validation times for aging therapies?

Given the time and the expense of validating aging therapies, what should be the criteria for prioritizing existing aging-associated targets and anti-aging interventions?

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