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The Scientific Quest for Lasting Youth: Prospects for Curing Aging

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Abstract

People have always sought eternal life and everlasting youth. Recent technological breakthroughs and our growing understanding of aging have given strength to the idea that a cure for human aging can eventually be developed. As such, it is crucial to debate the long-term goals and potential impact of the field. Here, I discuss the scientific prospect of eradicating human aging. I argue that curing aging is scientifically possible and not even the most challenging enterprise in the biosciences. Developing the means to abolish aging is also an ethical endeavor because the goal of biomedical research is to allow people to be as healthy as possible for as long as possible. There is no evidence, however, that we are near to developing the technologies permitting radical life extension. One major difficulty in aging research is the time and costs it takes to do experiments and test interventions. I argue that unraveling the functioning of the genome and developing predictive computer models of human biology and disease are essential to increase the accuracy of medical interventions, including in the context of life extension, and exponential growth in informatics and genomics capacity might lead to rapid progress. Nonetheless, developing the tools for significantly modifying human biology is crucial to intervening in a complex process like aging. Yet in spite of advances in areas like regenerative medicine and gene therapy, the development of clinical applications has been slow and this remains a key hurdle for achieving radical life extension in the foreseeable future.

Introduction

''Man will never be contented until he conquers death.''
—Bernard Strehler, 1977

Since the dawn of civilization, men have sought eternal life. In the Sumerian poem the *Epic of Gilgamesh*, one of the oldest written stories dating back over 4000 years, the protagonist is terrified by the thought of his own death and embarks on a (fruitless) quest for immortality. Stephen Cave in his book *Immortality: The Quest to Live Forever and How It Drives Civilization* argues that defying death, whether by spiritual means, technology, or by one's legacy, drives most of our lives and drives civilization itself.[1] Yet while nothing lasts forever and immortality is scientifically impossible, the idea that science can open the doors to eternal youth, in the sense of developing medical therapies that can ablate all detrimental aspects of growing old (including death from old age), has been slowly gaining strength.

About 50 years ago, Robbert Ettinger was arguably the first to propose a scientific approach to death in the form of cryopreservation of humans or cryonics.[2] More recently, the notion that aging can be cured like a disease and human life span radically extended flourished thanks to the work of Aubrey de Grey and his Strategies for Engineered Negligible Senescence (SENS) approach,[3,4] a series of rejuvenation therapies with the ultimate aim of reversing aging, as well as the predictions by futurists like Ray Kurzweil.[5] Many researchers have been critical of SENS, arguing that it is overoptimistic and implausible.[6–9] In spite of the discussions fostered by SENS, the idea that aging can be cured and people might start living hundreds or even thousands of years has been largely ignored by the scientific community.[10–14] With so many recent discoveries in the field, however, what are the prospects of abolishing old age? Here I discuss this timely and important topic, having in mind our knowledge of aging, intrinsic limitations of the field, and current and future technological possibilities.

I begin by briefly discussing whether we can and should cure aging from epistemological and ethical perspectives, respectively. I then recap the current state of affairs in the science of aging and the life-extension prospects based on contemporary work in the field. Finally (and readers already familiar with biogerontology may wish to skip directly here), I present and discuss my main thesis, which is that I see the key to radical life extension in the unraveling of the

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genome and the development of computational models to decipher the aging phenotypes that result from it and predict how best to intervene in them by reprogramming aging.

Can We Cure Aging?

> ''There is no likelihood man can ever tap the power of the atom. The glib supposition of utilizing atomic energy when our coal has run out is a completely unscientific Utopian dream, a childish bug-a-boo. Nature has introduced a few fool-proof devices into the great majority of elements that constitute the bulk of the world, and they have no energy to give up in the process of disintegration.''
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> —Robert Millikan, Nobel Prize in Physics, 1928

Given that aging is a complex process affecting practically every organ, some experts have questioned whether curing aging is possible.[6,7,15] Holliday[7] stated that: ''…to understand the whole set of events that occur during aging, one has to abandon specialisation and take a broad view of all the changes that occur during aging. This is, in effect, an impossible task.'' It is not possible to prove that aging can be cured, but there is no scientific reason to think that it cannot. History is, in fact, full of claims by experts that certain advances are impossible, only to be proven wrong soon after. Pioneer nuclear physicist Lord Rutherford, in 1933, famously dismissed harnessing nuclear power as ''talking moonshine'' and Lord Kelvin, President of the Royal Society, argued in 1895 that building airplanes was impossible.

Like the Wright brothers took inspiration from birds to construct heavier-than-air flying machines, researchers can take inspiration from species with negligible senescence, such as some species of fish, turtles, and salamanders, which appear not to age or at least age much slower than human beings.[16] If natural selection can eliminate aging in complex vertebrate species, there is no reason to think we cannot achieve it too via technology. Although all mammals are known to age, there are long-lived, cancer-resistant species like whales and mole rats,[17] showing that mammalian aging is malleable. Organisms with exceptional regenerative abilities, like planaria and hydra, also demonstrate that virtually unlimited regeneration is possible.

To put the notion of curing aging in a broader context of scientific breakthroughs, more ambitious projects are being undertaken in the biosciences. Human aging is a complex process, but not the most complex biological process of all. With $>10^{11}$ neurons[18] and $>10^{14}$ synapses,[19] the human mind is arguably more complex than aging, yet this has not stopped various expensive, high-profile efforts to attempt to understand the human mind and discover new ways to prevent and cure brain diseases, like the US National Institutes of Health Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative and the European Commission's Human Brain Project.[20] As detailed below, technological advances are making it possible to cope with the intrinsic complexity of biology both for studying the human brain and aging.

Acknowledging that aging can be eventually cured like a disease is not to say that developing a cure will be easy, or will happen in the near future. History is equally full of erroneous optimistic predictions, like the prediction in 1965 by Herbert Simon that ''Machines will be capable, within twenty years, of doing any work that a man can do.'' Curing aging is unlikely to be achieved by a single intervention, but rather by a combination of therapies dealing with different facets of age-related degeneration, possibly developed over time, and that might require periodic application to maintain youth indefinitely. Therefore, the development and application of the necessary technologies can take much longer than anticipated. Nevertheless, there is no inherent reason for not being able to cure aging.

Should We Cure Aging?

Scientists and philosophers have been divided on the issue of whether developing a cure for aging is socially desirable. Nearly everyone agrees that ameliorating health, discomfort, pain, and mortality from age-related conditions is welcomed, but the idea that eradicating aging altogether should be a goal of biomedical research has been attacked by many (reviewed in ref. 21). Common objections include fears of overpopulation, concerns over inequality, the idea that aging is natural and hence should not be tampered with, and that the finitude of life is a blessing. Advocates of life-extension research have argued that this is an ethical endeavor, even to the extreme point of curing aging and allowing people to live thousands of years, given that aging causes suffering whereas the putative social drawbacks of controlling aging are speculative and contested.[13,21,22] For example, doomsday overpopulation scenarios date back to the work of Thomas Malthus over 200 years ago with more recent failed Malthusian predictions of severe famines by Paul Ehrlich in the 1970s. Thus far, advances in science and technology that allow people to live longer have been paralleled by exponential progress in other areas. Besides, declining fertility rates in various countries, including Japan and several European countries like Germany, means that in some regions there is a population implosion, not explosion.[23]

Age-related disorders are an established priority of medical research. Few would disagree with the elimination of individual age-related diseases (*e.g.*, cancer, Alzheimer's disease) and with stopping and reversing individual age-related degenerative changes (*e.g.*, muscle loss, cognitive decline, visual impairment), so why oppose the elimination of all age-related diseases and degenerative changes? Furthermore, if developments allow for slowing aging by, say, 5%, no doubt efforts will be made to slow it by 10% and so on until aging can be stopped and reversed. The goal of biomedical research is to help people be as healthy as possible for as long as possible. This is an important point often overlooked: Ultimately, and whether we agree with it or not, biomedical research is progressing toward the development of a cure for human aging.

The Current State of Affairs in the Science of Aging: Longevity Regulators and Anti-Aging Drugs

To understand how life extension can be driven by technological and scientific progress, it is important to recap our current understanding of aging, its manipulation, and near future prospects for human applications. Of note, there has been rapid and impressive progress in manipulating aging in model organisms, with studies revealing that aging is surprisingly plastic.[24,25] Hundreds of genes, including over 100 in mice, have been identified that modulate longevity when engineered in model organisms.[26] Mutations in

some of these genes can extend life span dramatically; the current record is an almost 10-fold life extension in tiny nematode worms.[27] In mice, life span extensions have been more modest, but still impressive, with a roughly 50% increase in life span from single gene manipulations.[26] This genetic regulation of aging, unveiled in the past two decades, is arguably the field's greatest breakthrough to date. Progress has also been made in understanding environmental manipulations of aging, in particular caloric restriction (CR), which consists of limiting nutrient intake from diet without causing malnutrition, as well as in identifying various drugs that extend life span in model systems (reviewed in ref. 24).

One important finding emerging from animal studies is that not only can life span be extended but health can be preserved. Thanks to genetic manipulations or CR, mice not only live longer, they live longer healthier, with the onset of age-related diseases being postponed. That aging can be regulated to extend health span is important in terms of translating findings to humans because one common concern is that life-extension therapies will extend the period of decrepitude rather than preserve health. A 2013 survey by the Pew Research Center found that 56% of Americans would not want treatments to live decades longer.[28] This can be due to the perception that old people tend to be dependent and unhealthy and not wishing to extend life in such conditions. However, what the studies in rodents show is that extending life span is usually accompanied by postponing aging diseases and degeneration.

In light of this recent progress, are we any closer to curing aging? Probably not much. The prospects for drug discovery in the field of aging are extremely exciting,[24,29] as evidenced by the recent high-profile companies focused on longevity from Google (Calico) and Craig Venter (Human Longevity, Inc.). On the basis of genetic pathways that modulate aging, including via CR, many researchers in the field envision longevity drugs being developed in the foreseeable future. But even if we can develop therapies that mimic CR or the longevity effects of genes observed in model organisms, such therapies will not radically extend our life span. Extending life span by 50% would be extraordinary if applicable to humans, yet this would still be far from stopping aging. Besides, the benefits to humans of the longevity pathways identified in short-lived model systems are likely to be much more modest.[30] After all, how many times has cancer been cured in mice and then the ensuing clinical studies in humans fail? Recent studies of CR in rhesus monkeys support caution when extrapolating findings from rodents to humans by showing much more modest benefits than in rodents.[31] Life-extension mechanisms identified in model organisms may thus allow the development of interventions and drugs to target specific human age-related diseases, like cancer,[17] yet at most these will lead to a modest increase in human longevity.

Another difficulty is that the exact cellular and molecular processes involved in the manipulation of aging in model systems remain largely a mystery. A number of mechanisms of aging have been proposed, such as genome instability, stem cell loss, and telomere attrition.[32] Human syndromes resembling accelerated aging, the so-called progeroid syndromes, fascinating yet devastating diseases like Werner syndrome, whose patients have an average life span of 47 years, suggest genome instability as a possible cause.[33] Nevertheless, the underlying cause(s) of aging continue to be a subject of debate.[34] Therefore, it is dubious that reversing aging (*i.e.*, rejuvenation) is possible via known longevity pathways. Hence, if developing the technologies to eliminate aging and permit an extreme human life span are the ultimate goals of research on aging, then what are the necessary breakthroughs to achieve them?

Disruptive Technologies and a Roadmap to Human Life Extension

Life expectancy in industrialized countries increased over 50% in the 20th century, a product largely of technology in tackling infectious diseases. Thanks to various medical advances, life expectancy continues to increase (Fig. 1), albeit at a modest pace (which some argue may even level off [14]) that does not suggest a trend toward radical life-extension in the foreseeable future.[9] The only way to accelerate this pace is to tackle the process of aging itself. Contrary to infectious diseases, however, endogenous diseases caused by the body's intrinsic malfunctions are much harder to target therapeutically. It is not surprising that effective treatments are not available for various Mendelian diseases whose culprit genes are known, such as the aforementioned progeroid syndromes. Even if anti-aging drugs are soon developed (and I believe they will) to tackle age-related diseases and increase human life span, the current drug discovery paradigm is, by itself, unlikely to lead to a cure for aging. In fact, because small molecules are easier to translate to the clinic, we probably have focused too much on small molecules with limited effects. So which disruptive technologies are necessary to cure aging?

Therapies involving gene therapy, stem cells, and synthetic biology are leading the pack in disruptive medical technologies. SENS, in fact, is largely based on the development of regenerative medicine to reverse aging.[3] Even though our understanding of aging is incomplete, there is a finite number of human organs and components in cells and genes that can go awry with age. If there are a limited number of intrinsic mechanisms of aging, as appears likely,[32] although it is not impossible that there are more mechanisms of aging than we think, these in theory can be addressed one by one. Besides, at least some aging changes are hierarchical in the sense that they can be manipulated by pinpointing causal factors. For example, we can already reverse some forms of cellular aging *in vitro*, including in human cells via telomerase[35]; it is also possible to rejuvenate yeast by expressing a single transcription factor.[36] As interventions are developed and life expectancy increases, more interventions can be developed in the years of life gained, which has been argued could lead to the prevention of old age in individuals now alive[3] (but see Olshansky and Carnes[9] for a critique.

One of the major hurdles in medicine is the unpredictable nature of biological systems. For example, the percentage of compounds entering clinical trials that is eventually approved for clinical use is only 10%–20%.[37,38] Biology is intrinsically complex and thus, even with promising preclinical results from cells and model organisms, most drugs tested in humans do not behave the way scientists and clinicians predict, and they often have unpredictable negative

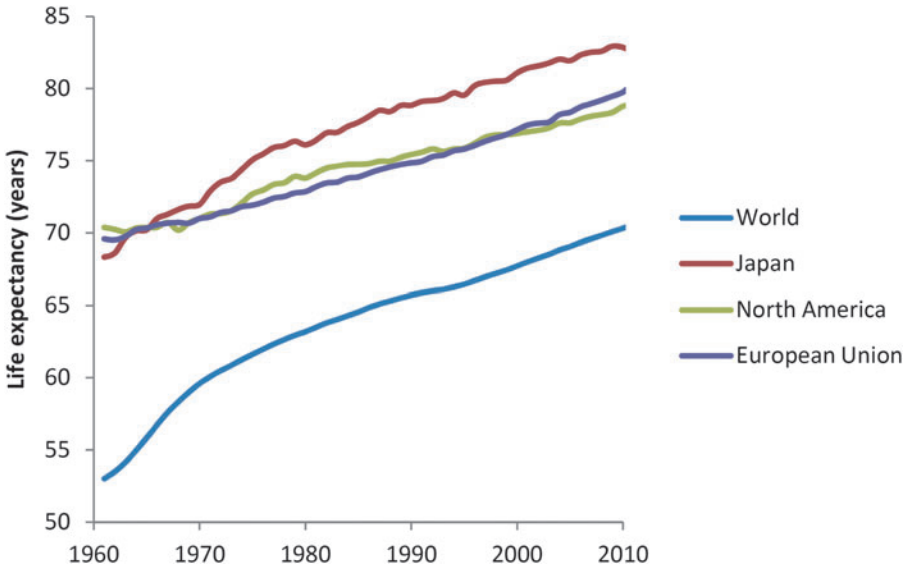

FIG. 1. Combined male and female life expectancy at birth for the world and for selected regions since 1960. Data source: World Bank (http://data.worldbank.org/indicator/SP.DYN.LE00.IN).

side effects.[38] Likewise, engineering biology, even in lower organisms, is still very limited, in part due to our incomplete knowledge of how organisms work at the molecular level.[39,40] Therefore, a much deeper understanding of biology is necessary to apply, for example, synthetic biology (the design and construction of new biological devices and systems) to clinical interventions.[41,42] These intrinsic limitations of biomedical science are particularly important in aging because experiments are so time consuming and expensive (even in animal models), and clinical trials are nearly impossible. Whereas fields like cancer research may be able to rely on large-scale trial-and-error approaches (*e.g.*, *in vitro* high-throughput drug screening), biogerontology has an intrinsic need to reduce the number of experiments necessary to obtain meaningful results. Fortunately, emerging technologies may allow us to tackle the complexity of life and develop more efficient therapies.

The genome is the digital blueprint from which each of us is created and our traits largely determined. Indeed, the genome determines, to a large extent, the pace of aging in mammals. For example, mice (even under the best environmental conditions) age much faster than humans. It remains a mystery why different species of similar body plan, biochemistry, and physiology can age at remarkably different rates, yet these differences must arise from differences between their genomes.[16] Presently, our understanding of how the genome determines us to age the way we do is still very limited. Besides, many facets of the genome remain a mystery and, at present, almost half of the ~20,000 human protein-coding genes have been poorly studied. In addition, emerging layers of gene regulation, like non-coding RNAs and epigenetics, remain largely unexplored. As an example, we recently performed an in-depth analysis of transcriptional changes with aging in the rat brain using next-generation sequencing and found a surprisingly large number of changes in non-coding transcripts; unfortunately, a mechanistic understanding of these changes is impeded by a lack of functional annotation of these elements.[43] If our ultimate goal is to engineer biology the same way we engineer electronics, we need a much more detailed knowledge of the basic biological components, specifically we must decipher the genome and the machines of life it encodes.

> ''By the year 2030, we will have (1) developed a complete model of all human cell types, obviating the need for many laboratory experiments [by doing computer simulations instead]; (2) lowered the cost of doing a complete genomic sequence for an human individual to less than $1,000 each; and (3) catalogued all the genes involved in aging. Therefore, human clinical trials to extend lifespan could already be underway by this date.''
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> —Francis Collins, NIH Director, 2001

The ongoing genomic revolution and, in particular, the development of faster and cheaper sequencing technologies, have the promise to turn biology into a mathematical problem and decipher the information underlying life.[44] Crucially, our capacity to generate data in a genome-wide fashion has been increasing at an astonishing pace (Fig. 2), in recent years even faster than computers increase in power (Moore's law). This is a fundamental issue because exponential progress is necessary to cure aging within the foreseeable future (*i.e.*, decades). Besides, large-scale phenotypic assays, for example, to characterize mouse mutants of all protein-coding genes,[45,46] RNA interference (RNAi)-based screens,[47–49] and large-scale efforts, such as ENCODE[50] that aim to identify all functional elements in the human genome, help address the complexity of biology. Results from ENCODE are particularly encouraging because they show that there are indeed laws governing genome biology in the sense that functional elements are indeed encoded in the genome; as predicted, they only require the appropriate readouts to expose them.[50,51] These developments also lead to the emerging paradigm of digital biology in which biological systems are treated as information systems. Such multidisciplinary approaches at the

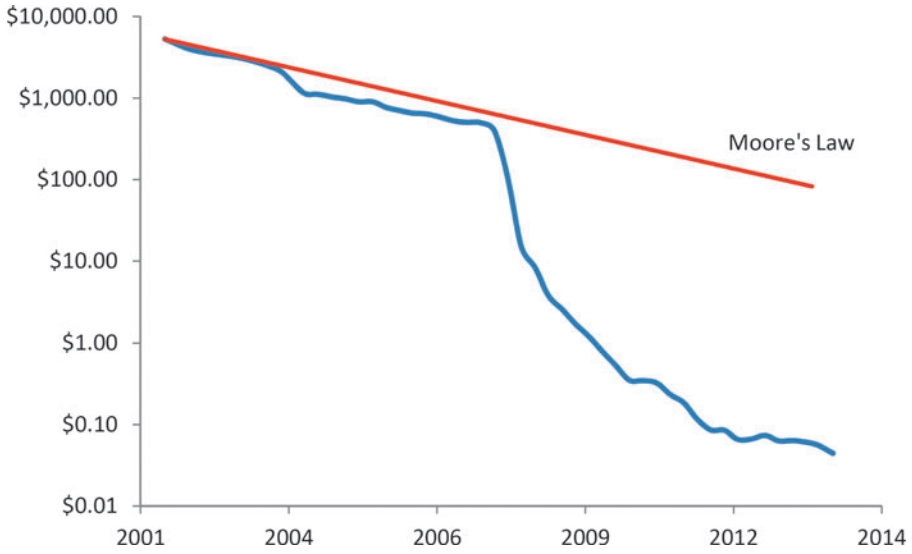

FIG. 2. Exponential growth in sequencing capacity (blue indicates cost in US$ per raw megabase of DNA sequence) as compared to the dropping costs of computer hardware (red indicates Moore's law). Source: NHGRI (http://www.genome.gov/sequencingcosts/).

interface of life and computer sciences underlie, in fact, large-scale efforts to understand the brain.[52]

There has also been significant progress in the capacity for computational predictions to guide experiments in the biosciences. For example, progress continues to be made in *in silico* drug screening and in large-scale prediction of drug activity.[53] Promising algorithms to predict multiple biological facets, like protein interactions from structural data[54] and spatial and temporal gene expression,[55] are being developed. The first whole-cell computational model was recently developed, although it focused on a simple bacterium.[56] In the context of aging, *in silico* progress has been significant in improving our understanding of the genetic pathways regulating aging.[57] For example, we and others have developed computational methods to predict with increasing accuracy new genes associated with aging,[58] CR,[59] and complex age-related diseases like cancer.[60] Increasing our predictive power will lead to more precise targeting of biological systems to preserve health and fight disease.

Holliday[7] makes the good point that to intervene in aging we need to understand its multiple facets and how they interact with each other. To cure death we must first understand life and this is not possible with a reductionist approach. I do disagree with Holliday, however, that the complexity of aging cannot be untangled. For instance, we have recently developed the Digital Ageing Atlas (http://ageing-map.org/), the first portal of age-related changes at multiple biological levels (Craig et al., in preparation). The goal of this new portal is exactly to help researchers study how aging changes at different biological levels interact with each other. With more than 3000 changes at the molecular, cellular, physiological, and pathological levels, this is only a beginning in helping to integrate disparate sources of age-related changes and interpreting them. Much work remains, yet it is important to keep in mind that at a conceptual level, aging, like the genome and the human brain, has a limited number of pieces that can, in principle, be understood well enough to permit us to engineer the whole process. Works like the Digital Ageing Atlas may help map the necessary multitude of interventions for rejuvenation.

Overall, I am convinced that *in silico* studies and models will be one of the major approaches for tackling the complexity of biology, allowing us to better develop tailored clinical interventions. The ultimate aim is to build models of biological systems and of their dysfunction during aging and disease that are accurate enough to make predictions about which components of the system should be manipulated by interventions to improve health, including in a patient-specific basis as part of personalized medicine efforts. Because we have a large search space and experiments in aging will continue to take a long time and be expensive (at least until aging reversal experiments become mundane), predictive *in silico* models that decrease the number of experiments to be performed can lead to rapid progress. Although systems approaches and synthetic biology are still at an early stage and restricted to very simple models and gene circuits, and deciphering the genome is a monumental task, the encouraging aspect of these approaches is that their capacity is growing exponentially (Fig. 2), although we cannot exclude a plateau at some point.

Deciphering the genome is also crucial to improving how we employ synthetic biology in clinical applications. To design new biological systems and devices, we require a greater understanding of the components that can be used in synthetic biological applications and also a greater predictive capacity about their outcomes in patients. For example, while regenerative medicine and stem cells hold great promise as interventions in context of aging and degenerative diseases, more sophisticated engineering of stem cells are warranted to improve the efficiency of treatments and avoid side effects. To exemplify, given the cancer resistance of mice with multiple copies of p53[61] or INK4a/ARF,[62] we can in principle engineer human stem cells for regenerative medicine that incorporate cancer-resistance mechanisms. In this context, genomics can help unravel the mechanisms by which cells from other organisms, like mole rats and

whales,[17] are much more resistant to tumorigenesis. Moreover, it is tempting to speculate that as we learn more about the genetic determinants of aging and age-related diseases, on the basis of studies in human populations, long-lived species, and model systems, we may be able to engineer stem cells, tissues, and organs to better resist damage and engineer organs that better maintain homeostasis and resist degeneration and pathology.

Re-Engineering Humans for Long Life

Massive-scale genome studies promise to transform our understanding of disease susceptibility and, not surprisingly, are at the basis of J. Craig Venter's Human Longevity, Inc. company and of other similar projects.[63,64] Related efforts are focusing on identifying rare protective alleles in long-lived individuals (*e.g.*, centenarians and super-centenarians) and in disease-resilient individuals.[65] There is still a large gap, however, between understanding the genome and clinical applications. Some genes may be suitable drug targets. Yet drugs have intrinsic limitations, and aging is much harder to intervene in than most diseases because it affects multiple tissues and eradicating it likely implies redesigning life.

A crucial issue, therefore, is that even if we can predict which genes we need to tweak to retard, stop, or reverse aging of a given tissue, we will still have to replace (*i.e.*, transplants with engineered stem cells) and/or modify our cells (*i.e.*, edit the genome) to avoid aging. In other words, how do we go from understanding how aging derives from the genome to develop interventions to cure aging? This, I think, is the biggest hurdle in developing a cure for aging.

Advances in genome editing, in particular programmable nucleases like zinc-finger and transcription activator-like (TAL) effector-like nucleases,[66–68] may open the door for rewriting the human genetic code for treating diseases and for rejuvenation. If approaches can be developed to edit the genome efficiently in adult patients, then the potential is enormous because there is evidence that at least some aspects of aging may not be irreversible at the basic molecular and cellular levels. In stem cells, self-renewal can be reinstated by suppression of certain factors.[69] The fact that a number of aging changes seem to be due to signaling pathways is equally encouraging because it means these may be reversible. For example, senescence in T cells appears to be regulated by signaling pathways that are reversible.[70] Moreover, forced expression in mice of a single transcription factor can partly regenerate a fully involuted thymus.[71] With four factors, it is possible to rejuvenate cells from centenarians and induce pluripotency,[72] and a single factor (Nanog) is sufficient to reverse the effects of aging in some types of stem cells.[73] Rejuvenating hematopoietic stem cells in mice is also possible with induced pluripotency,[74] and these results argue against aging of hematopoietic stem cells being driven by permanent genetic mutations. Such studies also demonstrate that the aging clock can be reset.[75]

Similarly, there is evidence that systemic factors are important in aging. Transplanting young ovaries to old mice slightly extends life span.[76] Factors both intrinsic to cells and extrinsic affect muscle regeneration,[77] and blood levels of a chemokine can also negatively regulate neurogenesis.[78] Taken together, these results suggest that, with the right understanding of the information underpinning biological systems, we may be able to pinpoint which changes to normal genetic programs we need to engineer to stop and/or reverse aging. Although it is unknown whether all aspects of aging can be reversed in all cell types, we may be able to employ, for example, the body's own repair mechanisms to develop therapies against age-related conditions.

To stop and/or reverse human aging, we will possibly need to replace cells and rescue aging cells, and not surprisingly regenerative medicine and gene therapy are high on the few discussions of engineering rejuvenation.[3,11] Nonetheless, progress in their development and clinical application has been slow in coming and their capacity is still limited. For example, *in vivo* genome editing in a mouse model of hemophilia helped restore function by $\sim 5\%$,[79] and gene therapy for aromatic L-amino acid decarboxylase deficiency in children resulted in improvements after gene transfer.[80] Likewise, RNAi-based approaches hold promise, for example, in a recent study showing that single-stranded RNAs can inhibit mutant huntingtin expression in the brain of mice.[81] But the efficiency of these approaches is presently low, and, even in these single-gene conditions, a cure is not yet possible. Many Mendelian diseases remain incurable because most are caused by loss-of-function mutations, and, with a few exceptions, delivering functional proteins at specific times and to specific cells remains a major challenge.[65] One can only speculate on the much more complex genome editing interventions required to eradicate aging: Possibly several genes will need to be edited and/or new genes added, probably in a tissue-specific fashion. (In this context, advances are also warranted to prototype new genomes accurately and inexpensively.) As such, it is easy to foresee that developing the technologies to significantly intervene in human aging is a daunting task.

As in the case of gene therapy, the potential for regenerative medicine and stem cell–based treatments is enormous and widely acknowledged and may help translate benefits of genomic advances. But practical applications are only just emerging. For example, mesenchymal stem cells from young donors transplanted to aging female mice extended life span,[82] although the effects were small ($\sim 16\%$) when compared to other life-extending interventions like CR. Thus, progress in developing the necessary technologies to intervene in human biology has been modest. Stem cells and gene therapy (coupled with synthetic biology in the design of new biological devices and systems that can improve existing tools or even create new tools) are no doubt promising but far from proven, with still very few clinical applications in spite of several years in development. On the other hand, the remarkable discovery of induced pluripotency (iPS) in 2006[83] may give renewed impetus to stem cell-based treatments and *ex vivo* gene therapy using gene-corrected iPS cells,[84] and it is encouraging that iPS clinical trials are already beginning to take shape.[85]

Taken together, I think our incapacity to intervene in biological systems is a major hurdle to eliminating aging and age-related diseases. For example, no doubt aging involves accumulation of dysfunctional cells that disrupt tissue homeostasis and organ function. Yet our inability to remove them is largely inadequate, as evidenced by failures in cancer research. Since US President Richard Nixon declared the war on cancer in 1971, the research and development spending on cancer has been estimated at

$100–$300 billion. New treatments have been developed, but while overall cancer survival has increased in recent decades, this is mostly due to early detection rather than some ''magic bullet.'' [86,87] Yet conceptually, cancer is a simple problem: All we need to do to cure it is remove the malignant cells. The fact that developing therapies that destroy harmful cells but not normal cells has not been solved yet, in spite of a massive financial investment and research effort, is a sign of the huge limitations we still have in understanding and modifying biological processes. Having a better understanding of biological systems will no doubt allow better cancer treatments, and there are encouraging recent results.[87] Yet while most forms of cancer may be curable with existing technologies (*i.e.*, drug-like approaches), curing aging will require not just the elimination of cells but possibly also cell replacement (and maybe whole organs) and the rescue of aging cells.

Overall, even if we understand the genetic code, it does not mean it will be easy to rewrite it in people. Although progress in sequencing and informatics has been exponential (Fig. 2), progress in medical interventions has been linear at best. For example, gene therapy clinical trials seem have reached a plateau.[84] So while we may be able to figure out which instructions we need to transmit to our cells to prevent them from aging, we still lack the technology to do so. This can be seen as a bandwidth limitation problem in transmitting information to our bodies and in how we need to develop methods to transmit significantly more information to cells to rejuvenate a whole organism.[88] Given the slow progress in solving these limitations, developing the technology to re-engineer humans may be the rate-limiting step in intervening in aging.

Conclusions

I think we can and should try to cure aging. Besides, independently of whether one considers curing aging should be pursued or not, biogerontology and biomedical research in general will continue to progress toward abolishing all diseases and eventually human aging. Concerning the science of aging, we know that: (1) Aging is complex, even if not as complex as other biological processes being tackled in the biosciences; (2) the causal mechanisms of aging remain largely unknown, yet there is a finite number of mechanisms and components that can, in principle, be understood and addressed; (3) aging can be manipulated to some degree in short-lived mammalian model organisms; and (4) experiments in biogerontology are and will likely continue to be time-consuming and expensive. As such, having a better fundamental understanding of the underlying biology can catalyze rapid progress by increasing the efficiency and capacity of experiments. Such understanding may be obtainable via disruptive technologies like ''-omics'' and associated computational models, whose capacity has been exponentially increasing, to allow us to tackle the complexity of biological systems and permit a better understanding of the biological mechanisms of aging. To achieve perpetual youth, we still then need to develop the tools to employ the knowledge gained to reprogram human biology in patients, which I see as the greatest challenge.

One additional consideration is that, although the work of biogerontologists is clearly important, *e.g.*, in unraveling the mechanisms of aging, radical life extension will mostly depend on broader technological breakthroughs in the life and medical sciences. The failure (thus far) of the war on cancer exemplifies how, no matter how much money and human resources are invested into a complex medical problem, solving it often depends on the overall technological development. This is not surprising since, historically, science progresses in bursts driven by new ideas and particularly by new technologies,[89] yet it has important implications for resource allocation, career choices, and marketing in context of life-extension research. It has also implications in terms of how inaccurate our capacity to predict future technological progress is. Even if likely to be proven wrong, my own view is that, assuming the exponential increase in sequencing and computer power (Fig. 2) holds, we will indeed have a genomic revolution in the next few decades that will allow us to elucidate the genetic and molecular mechanisms that drive aging. I am less convinced, however, that we will soon develop the capacity to safely intervene in human biology to the point of redesigning the human genome in adult individuals to cure aging. Developing such technologies is so much harder, time-consuming, and expensive, and is also hindered by regulatory hurdles, and I suspect this may well take many decades, perhaps centuries. Therefore, I think our understanding of the problem of aging will dramatically increase in the foreseeable future, but not so much our capacity to translate that understanding into medical applications.

At the current rate of progress (Fig. 1), radical life extension will take centuries. A revolution in medicine will be necessary to develop the combination of therapies necessary to stop human aging in this century. If information, analytic, and synthetic technologies continue to improve exponentially, our capacity to understand biological systems will eventually reach a turning point, in which case a scientific revolution will indeed occur. We may then be able to rewrite and upgrade the software of life to avoid death. Time will tell if we will continue to slowly gain years of life or conquer lasting youth with such a revolution.

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