Part II

Geroscience Research Landscape Overview 2017

Longevity Research Landscape Overview 2017

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Part II: Geroscience Research Landscape Overview 2017

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Glossary of Terms

Geroscience Umbrella term for the interdisciplinary field that aims to understand the relationship between aging and age-related diseases and the prospects for biomedical intervention. A great many molecular biologists, neuroscientists, protein chemists, cell biologists, geneticists, endocrinologists, pharmacologists, and even mathematicians intersect with this field.

Geriatrics Branch of medicine dealing with particular diseases and debilities of aging directly, and the care of aged persons.

Gerontology Study of aging in general, including all social, cultural, psychological, cognitive, and biological aspects.

Biogerontology Sub-field of gerontology concerned with the biological aging process, its evolutionary origins, and potential means of intervention. Involves interdisciplinary research on biological aging causes, effects, and mechanisms.

Biomedical gerontology Collective name for attempts to intervene in the biological aging process, acting directly from knowledge gained from biogerontology research.

Regenerative medicine Branch of translational research dealing with the repair of damaged tissues and organs using tissue engineering and molecular biology to restore normal function.

Rejuvenation biotechnology The application of regenerative medicine to age-damage, reversing its accumulation. This discipline aims to prevent and repair the fundamental damage that causes aging. This damage can include: somatic DNA damage, telomere attrition, transposonrelated genomic instability, reduced autophagy and protein turnover, epigenetic drift, stem cell exhaustion, advanced glycation endproducts, and more.

The Silver Tsunami

"The scourge of a greying population is only a scourge if it is depicted as such»
- Douglas Murray

Figure 5: The Economist's Depiction of the Future [33]

Infectious disease is not the mystery it once was, and is now largely under biomedical control. The war on human illness has evolved from an invasion into a counter-insurgency operation.

With all our old foes dispatched, the future of late life is old age. Those stubborn illnesses inflicted from within -- cancer, Alzheimer's, arthritis, osteoporosis, not to mention more subtle defects such as progressive hearing loss and cognitive decline -- are biomedicine's next and perhaps final challenge.

The phrase "Silver Tsunami" has been used in mainstream publications to describe this coming future. It came up recently in Forbes[1] to describe rapid population[2] aging and has been used by medical journals and professional organisations such the American Psychological Association[3] to describe the impact on health and the economy.

This coming tsunami will be a global deluge. All but 18 of the world's countries have an ageing population and rising life expectancy, according to the UN[4]. As the world's population increases, a greater percentage of it is being claimed by the elderly, and it is predicted that by 2050 over 16% of it will be over 65, compared to under 6% only 100 years earlier in 1950[5].

An ageing population is sustained by two factors: an increased life expectancy and decreased fertility. Life expectancy has grown steadily over time. In 1840 the average female reported life span was 45 years; in 2009 it was 87[6].

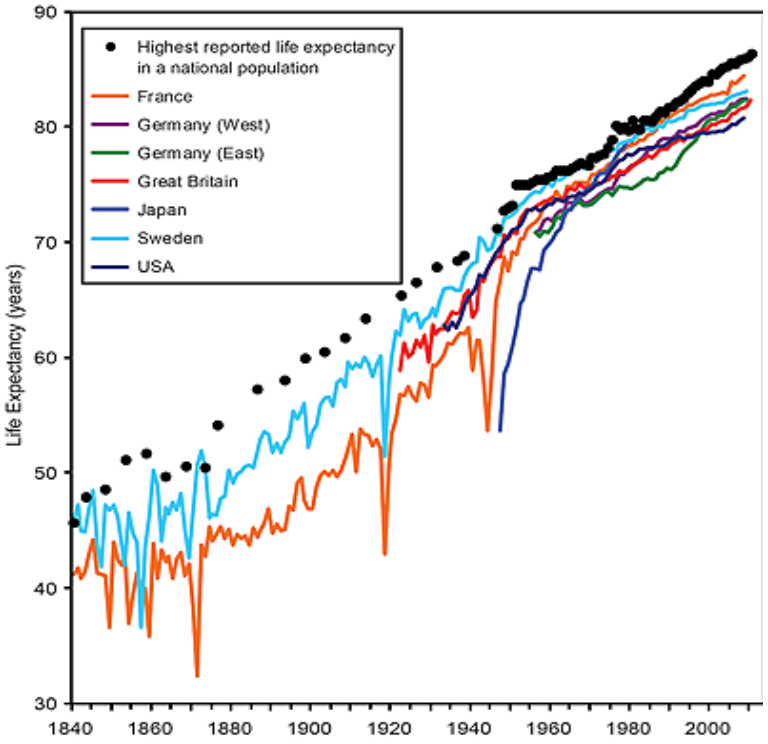


Figure 6: Global aging population [89]

This steady increase can be attributed to medical breakthroughs throughout this period, most importantly vaccines developed to counter major diseases and greater general knowledge concerning nutrition.

'Total fertility rate' is defined by the OECD as as "the total number of children that would be born to each woman if she were to live to the end of her childbearing years and give birth to children in alignment with the prevailing age-specific fertility rates"[31]. The global average of this has dropped from 2.8 children per woman in 1940 to 1.7 recently in 2014, meaning most women are now only having 1 or 2 children[7]. While some populations have had fluctuations in their fertility, the overall trend has been a decrease. For example, the United States experienced a significant increase in fertility post-World war II, from around 1946 to 1964, in an event often termed the "baby boom". This saw fertility rates rise above 2 children per woman[8], something that had not occurred since before 1927[9]; resulting in an estimated 78.3 million Americans born during this period[10]. The subsequent decline is due to many factors, mainly social changes over subsequent decades such as young women working and waiting until the 1970s to start families[11].

A woman's fertility is said to peak in the early 20s and drop around 35[12], yet in many developing countries women are having their first child around age 30[13], when it is harder to conceive, so for many women it becomes too late to bear children. Indeed 28.9% of American women between the ages of 30-34 have had no children at all according to a 2014 survey conducted by the U.S. Census Bureau[14].

As the economy has grown in America and other parts of the developed world, the main cause of death changed from infectious disease to chronic, non-communicable diseases such as heart disease, cancer, chronic lower respiratory disease, cerebrovascular disease and Alzheimer's. Unfortunately, while admirable progress has been made in respect to lifespan, many more people are consequently living with chronic, incurable conditions.

While often considered a problem of 'developed' nations, in fact these challenges are common to many countries with a wide range of wealth; in particular BRIC nations such as China and India, which are both predicted to experience a massive increase in their elderly population. Experts agree that this wider 'age shift' is being driven as aspiring countries converge with the wealthiest in regards to nutrition, public health, and better education, rather than by disruptive technologies directly extending the life span of individuals.

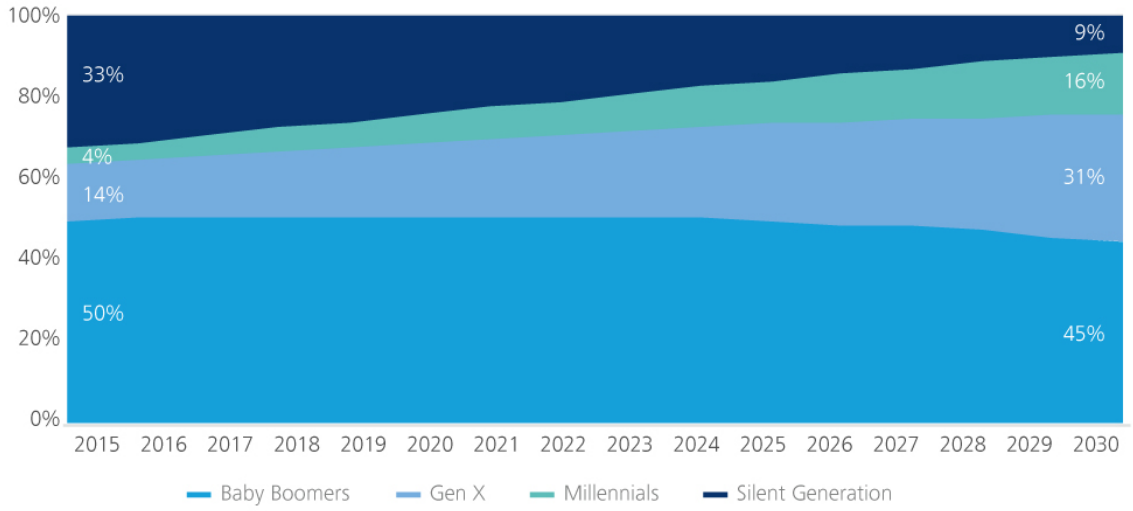


Figure 7: The baby boomer financial psychology
http://www.mybudget360.com/psychologically-damaged-baby-boomers-wealth-retirement-funds-amount/

Baby Boomer Purchasing Power

The Baby Boomer generation, born after WWII, is a very large population cohort that is currently beginning to retire en masse. The oldest Boomers turned 65, US retirement age, beginning in 2011. They are also the wealthiest generation in history (holding 45-50% of all household wealth) - investor recognition of this purchasing power should incentivize the development of effective rejuvenation therapy to cater to the Baby Boomers. However, as biomedical research usually requires a lot of time before therapies are readily available, we must aim to accelerate the translation of basic research into treatments and medicines. Doing so will allow the Baby Boomers to benefit in time to avert major economic consequences.

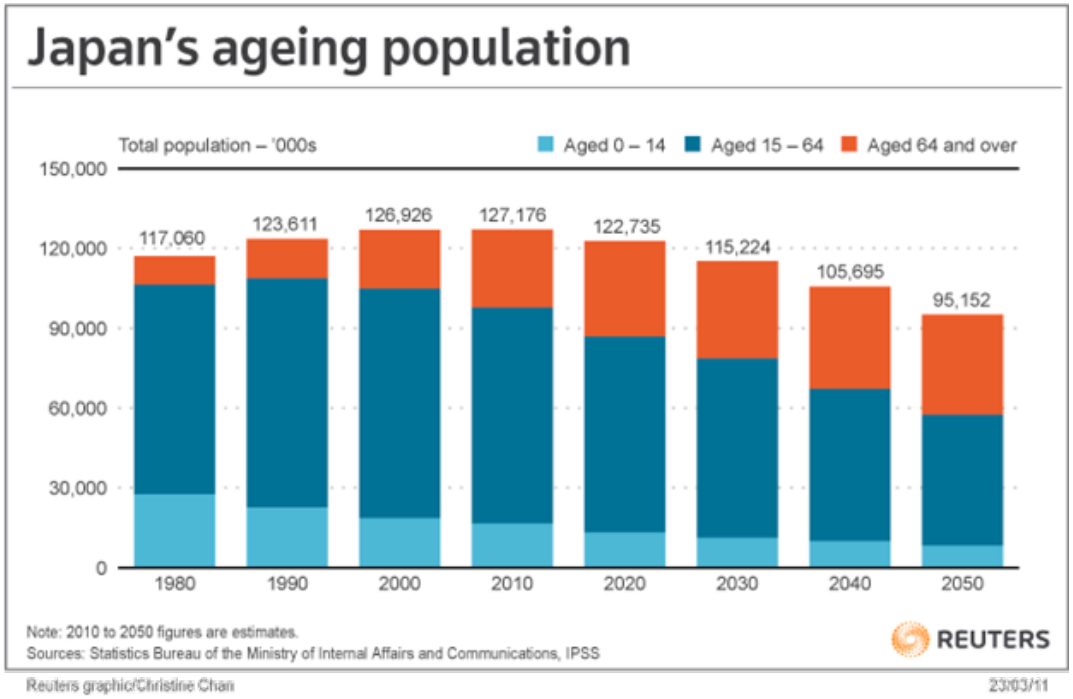


Figure 8: Japan's Aging Population [32]

Japan

A plain example of an aging population is Japan, and as its problems grow plainer, it could be seen as our canary down the mine. It has both high longevity and low fertility. The life expectancy is 81.7 years for men and 88.5 years for women[15], owing to adept medical care and technologies, as well as the healthy diet and nutrition in the available to the Japanese people. But declining fertility is the main cause of this population ageing, with the total fertility rate being 1.41 children per woman in 2016[15], and even reaching an all time low of 1.26 in 2005[16]. There are many contributing factors to this, one being that most of the population is urban: 94.5% (as of 2017)[17] with around 25% of the population residing in the greater Tokyo area[18] and around 11% in the Tokyo prefecture alone[19], giving it a population density of 6,150 persons per square kilometre (2015)[19]. Due to being such a densely populated city many residences are very small in order to accommodate the population; with an average of 1.91 persons per household (2015)[19]. Combine this with the busy working life of a vast number of Tokyo citizens and there is not much space or time to focus on starting a family, and many men find themselves uninterested in getting married. Surveys on single Japanese men conducted in 2010: it found that 61% of men in their 20s and 70% in their 30s deemed themselves "herbivores"[20], a term used to describe men with no interest in intimate relationships with women[21]. The Japanese government believes this is contributing to the country's declining fertility[22].

Japan's aging bachelor population [76]

This ageing of Japan is changing the country in numerous ways, such as increasing the cost of care for the elderly. More nursing centres and adult day-cares are being constructed, forcing 400 primary and secondary schools per year to close due to the dwindling number of children and the need for some to be converted into adult care centres[24]. More nursing homes have increased the demand for care workers, with 6,000 centres caring for 420,000 elderly people.

This has caused the national budget to increase. In the early 1970s, only 6% of the country's budget went towards social welfare aspects; in 1992 it jumped to 18% and is projected to be 28% by 2028[25], diverting funds from other important areas such as education. Less young people means less able-bodied people in the work force. Many industries are burdened with irreplaceable ageing workers. This caused a number of companies to raise the mandatory retirement age from 55 to 60 or 65 in the 1980s and 1990s, with retired workers recently receiving permission to continue working after official retirement[25]; so as to avoid strain on the national pension system. This has incentivised many retirement age workers to continue working, in order to stay out of poverty brought nearer by the 1986 raise in the ages of entitlement to various state benefits[25]. This number will continue to increase if Japan cannot replenish its workforce, forecast in 2002 to drop by 18% by 2030[26], which unless countered leads inevitably to a shrinking economy[27].

The Japanese government have responded with policies to incentivise childbirth and keep more of its population in the workforce[28], such as benefits for people with children and more time and opportunities for childcare [23]. The Child Care and Family Care Leave Law for example, implemented in 2010, allows for a more lenient work schedule for those with children[29], by enabling new parents to take up to one year's leave after the birth of a child, and also allowing an extra six months off if the child isn't accepted into nursery. It also provides allowances and benefits to employees with preschool-aged children, such as up to five days leave if a child is sick or injured[30]. This law aims to improve female employment rate, decrease the percentage of those working 60 hours or more a week, increase the use of annual paid leave, increase the rate of child care leave for both men and women and also increase the hours spent by men on childcare and housework in households with one child under the age of six; all over a period of 10 years[29].

Government initiatives such as these are currently the only means available to us for withstanding the tsunami. Any more drastic response to population growth, such as a misguided attempt to curtail birth rates, would result in even fewer young people and reduce the quality of life for the elderly.

Ultimately it is we who will decide how population growth impacts the world.

This report seeks to offer a brief overview of the biomedical means of taking control of this situation.

A History of Modern Geroscience

The diseases and debilities of aging were described in the previous section as 'stubborn'. This is an understatement. They are distinguished from other types of disease and debility by the fact that they are inflicted from within by essential metabolic processes, and are therefore as much an eventuality of these processes as starvation is of fasting. Unlike Cholera for example, there is a 100% chance that Alzheimer's will kill you as you age if nothing else does first.

Geriatric medicine, the branch of medicine dealing with the individual diseases of old age in aged persons, is therefore fighting a losing battle. Further progress will require more profound interventions, and ultimately the full might of an entirely new industry.

The ultimate mystery

The longevity industry described herein comprises several very different technologies, and has undergone multiple direction changes over the past century. The first documented quest for a redress to human aging was in the Epic of Gilgamesh (circa 2500 B.C.) in which the fabled Mesopotamian king sought a divine herb conferring immortality. Since then aging has gone from being the ultimate mystery of nature to biomedicine's ultimate adversary, and multiple disparate approaches to aging have emerged ranging from purely academic geroscience to technologically motivated biomedical research and engineering. In recent years their paths have intersected, creating new synergies and resulting in the unique industry landscape described herein.

The Fountain of Youth, Hieronymus Bosch

Early insight

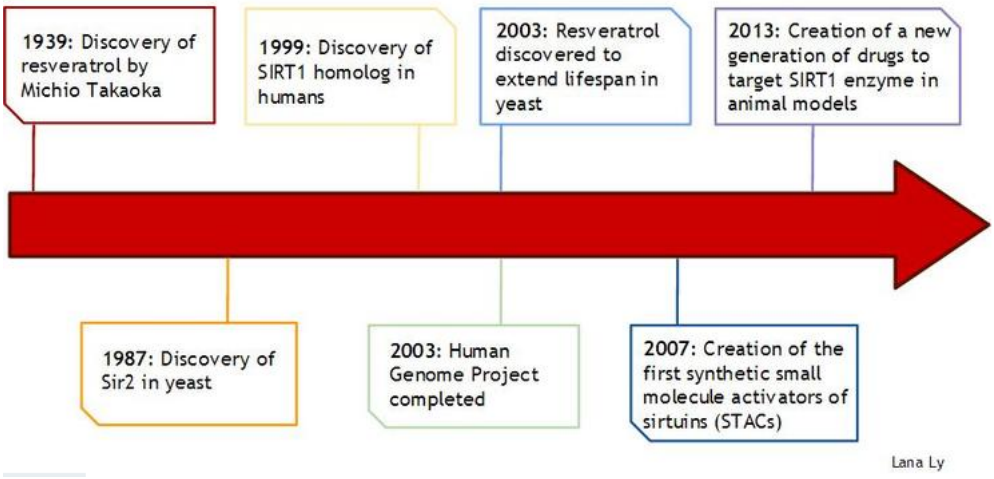
By the beginning of the 20th century, the biology of aging was still largely opaque. Various vague theories had surfaced, ranging from vitalism, the belief in a depleting life force, to simple notions of wear and tear, but nothing concrete. The full light of science was not thrown on the biology of aging until the the middle of the 20th century. The discovery of DNA in the 1950s opened up new lines of enquiry into the genetic basis of aging. Scientific articles written since the 1960s on the pathogenic role of free radicals and the role of telomere shortening in chronic diseases made these into household terms, and decades of research into human and animal metabolism opened up new fields of speculation and theorising on the causes of aging.

1960s: Early research into DNA [68]

By the end of the 20th century, biogerontology, the study of biological aging, and geroscience, the interdisciplinary field that aims to understand the relationship between aging and age-related diseases, had come into their own.

Early interventions

The 20th century had been a century of physics. These early insights laid the groundwork for a century of biology. The first decade of the 21st century rapidly threw up various proposals for biomedical intervention based on early conclusions reached by the emerging biological science of aging which had become known as 'biogerontology'. For example laboratory research into the metabolisms of organisms ranging from nematodes to rats revealed that a sharp reduction in caloric intake sharply slowed



Fifty years of aging research [77]

down aging, and so lengthy calorie restriction trials on primates were commenced with a view to artificially bottling the metabolic effects of this dietary alteration. But despite the undeniable promise of these biogerontological attempts to extend life, as knowledge of genetics and metabolism grew, the challenges of bringing aging under serious biomedical control grew plainer. It quickly became apparent that human genetics and human metabolism were an irreducibly complex tangle with aging as its inextricable consequence. Radically extending lifespan by taming metabolism would be like solving a Rubik's cube with a thousand sides.

Road to rejuvenation

In the second decade of the 21st century, just when we thought we knew the probable limits of successful intervention, the industry underwent a revolution in thinking when biogerontology began to intersect with regenerative medicine, an umbrella term for therapies which restore or regrow damaged tissue, from tissue engineering to stem cell and gene therapies. Technologists coming into biogerontology from other industries began to notice that biogerontology's findings could be used to fashion a damage report which could then be handed over to to regenerative medicine.

In the eyes of regenerative medicine, there is an overlap between accidental injury and age-related pathology. For example in 2010 scientists from Keele University in the UK began trials for a stem-cell therapy for repairing osteoarthritic knee-joints, partly a result of mechanical stress, but sometimes unavoidable for people in late life. It is a facet of old age, but one which falls within the purview of regenerative medicine.

This prospective application of regenerative medicine to the conditions of old age —

through methods such as removal of unwanted matter from in and between cells with implications for conditions ranging from macular degeneration to immune system decline -- is termed 'rejuvenation biotechnology'. By simply seeking to repair aged tissue and avoiding the need for decoding genomes and mapping metabolisms, rejuvenation biotechnology sets the longevity industry on a very potent course indeed.

The twentieth century gave us biogerontology, an innovative approach to the problems identified by geriatric medicine, and the twenty-first century is in the process of producing rejuvenation biotechnology, an innovative approach to the damages identified by biogerontology.

The next section will take a closer look at further innovations as well as various converging trends technological, social and political, presently setting the future course of the industry.

Why We Age - Science Magazine Cover (Dec 2015)

Public and professional perception

Perhaps the most manifest development in the longevity industry has been public awareness, a fact which in a democracy has clear political and practical ramifications.

Throughout the 20th century, life extension as a biomedical aspiration went from being an academic backwater with vague connotations of Victorian crankishness, to an ill-defined and remote technological prospect of which only a few were dimly aware, to a technological revolution as abrupt and disruptive as the digital, with a clear presence in mainstream culture and ethically-motivated popular movement behind it.

It may seem hard to remember now, but prior to the 1990s not even the notion of DNA had fully penetrated public awareness, let alone any clear notion of the mechanisms of aging. Cancer had long been correctly imagined as an unwanted growth which everyone wanted a way to get rid of. Whereas aging was...what? Nobody told us. Little wonder then, that there was little public pressure to do anything about it, whatever 'it' was.

In the 1990s, terminology related to the biology of aging such as 'telomere' and 'free radical' sept into everyday vocabulary. TV documentaries and magazines made scientifically sound illustrations of the aging process widely available. These provided the public with the images they needed to envision the problem and the words they needed to demands solution.

And moreover these terms implied that aging was something tractable, at least in principle. Aging became imaginable and therefore vanquishable.

Yet there remained a conspiracy of silence over the possible mutability of aging. Or rather an inertia, brought about by the lack of any professional prognostication on the prospects of longer lifespans.

An 'anti-aging movement'

This changed somewhat in the mid-00s when technologists such as the inventor and futurist Ray Kurzweil and software engineer-turned-biogerontological theorist Dr, Aubrey de Grey began to notice the latent potential of nascent regenerative medical technologies, and set imaginations in motion with their visions of what they saw as biomedicine's limitless potential to increase lifespan. De Grey in particular became known for what he called his, 'engineering approach' to aging, and his prediction that the first person to live to age 1000 had already been born (as of about 2005). This brazen forecast drew opposition from fellow biogerontologists, who feared that such careless pronouncements would drag the field back to the backwater from which it had just clawed its way out.

But de Grey was speaking in his capacity as a technologist making a call to action

rather than a scientific theorist pushing a hypothesis. It was a conditional statement tc the effect of: "If, and only if, there is a concerted global effort to apply the regenerative medical toolkit to repair the human body faster than it accumulates damage, the sky's the limit."

A contestable statement to be sure, but as a complete regenerative medicine approach to aging was an unprecedented proposal at the time, there was no such thing as received wisdom one way or the other on the expectable longevity benefits, not even down to a particular order of magnitude. It received diverse responses ranging from outright derision to wholehearted popular and professional enthusiasm. But the overall effect of the controversy was that received wisdom came to regard the near-future of human lifespans as a wide open question.

In retrospect, de Grey would be seen the father of 'rejuvenation biotechnology' now the established term for the application of regenerative medicine to age, named after a seminal annual industry conference held every year in the San Francisco area. In the past decade the core concept of rejuvenation biotechnology has given a fresh sense of direction to a nexus of institutions with regenerative medical expertise, all lending their efforts to this overarching objective.

Institutions and expertise

See Part 4 : Top 100 Research Labs in Geroscience

An early focal point for this agenda was the SENS Research Foundation (or SRF, 'SENS' standing for Strategies for Engineered Negligible Senescence) in Mountain View California, the world's first biomedical research charity dedicated exclusively to the repair and restoration of aged tissues, and the host of the seminal Rejuvenation Biotechnology industry conference series. It was co-founded in 2009 by de Grey in a pragmatic split from the Methuselah Foundation, an earlier biomedical research foundation with a broader remit, with initial capital from venture capitalist Peter Thiel. It specifically subdivided its efforts into seven projects, each focusing on an particular category of age-damage, with names such as 'LysoSENS' (removing waste from the cell's lysosome), or AmyloSENS (removing waste such as amyloid from between cells), and so on.

At about this time the think-tank and business incubator Singularity University was established by Peter Diamandis and Ray Kurzweil at NASA retail park, with a focus on 'exponential technologies', of the life extending variety in particular. In 2013 Google and Arthur D. Levinson launched Calico with a mission statement echoing that of SRF, but a broader remit of "health, wellbeing and longevity", and in partnership with the pharmaceutical company AbbVie, founded the same year, set up a R&D facility focused on aging and age-related infirmity such as neurodegeneration and cancer.

As the fledgling rejuvenation biotechnology industry took flight it drew interest and co-operation from luminaries in diverse fields. No scientific or industry conference was

complete without the presence of molecular geneticists such as **George Church,** regenerative medical technologists such as **Tony Atala**, molecular oncologists such as **Maria Blasco**, ethical philosophers such as **Peter Singer** or celebrity endorsers such as **Edward James Olmos.**

See Part 9: Top 100 Geroscientists

Around this Silicon Valley-based hub an international community of institutions formed like spokes. The industry relied on the labour of research facilities throughout the West from the **Wake Forest Institute for Regenerative Medicine(WFIRM), Rice University, Albert Einstein College of Medicine,** and **Stanford University**, to Britain's **Oxford** and **Cambridge** Universities.

Such a hodgepodge of expertise and approaches was always going to be necessary in the treatment of aging, for aging itself is a hodgepodge of metabolic processes, damages and pathologies with multiple points of possible intervention, and the road ahead therefore presents us with a great many potential false avenues. But there are already emerging attempts to navigate those avenues effectively and orchestrate research internationally, such as the use of artificially intelligent investment system to derisk global investment for maximum progress.

Media coverage

By this point the prospect of radical life extension was already gripping the main-stream media.

Since the mid-'00s, radical life extension has been an increasingly common subject of books, TV documentaries, films and talks. After Kurzweil broke some the ice with his 2005 book **Fantastic Voyage: Live Long Enough to Live Forever,** Aubrey de Grey began to appear on prime time discussion shows such as **BBC's Hardtalk, Channel 4's Richard and Judy, CBC News**, and even **The Colbert Report** (to discuss his 2007 work **Ending Aging**) and documentary films such Mark Wexler's **How to Live Forever** the the Christopher Sykes documentary **Do You Want to Live Forever.**

See. Part 8: Top 100 Longevity Books

Longevity science and technology news has saturated popular online culture and is a major subject of **TED talks** and debates including one very major '**Debate of the Ages**' at Oxford's **Sheldonian Theatre** in 2012.

An increased public consciousness of the prospect of a technological redress to aging may even have influenced fiction. The 2011 dystopian film **In Time**, about a near-future post-aging world, appeared to rely on this public consciousness of it when it offered remarkably little explanatory prolog to explain how that world came about. It consisted of the single line *" I don't have time to explain how it happened. It is what it is. We're genetically engineered to stop aging at 25. "*

Key moments from the last decade

2010	Public interest in longevity has risen over the preceding decade. Peter Thiel, having already supported biogerontology research around the world, is showing an interest in rejuvenation biotechnologies: "If you have radical life extension, that could obviously lead to repercussions for society. But I think that's a problem we want to have." says the businessman. The SENS Research Foundation is a regular recipient of his donations. The entrepreneur James Hope also gave $500.000 to SRF. In the same year SRF's yearly budget has now reached $1M, allowing them to open an independent laboratory.
	An experiment in rejuvenation transplantation is conducted. It shows a neonatal thymus grafted to old mice to significantly reduce mortality rate, while restoring immune system function, most likely due to depleting number of T-cells in elderly organisms. The resulting paper sparks further interest in tissue engineering.[34]
2011	SRF continues to expand its efforts. After Aubrey de Grey donates most of his networth to the Foundation it is finally able to simultaneously operate in all seven of SENS research branches, two years after the foundation of SRF.
	Scientists at the Mayo Clinic College of Medicine conduct an experiment on the clearance of senescent cells. The study proves the hypothesis that senescent cells play a large role in age-related decline by negatively affecting adjacent cells, provoking inflammation. [35]
2012	The most prevalent trend of the year is the commercialization of emerging longevity technologies. Gensight Biologics and Covalent Bioscience are founded, building on the Methuselah Foundation's technology in mitochondrial and neurodegenerative dysfunctions and SRF's catabody research.
2013	Alphabet launches its own biogerontology company known as Calico. This move gains yet unseen mainstream attention and has significantly increases public knowledge of the industry.

	 Probably the most important year in the industry from the public outreach point of view. The landmark publication titled 'The Hallmarks of Aging' is published in Cell. The team of Carlos López-Otín has shown a new framework of aging research that serves as an alternative to SENS, providing a more holistic approach to aging, connecting different hallmarks hierarchically. To this day The Hallmarks of Aging remains the most cited biogerontology article [36]
	The Methuselah Foundation continues to focus on tissue engineering. After launching the New Organ initiative and supporting organ engineering company Organovo in the previous years, the Foundation announces $1 million prize for a tissue engineered liver. The competitors must create a working liver from the patient's own cells. The call is active until the end of 2018. [37]
2014	The Buck Institute for Research on Aging has launched their own version of longevity research framework, known as the 'Seven Pillars of Aging'. This framework bears similarities to the SENS 'seven damages' approach and serves as a practical roadmap for life extension. [38]
	SRF reaches a breakthrough with its catabody technologies. Misfolded proteins form amyloids responsible for declining tissue function and increased death rates. The Foundation's catabodies prove capable of destroying a transthyretin amyloid, a particularly prevalent variety.

2015	The first senolytic drug candidates are introduced by the scientists of Mayo Clinic. These drugs, dasanitib and quercetin are capable of removing senescent cells, while leaving other cells unharmed. Senolytics are now a prospective drug group that can successfully combat one of the hallmarks of aging [39]
	SRF is now focusing on the anti-cancer telomere research. They conduct experiments both on telomerase blocking and alternative lengthening of telomeres (ALT) technologies. Meanwhile, transthyretin amyloid technologies are on their way to commercialization.
2016	Senolytic research is rapidly developing. Scientists from across the globe are actively finding evidence that removal of senescent cells improve respiratory, cardiovascular and immune functions.
	SENS Research Foundation launches a crowdfunding campaign as a part of the OncoSENS branch of their research program. The crowdfunding aims to further the ALT research. SRF states that the most effective way of fighting cancer is to strike at something that all cancers have in common: perpetual lengthening of telomeres.
	The Methuselah Foundation, now in collaboration with NASA, launch another prize. The $500.000 will be given to the group that will be able to produce thick vascular tissue [40]
2017	More than 10 different senolytic drug candidates are now being developed by both non- and for-profit facilities. Various organizations are racing to present the first true anti-aging medication.
	The Methuselah Foundation founds The Methuselah fund in order to assist emerging longevity-related companies in their earlier stages of development. [41]

Increasing insight into the genetic basis of aging

The genetics of aging and longevity remains a poorly understood topic, given the complexity of gene interactions and the usual lack of any significant effect associated with the expression of a single gene.

Current studies of longevity genetics usually focus on long-living populations to identify DNA sequences which correlate with longer lifespan.

A number of such studies have shown that a group of genes that encode forkhead box proteins (O subclass, to be specific) exist in many centenarians in various populations

across the world. One such protein, FOXO3 has been found to induce apoptosis (the form of regulated cell death that hampers cellular senescence, a facet of aging), while FOXO4 is linked to various processes, including apoptosis regulation and oxidative stress pathways [80].

At this point studies diverge along two different paths with one being significantly more effective. The more obvious one involves discovering ways of expressing those genes. This is however a cost-inefficient approach, as the processes associated with FOXO genes happen across the organism, which makes them a hard target for somatic gene therapy. A more efficient approach is the study the molecular mechanisms that these proteins use to increase lifespan. This research will enable the design of pharmaceuticals that can emulate the proteins efficiently without the need for genetic intervention.

Increasing insight into oxidative stress

Oxidative stress is an aspect of aging that greatly harms the organism in the long run. As it is directly linked to mitochondrial function, combating mitochondrial dysfunction is considered a priority in longevity research, but has proven difficult.

In some cases it is easier and more effective to kill old mitochondria and recycle them in order to create new ones. This can be achieved by a special form of autophagy, known as mitophagy.

Recent studies are showing that mitophagy properties decline with age, and that active mitophagy greatly improves healthspan, suggesting that possible interventions could extend lifespan [81]. The next thing to do in this sub-field is to determine the most effective way of utilizing mitophagy mechanisms.

Increasing insight into environmental factors

The influence of environment on lifespan is an often omitted part of biogerontology research. While concentrating on developing novel means of extending lifespan, longevity scientists tend to overlook the impact that factors such as chemical pollution and radiation can have on life expectancy.

As China remains the most polluted region on Earth, it is an apt model for estimating the effect of pollution on lifespan. Recent studies show [82] that living in highly polluted areas, such as China's Huai River region decreases median life expectancy by 3 years. Moreover, they show that bringing the air policy in line with the WHO's Class I standards will bring almost 4 billion life-years to the populous as a whole.

Although not beyond dispute, there appears to be a simple correlation between the level of pollution and median wealth in the populace, and it is hard to deny the harmful effects that the negligence in the environmental protection will bring. As environmental studies and biogerontology don't have many intersections currently, it is hard to estimate the potential of any such future interdisciplinary research, but there is no doubt that improving living conditions will extend lifespan and, more importantly, healthspan.

Further progress to watch

As stated previously, the technological threads comprising this industry are extremely diverse and can approximately divided into the following strands:

Geroprotective drugs include small molecules, peptides, and proteins. Studies have identified over 1,000 compounds which extend the lifespan of at least one model organism. These include antioxidants, anti-inflammatory, anti-glycation, anti-amyloidogenesis, inhibitors of growth signaling, chelators, sirtuin activators, calorie restriction mimetics, and many more. Regenerative medicine involves the use of stem cells from various origins to rebuild, “regenerate” or improve the function of damaged organs and tissues.

Clinical translation in this area has been simplified greatly by the fact that many labs have been repurposing old drugs for longevity (examples include rapamycin, metformin, aspirin). So since these drugs have already been approved for human use, they need not undergo phase 1 trials a second time.

Regenerative medicine involves the use of stem cells from various origins to rebuild, “regenerate” or improve the function of damaged organs and tissues.
This can be promising for combating the degenerative pathologies of aging. Entire “replacement organs and tissues” can be grown outside of the body, using methods such as growing tissues on biodegradable scaffolds, 3D tissue printing.

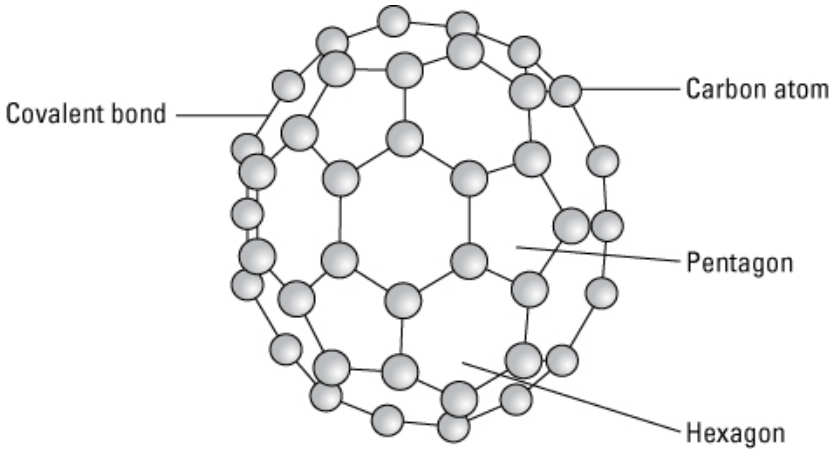
Geroprotectors [84]

An important recent development has been the induction of regeneration within the body by pharmacological means, e.g. using inhibitors of prostaglandin breakdown thus promoting cell proliferation.

Nanotechnology, in medicine, is limited mainly to the treatment of cancer with nanoparticles.

But recent interventions into aging have also reached the “nano” level. Some involve

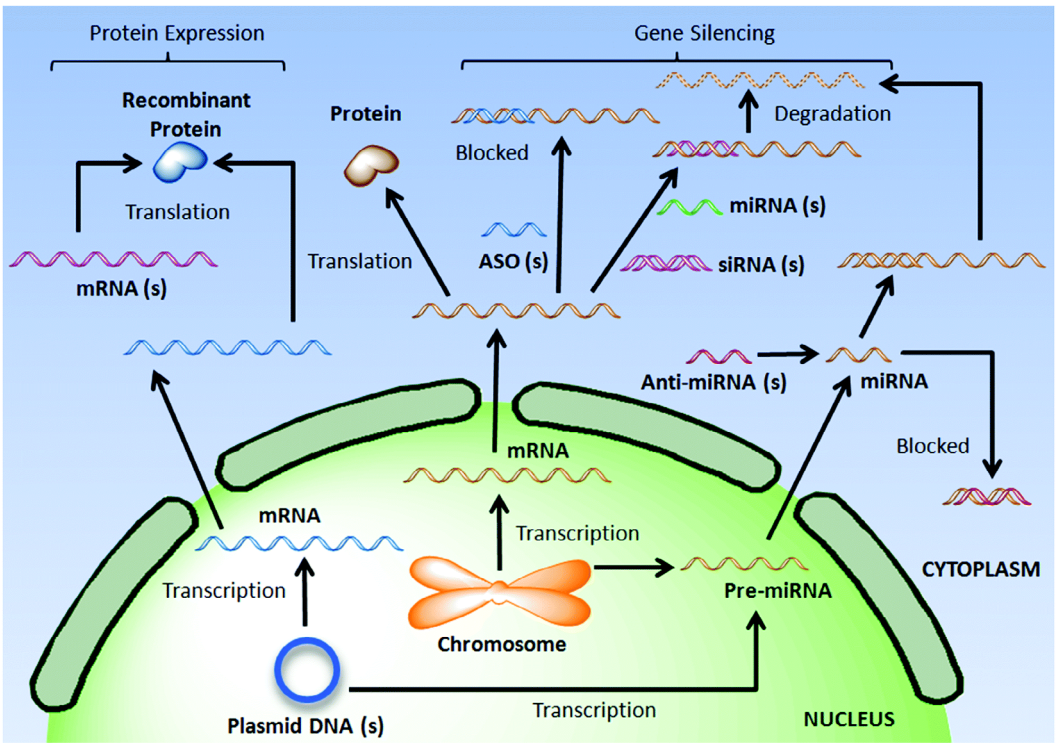
nanoparticles such as Buckminsterfullerene or “bucky-ball” C60, believed to have antiviral, antioxidant, anti-amyloid, immune stimulating and other therapeutic effects, with reports of extended lifespans in mice.



[83]

Early operating medical nanodevices have even been announced, mainly intended to assist with precise drug delivery, acting as prototypes of artificial immune cells. These nanodevices are mainly intended to eliminate cancer cells, but could also be used to eliminate other types of problem cells such as senescent cells. In another area of development, oxygenated micro-particles hold some promise for healthspan extension, especially in critical conditions where oxygen deprivation is the ultimate cause cause of death.

Polynucleotide therapeutics (gene therapy, anti-sense RNA, etc). Gene therapy with telomerase has already been shown to increase life- and healthspan in mice and gene therapy with myostatin inhibitor may help to prevent frailty in elderly people.



Methods of Polynucleotide Delivery [92]

The SENS Research Foundation is currently researching methods for inserting large pieces of DNA in the genome in a site-specific manner, and anti-sense therapeutics against lipoprotein(a) for the treatment of cardiovascular disease are currently in clinical testing.

Apheresis is a procedure in which blood is withdrawn from a patient, after which a specific component of the blood is removed, such as a particular type of cell, after which the blood is reintroduced in the patient.

One particular procedure to this effect is called heterochronic parabiosis: connecting the blood supplied of animals of different ages – used in stem cell and aging research for the last few decades. The evidence that heterochronic parabiosis extends the lifespan of old animals can be interpreted in two ways.

Either the shared blood supply helps to dilute a pro-aging factor in the blood of the old animal, or it helps to introduce an anti-aging factor into the blood stream produced by the young animal. If the former turns out to be true then apheresis could potentially be used to remove the pro-aging factor from the blood of elderly people.

The SENS Research Foundation has already patented an apheresis device to remove senescent white blood cells from the circulation (US20120145641 A1).

Probiotics are living microorganisms that, when administered in adequate amounts, confer a health benefit on the host. As the gut microbiome may play a role in aging and age-related diseases (such as atherosclerosis, rheumatoid arthritis, and type 2 diabetes) the use of probiotics may help to promote longevity. However its is likely to remain small.

Bionics is the replacement of diseased or damaged tissues, organs or other body parts with mechanical or other artificial substitutes.

Physical therapy. Anti-aging interventions need not be chemical and biological, but can also be physical, in particular as relates to various resuscitation technologies, e.g. hypothermia and suspended animation, oxygenation, electromagnetic stimulation.

Such technologies represent veritable means for life extension, demonstrably saving people from an almost certain death. But similar principles could also be used for preventive anti-aging treatments and in less acute cases.

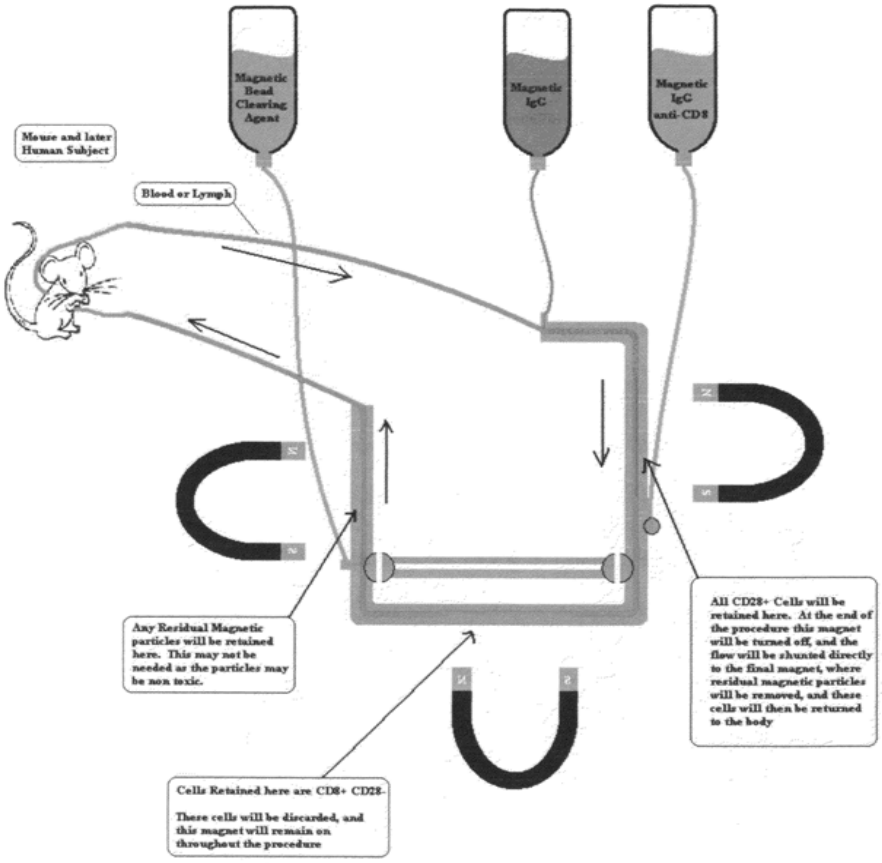
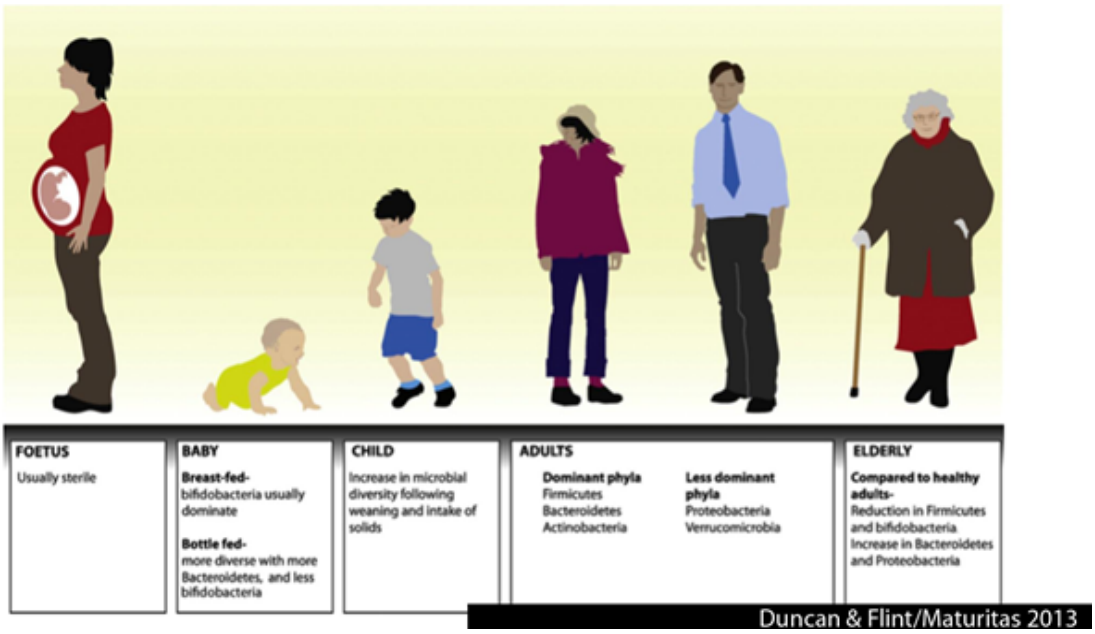


Figure 3

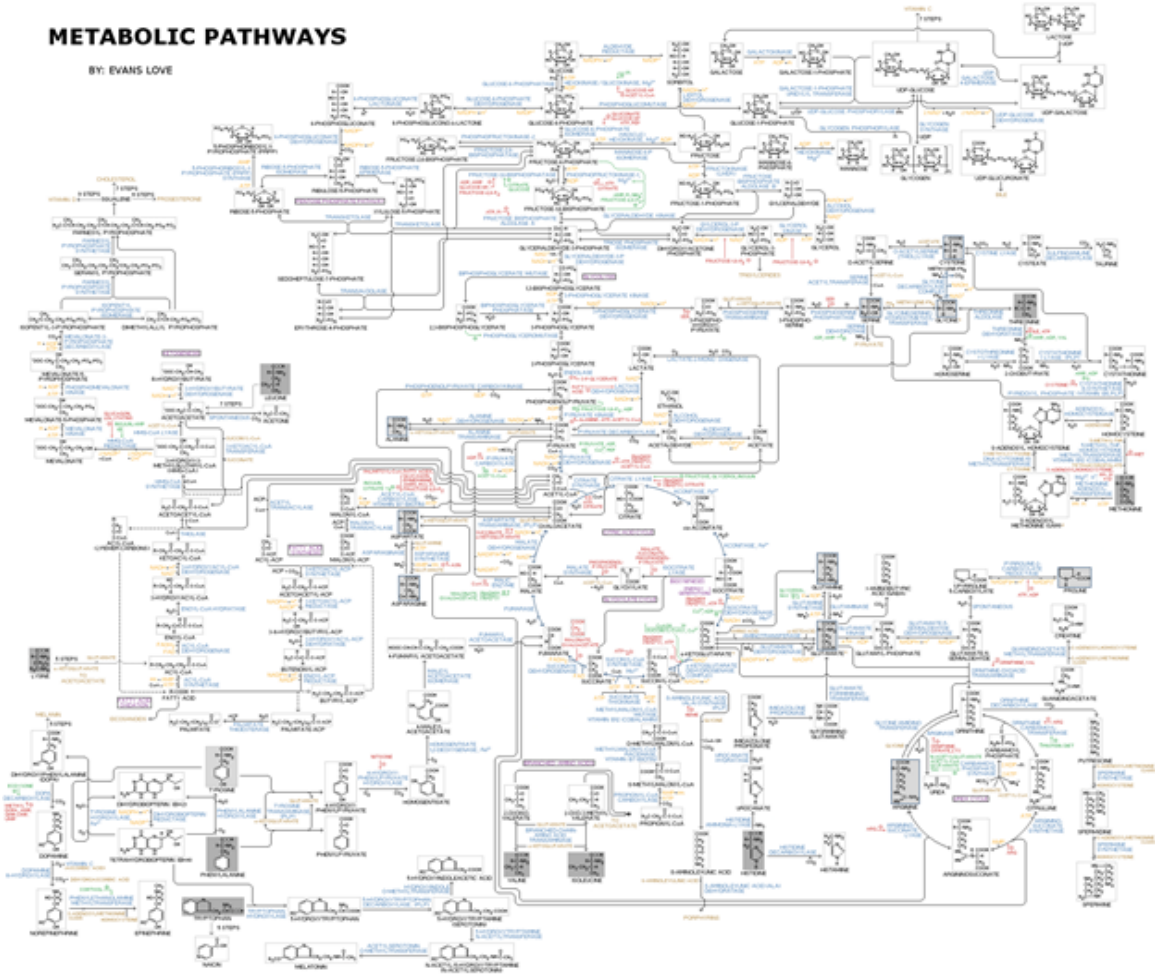
SENS Research Foundation patented apheresis device (US20120145641 A1) [85]



The role of probiotics in aging and longevity [90]

The Convergence of Regenerative Medicine, P3 Medicine and Geroscience

The widest ceiling over the aspirations of geroscience has always been the inextricability of disease from aging and the inextricability of aging from human metabolism, which, being so complex and integral to our day-to-day functioning, can only be amended rather than reconstructed.



A very incomplete overview of human metabolism (Wikimedia Commons)

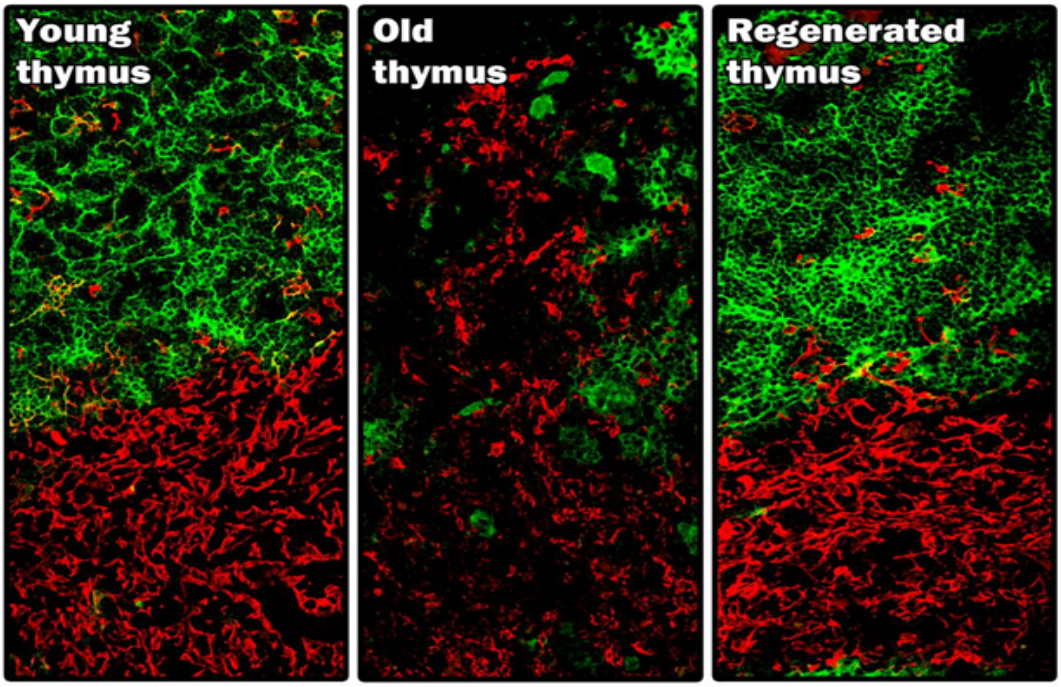
This limits us because it robs us of the most obvious approach to radical life extension: radical interference in human metabolism. For just as we might like to be able to alter a car's inner workings so that they inflict less wear and tear, so too might we like to be able to somehow rearrange metabolism so that it inflicts less wear and tear on body tissues.

Sadly this is not an option. While subtle interventions in areas such as calorie restriction mimetics hold some promise to appreciably increase life expectancy, anything amounting to a successful radical intervention in metabolism which radically extends life span is inconceivable for the foreseeable future for the above reasons.

This brings us to the alternative approach to vehicle longevity: repair and maintenance. Which in human terms means the continuous restoration of human tissues, irrespective of the various processes that age them.

These two approaches differ starkly. The former could be thought of as like meddling with the inner mechanisms of a clock, cogs and all, in order to slow it down. The latter could be imagined as forcing back the hands of a clock, setting back the progress, while inner clockwork, the process, remains unaffected.

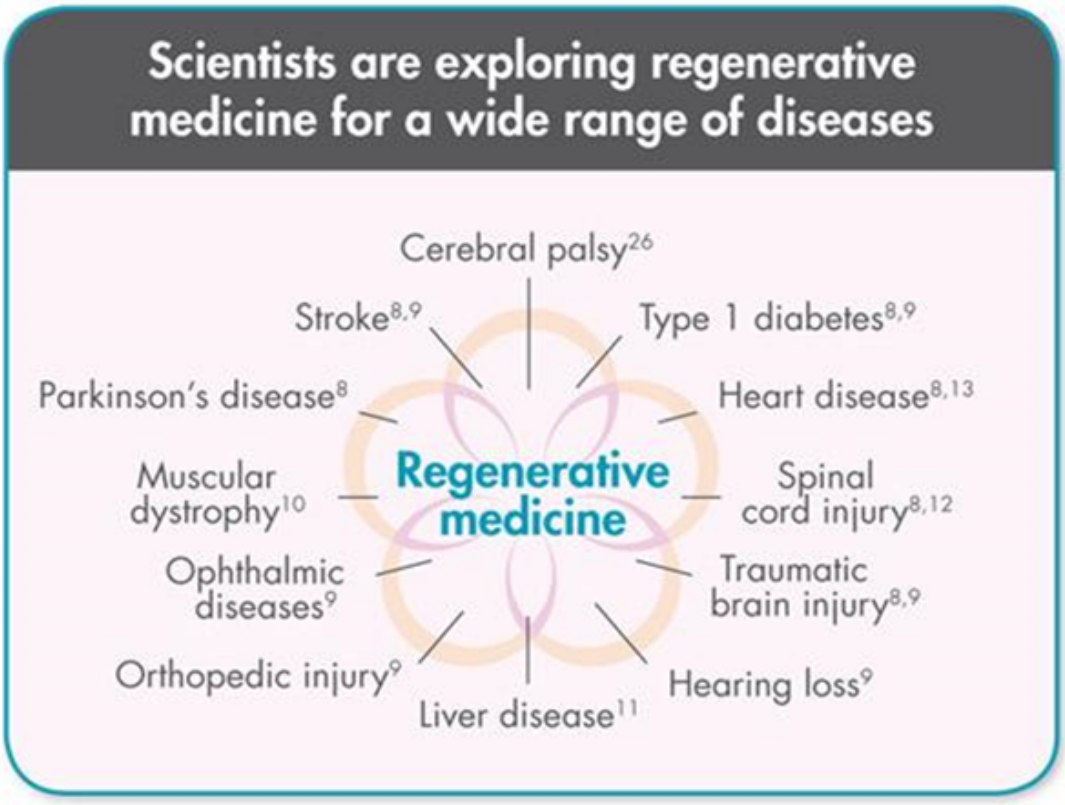
In human terms 'setting back the hands' means taking knowledge obtained by geroscience, fashioning it into a damage report and devising a repair strategy. And just as setting back a clock does not require the same extensive knowledge of horology as would be involved with meddling with the clockwork, nor does the restoration of aging tissue require an unfeasibly extensive knowledge of geroscience, only enough enumerate of the manifest differences between old and young tissue.



The thymus of an old mouse rebuilt by scientists at Edinburgh University [75]

So could we then aspire to repair these enumerated damages comprehensively enough and rapidly enough to appreciably postpone disease? In other words might there be an extent to which we can afford to allow aging to proceed as it normally does while simultaneously clearing up the damage it leaves behind, kicking the can disease down the road?

We are in effect describing the application of **regenerative medicine** to aging. Regenerative medicine is an area of biotechnology which aims to restore damaged tissues and organs. So why not tissues and organs damaged by the miscellaneous ravages of age?

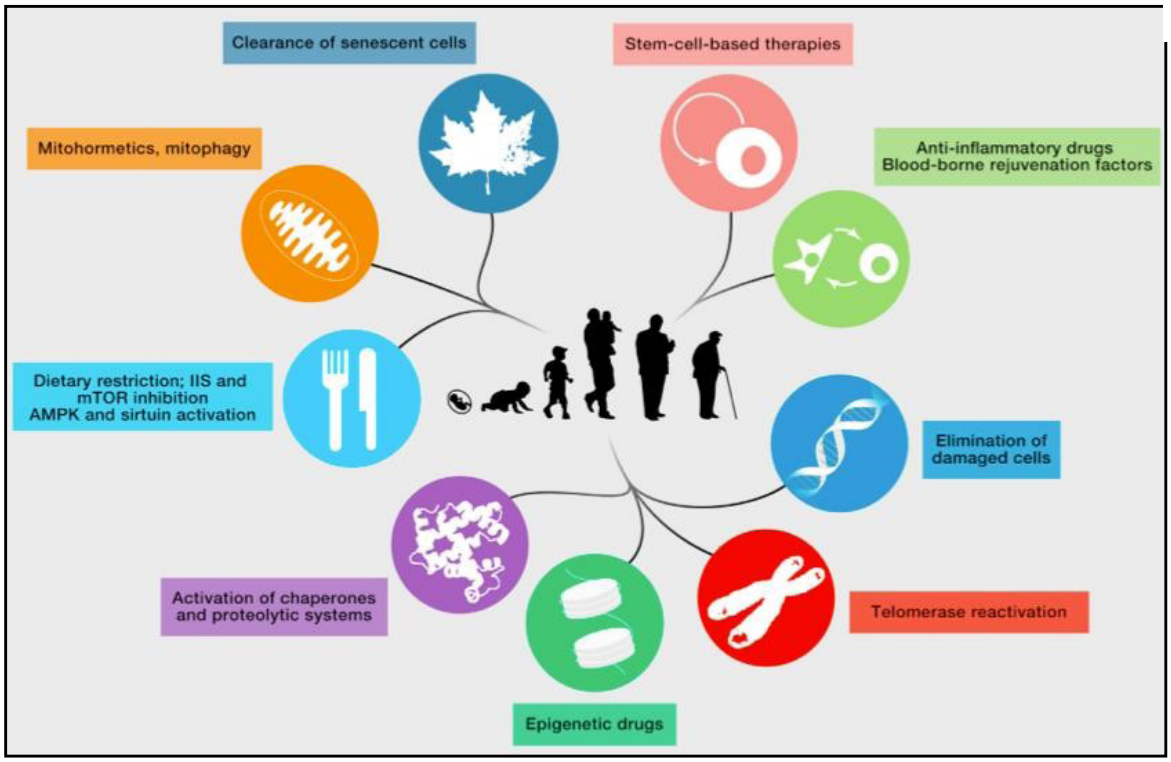


Applications of regenerative medicine [43]

Prior to the proliferation of regenerative medicine technique in the 1990s, organs and tissues were restored by one of two methods: either biomimetic implants (artificial organs', 'prosthetics') or transplants, biological material donated from another individual. Regenerative medicine is different from both. Unlike **implants**, products of regenerative medicine are organic living tissues, not bionic machines. Regenerative medicine shares this trait with **transplants** also. But whereas transplants are made from tissues and organs donated by another individual, regenerative medicine utilises a patient's own cells and tissues.

There are advantages to the regenerative medicine approach over the transplants and implants. One is that both transplants and implants require immunosuppressants to keep the recipient organism from rejecting received organs, whereas regenerative medicine technologies avoids this need by utilising patient's' own stem cells.

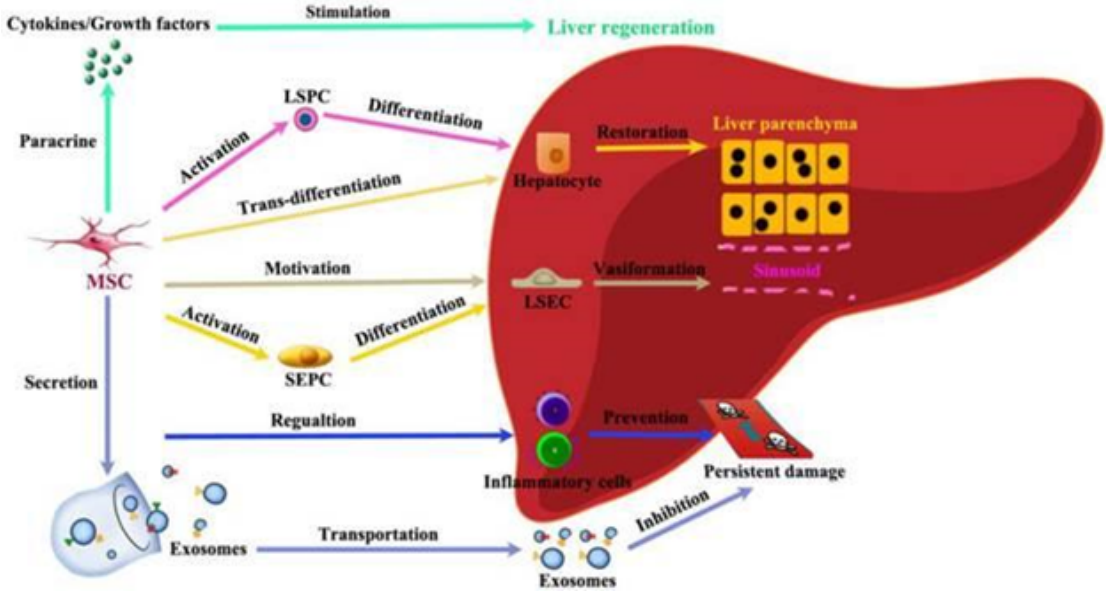
But more importantly regenerative medicine technology allows treatment on a much smaller scale. Whereas implants and transplants can only replace tissues and organs, regenerative medicine can set things right at a cellular level. A 2013 academic paper in Cell entitled *Hallmarks of Aging* concluded that the main pathologies of aging are linked to errors in cell function, and specifically describes regenerative medicine as a solution. [44] Age, in other words, can be treated quite validly as an assortment of tissue damages at a cellular level, and regenerative medicine, acting on geroscientific knowledge to identify the damage, is an indispensable repair toolkit.



Prospective interventions to combat aging. [45]

Regenerative medicine is a relatively new concept. The term was first coined in 1992 to describe various treatment at the time that hampered chronic illness and regenerated failed organs. This marked the beginning of a general period of research into the possibility of inducing at will the natural self-regenerative capabilities in human.

Despite being fairly common among organisms (from the simple hydrae to the complex vertebrates), natural self-regeneration in human (as well as most mammalian) tissues is unusual, as most organs and tissues do not possess any restorative capabilities. There are however, some exceptions. The most notable being the liver.Research into liver regeneration is still at an early stage but has already revealed that the liver can completely regenerate from a quarter of its original size, due to the stem capabilities

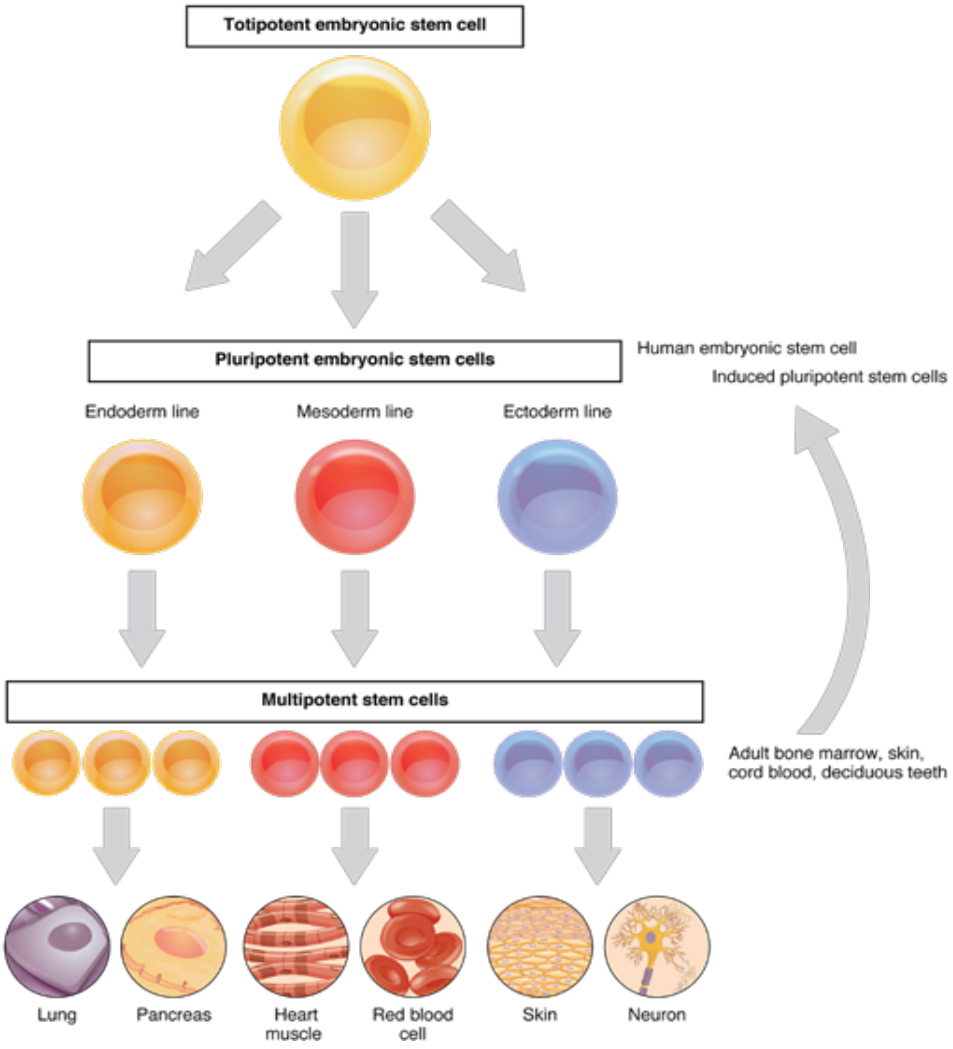


Liver regeneration [46]

of hepatocytes, the main cell type in the liver [46], and there is also evidence of other factors, such as cytokines and exosomes involved in this process [45].

Although regenerative medicine involves a great many methods and procedures, the most common involve the use of stem cells.
Stems cells are a type of cell that can form other types of cells in our body. They are categorised according to their their potency, which means their ability to differentiate into other cell types:

- Totipotent stem cells are cells that can differentiate into any cell in the organism. They are created after a sperm fuses with the egg and are quickly spent. To date no therapy has been yet been developed which uses totipotent stem cells.
- Pluripotent stem cells. They are formed from totipotent stem cells and are capable of forming into ectoderm, mesoderm, or endoderm..
- Multipotent stem cells can form a smaller yet more specialised group of cells, usually related to the specific organ or system.
- Oligopotent stem cells are even less potent than multipotent. They differentiate into only a small subsection of cells.
- Unipotent stem cells can only replicate themselves, however, they are still able to renew themselves and thus regaining stem properties.

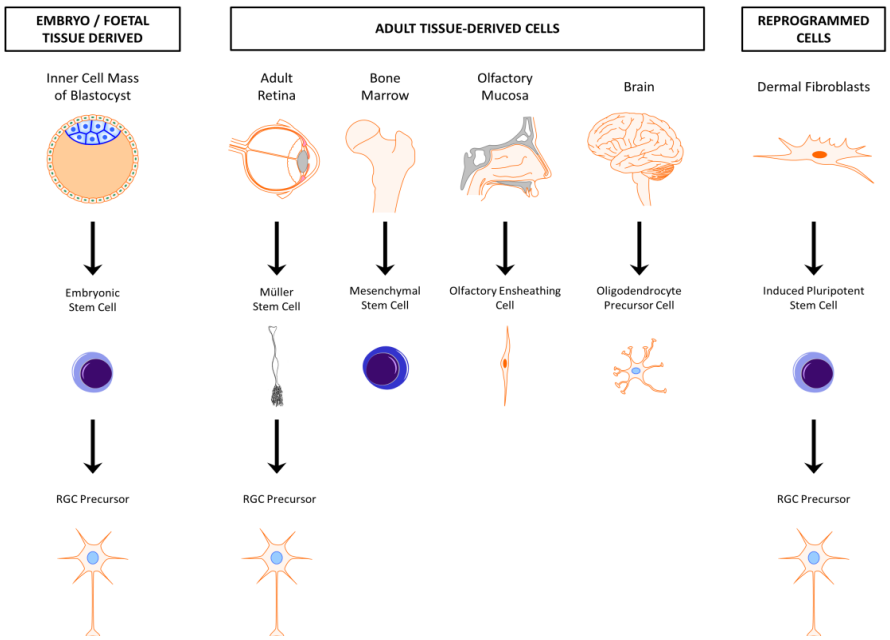


Stem cell differentiation [47]

There are multiple methods for obtaining stem cells for medical use, each with advantages and disadvantages, both practical and ethical. Stem cells can be obtained as:

Fetal or embryonic stem cells. These are stem cells received from aborted fetuses. They have high potency but come with practical and ethical concerns. These cells are directly linked to the increased probability of tumour formation. [51] Moreover there are fears that widespread use of fetal stem cells would eventually lead to modified fetuses created solely for the creation of such cells.

Adult stem cells. The most widespread type of stem cell. Generally it is advised to use **autologous** adult stem cells, meaning derived from patient's own tissues such as blood or bone marrow.**Induced pluripotent stem cells (iPSCs).** Although autologous adult stem cells are safer and more effective than fetal stem cells, they lack potency. Recent breakthroughs have shown that it is possible to reprogram adult stem cells so that they become pluripotent. This discovery was so important it earned J. Gurdon and S. Yamanaka were awarded a Nobel Prize in Physiology or Medicine in 2012 [49]. Induced pluripotent stem cells have advantages over both previous types and are the source for



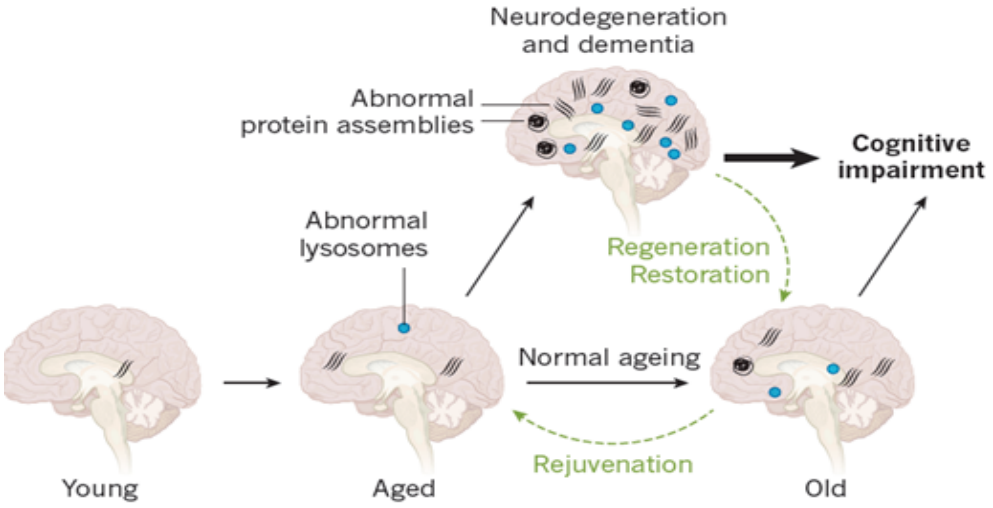
Possible origins of stem cells[52]

the most disruptive stem cell therapies.

Since the discovery of iPSCs the rate of regenerative medicine research has been accelerating. It is now possible to use stem cells in the treatment of blood and eye disorders, with further applications currently being sought. Already research suggests that stem cell therapies can be implemented to treat cardiovascular disease, vision impairment, viral infections, such as HIV/AIDS, and neurodegeneration.

Neurodegeneration, the aging-related functional decline of the nervous system, is of particular importance here.

As the nervous system, and the brain especially, remain one of the most scientifically obscure areas of our anatomy, it is clear that without further advance in neuroscience itself, the preventive treatment of the neurodegenerative diseases will remain a chal-



Neurodegeneration [52]

lenge for the longevity industry.

Neurodegeneration is not a singular process, but a confluence of processes which lead to overall cognitive decline, which in turn leads to a number of distinct disorders that include Alzheimer's disease, Huntington's disease, Parkinson's disease, Amyotrophic lateral sclerosis (ALS), and other miscellaneous cognitive impairments.

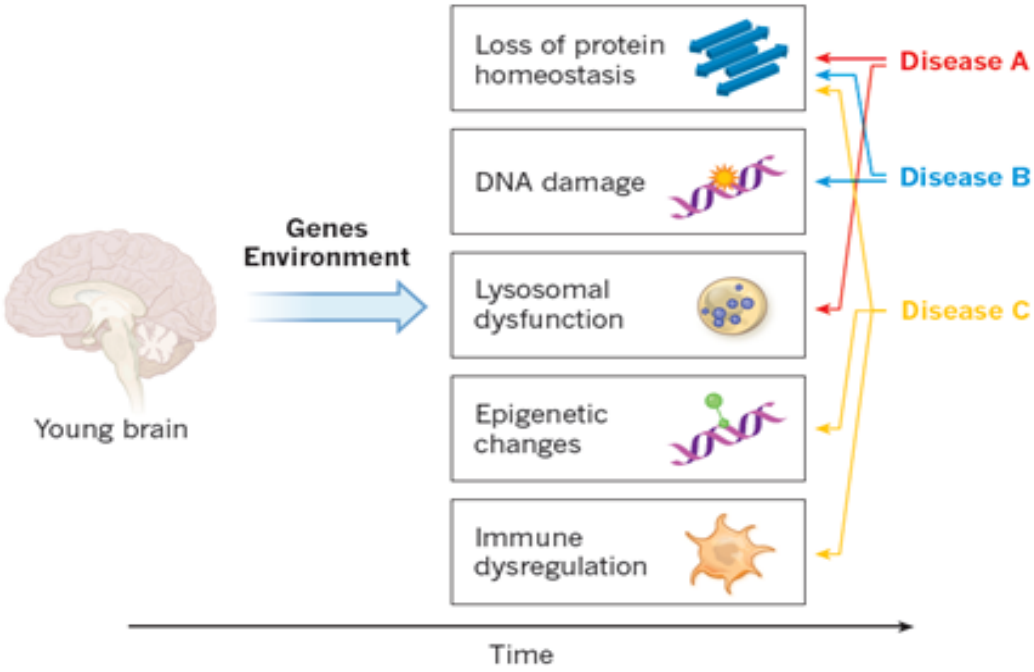
These diseases severely reduce life expectancy. For example the estimated lifespan of an Alzheimer's patient after diagnosis is usually no more than 9 years. [53]. And for the majority of these diseases there are no known cures.
Many prospective drugs for Alzheimer's and Parkinson's disease are being developed by companies all around the globe, but given the development cycle of therapeutics, they aren't likely to hit the market in the nearest future.

The treatments currently on the market are essentially palliative care therapeutics. The goal of those drugs is to slow down rather than halt the inevitable decline. [54]

The contributing factors to neurodegeneration fit into three main categories:

Genetic factors. Individuals who have a family history of neurodegenerative diseases have much higher risk of having it themselves compared to individuals that lack any such history (for example, the heritability of Alzheimer's diseases is 79%). [55]

Epigenetic factors. The involvement of epigenetics would explain the late onset of the majority of neurodegenerative disease. All three main epigenetic mechanisms (DNA methylation, histone modification and non-coding RNA (ncRNA)) influence the diseases. A number of therapeutics targeting each of these mechanisms is likely to hit the market soon.



Mechanism of neurodegeneration [55]

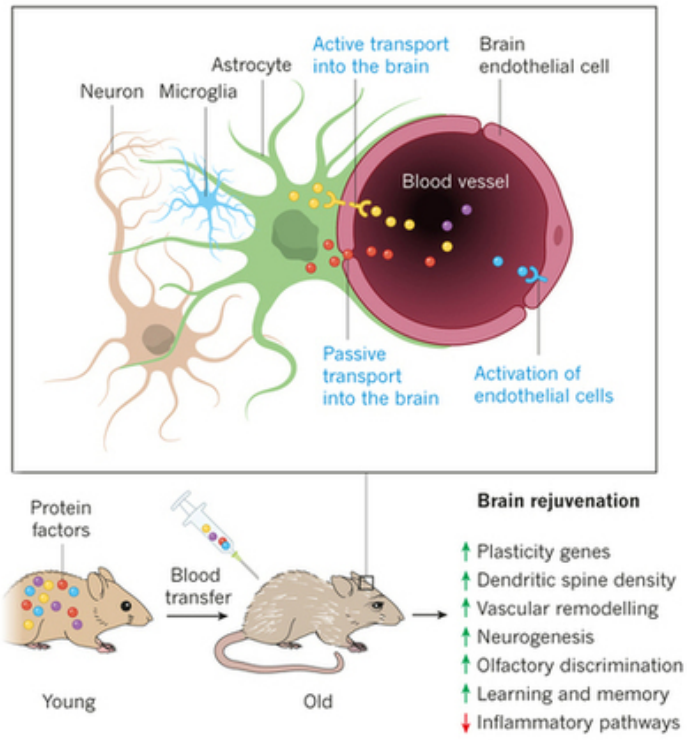
Environmental factors. There is some evidence to suggest that environmental conditions directly affect the probability of neurodegenerative diseases. Research into this area is very incomplete, but there is at least evidence to suggest that poor environment can influence neurodegeneration at least indirectly, as the patterns of the epigenetic changes are modified by the environmental factors. [56]

The established approach to neurodegenerative diseases has been to seek treatments disease-by-disease, but this has been a losing battle biogerontological research has shown multiple neurodegenerative diseases to be clearly rooted in aging.

The remaining way forward for neurodegeneration is, aptly enough, a form of neuro-regeneration. Namely, the regenerative medical approach applied to this facet of aging.

In February 2017 two landmark research institutions: The SENS Research Foundation and Buck Institute for Research on Aging launched a joint research program on age-related neurodegeneration.

'*Our ultimate goal is to find treatments for Alzheimer's and Parkinson's disease. Working with SRF will enable us to look at whether it is possible to use a new method to reverse and prevent the formation of tau tangles* — said the program leader Dr. Julie K. Andersen, referring to the insoluble twisted fibers found inside the aged brain's cells



Prospective brain rejuvenation to combat neurodegeneration [54]

-- '*which will help us make significant progress in addressing these complex disorders*'. [57]
In light of SRF's previous work on macular degeneration and atherosclerosis, it is hoped this collaboration too will bring regenerative medical solutions to neurodegeneration a step closer to realisation.

The prospect of success in this area in particular makes regenerative medicine a potential pillar of the longevity industry, accelerating progress by an order of magnitude.

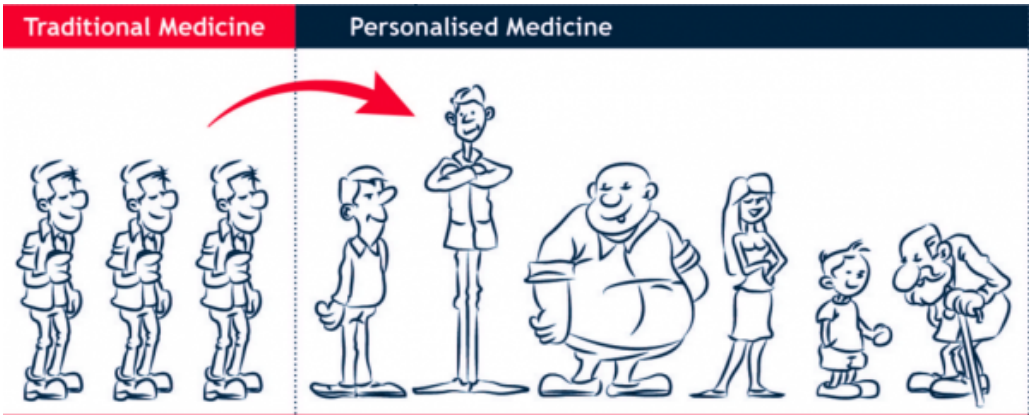
But it is fraught with risks, such as the propensity of stem cells to become cancerous. Indeed regenerative medicine is a toolkit of highly innovative, highly invasive technologies with clinical trials still a great many years off. Anti-aging gene therapy trials, for example, are still in their absolute infancy, as are the therapies themselves.

But what if there is a way to sidestep these risks also? What if we could make prospective interventions safer and less invasive, reducing the remaining degree of risk to be subject to trial, and thereby accelerating progress?

Enter **personalized or precision medicine,** already drawing popular, business, and academic interest. The core concept of personalized medicine can be summarized as follows: as people vary among themselves in various ways, including genetics and epigenetics, therapies should be adjusted based on personal characteristics of each individual patient.

Often personalized medicine is used in conjunction with **participatory, preventive and predictive**, and hence it has become known as '**P3 medicine' approach**:

- To take personal traits of the patient into the consideration



Traditional vs. Personalised Medicine [86]

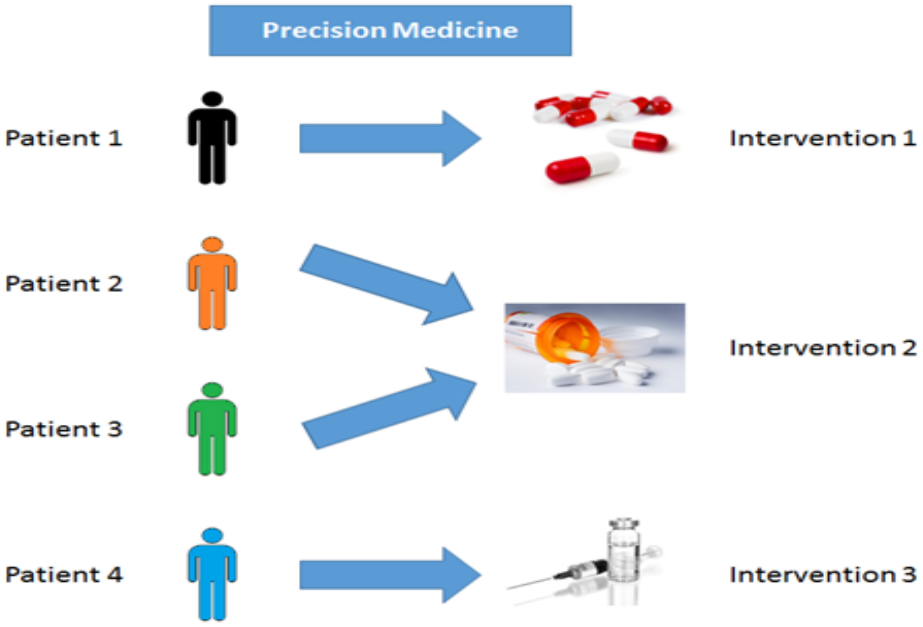
- To involve patients in collaboration in the healthcare process
- To prevent diseases when possible, rather than to treat them
- To predict diseases before they do any substantial damage

Personalized medicine is heavily tied to the field of **genomics** and **bioinformatics.**

Whereas **gene therapy** strives to create genome-altering therapeutics for treating genetic ailments, P3 medicine seeks to learn from an individual's genetics instead of altering it.

This approach is safer and less invasive. However implementing it in the healthcare system can be truly a daunting task.

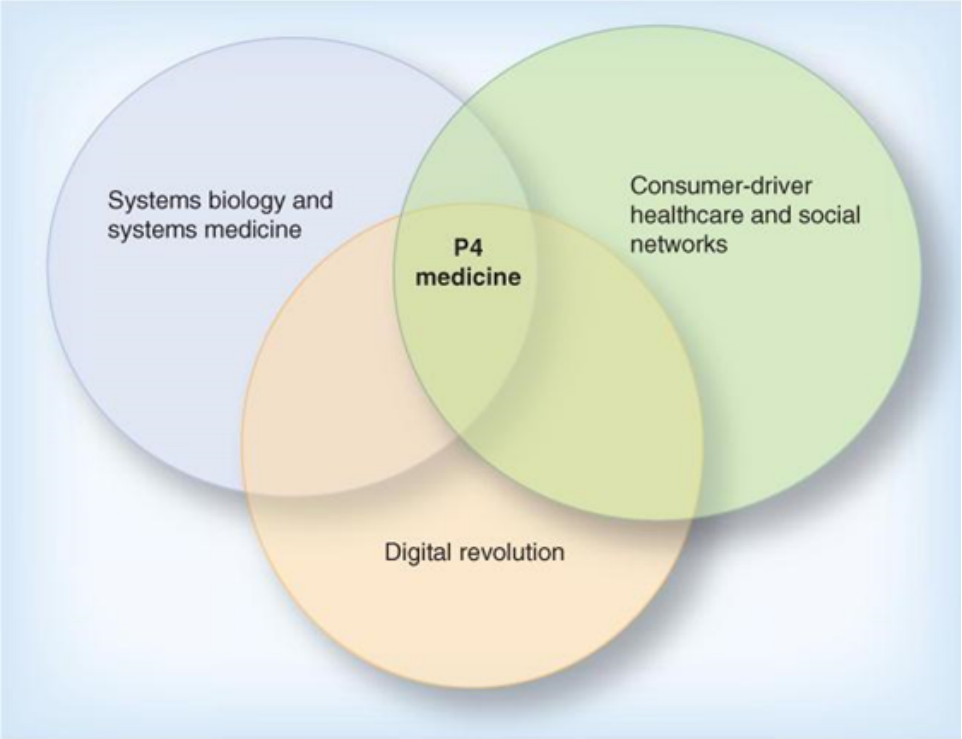
Even though the mass implementation of the P3 medicine was a long expected event, it took a long time to bring this approach to the healthcare system. But once the Human Genome project was completed, it became possible to reference human genetic information for meaningful results.



P3 Medicine [58]

The development of P3 medicine was precipitated by three key enablers:

- Consumer-driven healthcare in conjunction with social networks has managed to bring big data to medicine, creating the ability to categorise patients for better personalized treatment choice.
- Systems biology has brought previously unknown bioinformatic capabilities. Now-adays, it is possible to sequence the entire human genome for only a $1000, while in 2001 it cost up to the $1T.
- The digital revolution itself had to happen in order to bring about modern machine learning and big data which are essential to P3.

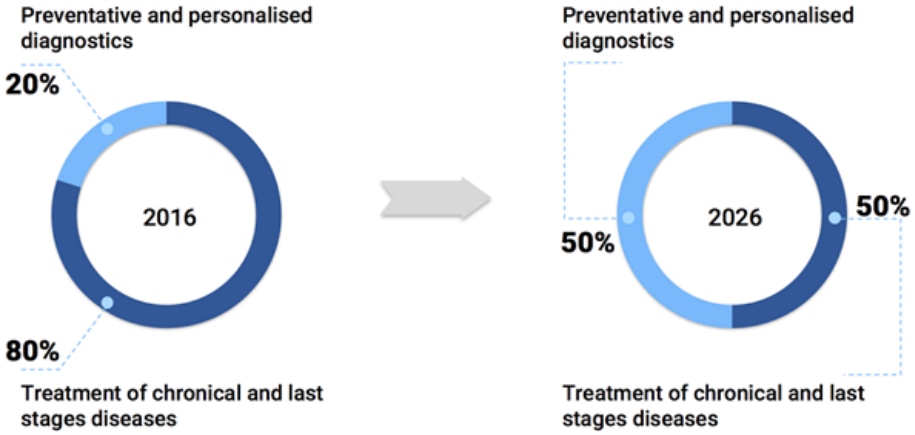


Key enablers of the P3 medicine [59]

Personalized medicine has already sown the seeds for five transformations in the modern healthcare system:

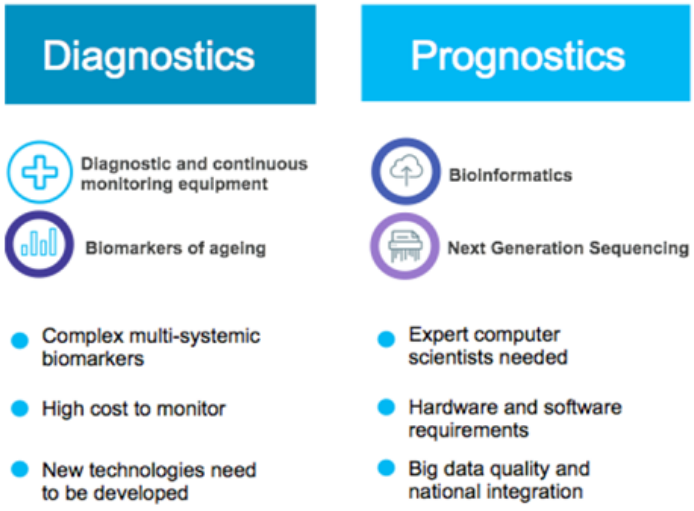
1. Medical data generated from the general human population instead of the limited clinical trials test groups. It will be like Phase IV clinical but on an unprecedented scale.
2. A global increase in cost-effectiveness of drug discovery enabled by break-throughs in molecular and cellular studies.
3. A accelerated pace of innovation boosted by a combination of drug discovery and therapy innovations.
4. A proactive, rather than reactive, science-based approach to the medicine, and a patient-assisted self-surveillance of the benefits.
5. A rapidly-growing P3 medicine industry that will become bigger than the traditional healthcare system. [60]

The pace at which these trends will bear fruit is difficult to estimate precisely, but a rapid growth of personalized medicine in the healthcare system is expected in the next ten years.



Perspectives on personalized medicine in the next 10 years

Finally, an important aspect of P3 medicine in the context of the longevity industry is the diagnostic and prognostic methods. In order to use personalised medicine to maximum effect the following would need to be implemented:



P3 diagnostics and prognostics for anti-aging

- Biomarker-based diagnostics for the efficient recognition of the hallmarks of aging
- Digital methods of prognostics based on bioinformatics and big data:

Personalized medicine promises to transform the healthcare industry and with it the future of human longevity. But it is still contingent on a multitude of enabling technologies and needs interdisciplinary research to make them work together in order to create a safer, more effective and more precise healthcare system.

AI in Healthcare and Geroscience

"Any sufficiently advanced technology is indistinguishable from magic"
~ Arthur C. Clarke

Artificial intelligence may just amount to this sufficiently advanced technology.

In the past ten years, while regenerative medicine was transplanting tracheas, building blood vessels, building bladders, growing heart valves, creating inner ear cells, and treating brain injuries, artificial intelligence has been driving vehicles, delivering parcels, managing households and marketing music.

And it may well prove to be another string to the bow of the longevity industry.

Precision and big data

Thus far we have looked at geroscientific interventions in metabolism, regenerative medicine workarounds to the limits of geroscience, and the precision approach to both of these.

But precision in medicine is only made possible by the consolidation and analysis of vast quantities of medical data.

Consider for example the precision approach to cancer. The approach to cancer as a single disease is already obsolete. We're identifying an ever-growing number of subsets of patient genetic profiles correlated with different mutations and variants of cancer. And drug candidates must be tailored for each subset.

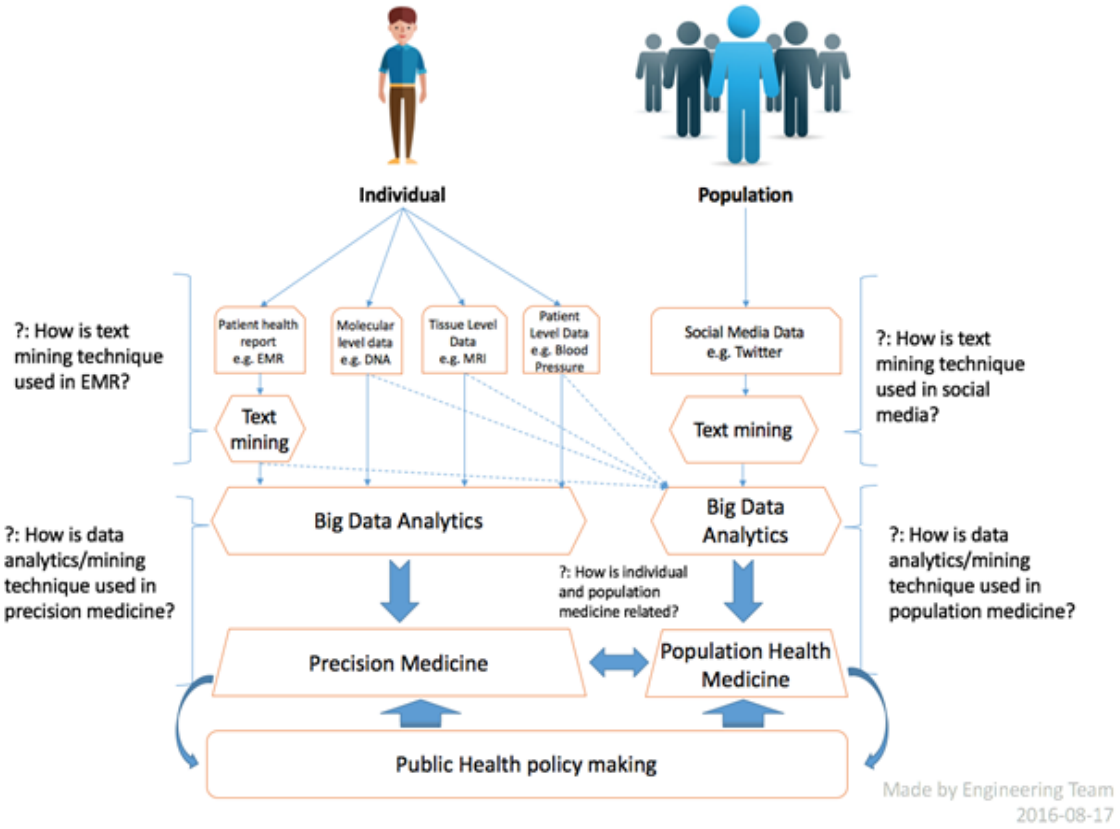
The same goes for Parkinson's and Alzheimer's.

This precision approach to disease therefore requires a vast array of data types: complex genome sequences, cell structures, organ structures, patient demographics, patient medical records, lab test, experimental results, medical imaging data, records of drug interaction with affected cells and so on.

Or to put it simply, high precision requires big data.

The problem with big data

Data is only useful when it becomes information. That is, when it is properly processed, parsed, categorised and organised. And more healthcare data is being collected than can be processed manually. This currently involves error-prone specialists and clinicians sifting through seemingly endless amounts of data in order to develop the most rational diagnoses and treatments for a patient. Specialists and doctors spend far more time on this than on attending to patients and conducting new research. This increases the delay between



The role of big data [91]

diagnosis and treatment, and de-prioritises prevention and early detection of disease.

And as medicine becomes more 'data-driven', this workload will only increase.

Big medical data is particularly unwieldy in the following respects:

Medical data is not all in one place. Data from healthcare comes from many different sources and in various formats - from digital medical records to wearable devices.

Medical data is not integrated between medical facilities and their multiple departments, which inhibits accessibility to important data that could be used to help diagnose and treat patients with similar histories and diseases.

Medical data not all digitised. For example there are still old research papers and textbooks containing the necessary data.

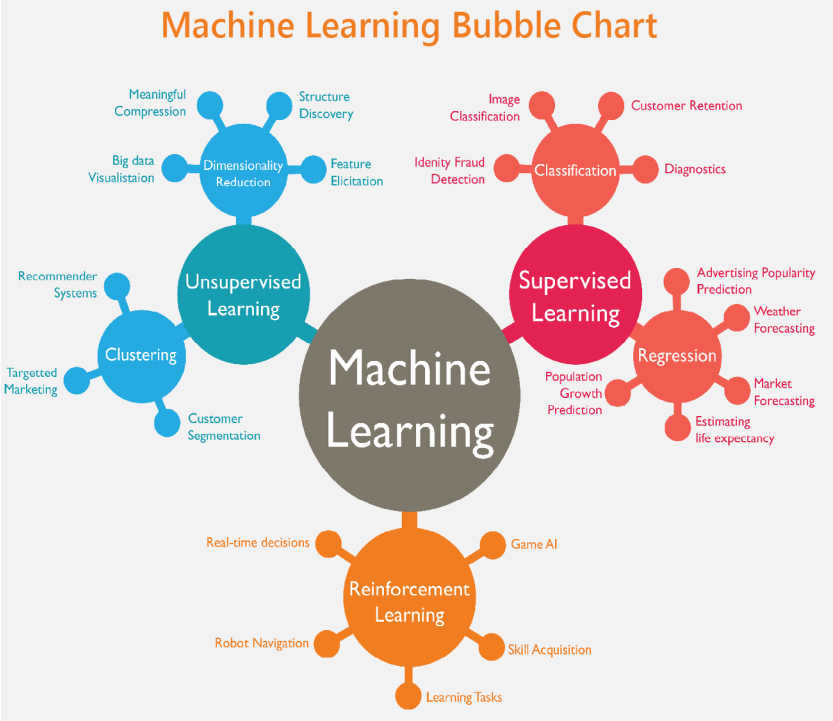
Medical data is inconsistent. It is not yet centralised and the concepts and definitions used globally throughout the history of medical research are not strictly comparable, so it is difficult to glean from the sum of it definitions of what should now be considered to be 'best practice'.

Medical data is constantly updated. New research is constantly conducted all over the world which leads to changes in our medical understanding and new information. Professionals are encouraged to keep abreast of new research but this is difficult for the above reasons.

There is also inconsistency in how the data is collected, so that even well structured data such as patient medical records is compiled in a manner unique to the establishment from which it originates. This adds a further layer of irregularity that makes data collected from multiple establishments difficult to analyse.

Introducing artificial intelligence (AI) and machine learning (ML)

If the problem is vast quantities of globally scattered, inconsistent and constantly updated medical data of diverse formats and disparate origins, then preparing it for use will take a miracle. Or 'a technology indistinguishable from magic'. We are alluding here not only to artificial intelligence (AI), the attempt to automate intelligent behaviour, but to 'machine learning' (ML), the use of AI to glean meaningful information from masses of raw data.



Machine Learning Overview [93]

Fortunately biotech and AI are no strangers. Various innovators such as Elon Musk already see A.I. as a cornerstone of the industry. His company BioSpace, who are the brains behind SpaceX and Tesla, launched the biotech company Neuralink, whose ultimate goal is to link the human brain with a computer. The idea is to implant computers into a human brain as a way to merge man-made software with the brain in order to improve memory. Neuralink is currently developing a technology called "neural lace" that would allow the brain to communicate with a computer without having to physically interface with it. Following in the same footsteps, MyndYou, a data-driven platform that provides tools for maintaining cognitive abilities, has created an artificial intelligence diagnostics tool to track the subtle changes in speech patterns of Alzheimer's patients. The technology encompasses a unique method for analysing multiple parameters related to change in cognition that are collected as part of day to day life, which includes speech

patterns. At present, the program is being tested through a collaboration with Massachusetts General Hospital. The study will validate MyndYou's technology for the remote, automated detection of subtle changes in speech patterns of Alzheimer's patients. And in July, the Mayo Clinic together with the Massachusetts-based nference, who seek to synthesise the world's biomedical knowlege, launched a startup company called Qrativ, focused on drug development which, according to Murali Aravamudan, co-founder and Chief Executive Officer of Qrativ and nference, is powered by "*a core technology based on a neural network ensemble for identifying nascent drug-disease, drug-gene and other therapeutically-relevant associations from the vast biomedical literature".*

So already machine learning is making its influence gradually felt in biotech. But why only now? One reason is the sudden availability of data. Historically, even well into the information age, it has been difficult to access large quantities of biomedically relevant data, but now we see the sudden emergence of databases in the public domain. This was precipitated not only by recent advances in computing power and AI algorithms, but also a mandate from the USA's National Institute of Health (NIH) that any research body receiving Federal funding must place such data in the public domain.

Machine learning and big data

AI alleviates the burden of big data by intelligently consolidating vast quantities of irregular medical data into a single central database. This then becomes information that can be sorted through instantly so that relevant articles can be prioritised for different clinicians and specialists on a case by case basis.

It allows collaboration across a complex ecosystem of entities spread across the globe: universities carrying out primary research data, biobanks holding biomedical sample and sample data, pharmaceutical companies holding drug data and biotech companies holding patient data among many other things.

Collaboration among these entities, including innovative partnership models, customer engagement and trust in data is of paramount importance as it creates a platform for facilitating data processing and data access to all stakeholders.

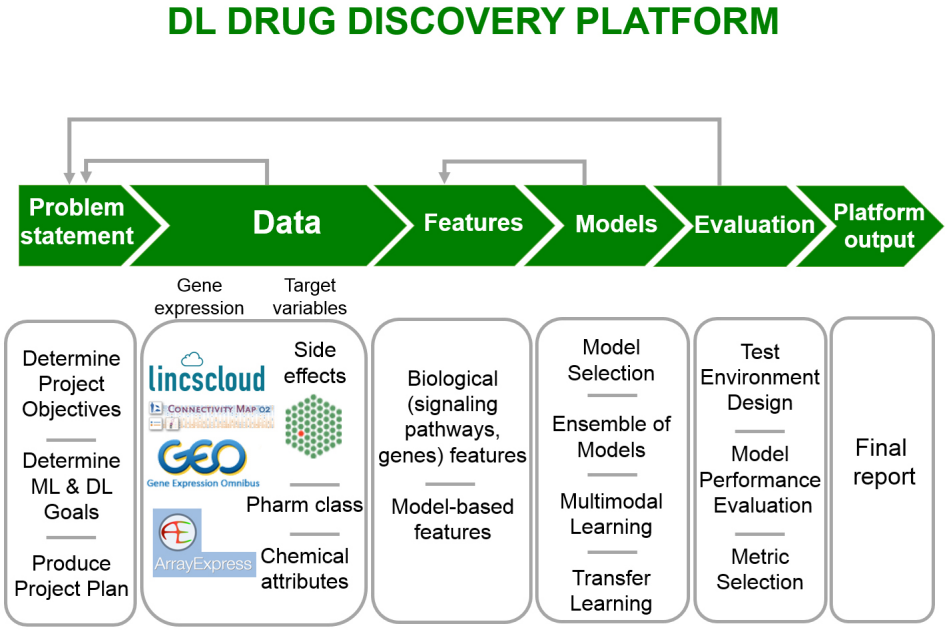
Data thus consolidated also has the advantage of unmasking regular errors made by doctors or hospitals so that they could be held accountable and given the chance to improve.

How AI & ML are transforming drug discovery

Drug discovery comes at a very high cost, but success brings significant benefits to mankind. A breakthrough drug can cure a critical disease for hundreds of thousands of patients across the globe and can earn the company making the drug billions of dollars in revenue. That is why, just to bring one of the breakthrough drug to market, companies spend hundreds of millions of dollars on decades on a single avenue of research, not knowing where the research will bear fruit.

This deep exploration of potential false avenues brings with it the potential for a tremendous amount of wasted time, money and effort.

But this research landscape is changing. Machine learning, unencumbered by human intuition and armed with vast quantities of data, can cut down on waste by prioritising research.



Deep Learning for Drug Discovery [93]

The reliability of of AI-driven drug trials lies in the fact that hypotheses are generated not from occasional human epiphanies but from masses of cold hard data, yielding less wasteful hypotheses. Drug companies have already been using artificial intelligence to decide in advance whether, for example, it is worth investigating whether a particular drug might bind to a particular protein. But there is trend toward ever more advanced estimates, such as how the same drug might subsequently affect a patient's cells or tissues.

Machine learning also has implications for patient safety and regulatory hurdles. The use of patient-derived data could help pharmaceutical companies better identify and recruit patients for clinical trials for the therapies most likely to work for them, boosting the chances of approval by regulatory agencies such as the [US's] Food and Drug Administration (FDA).

Project Survival, for example, is a $17 million seven-year study bankrolled by Berg, a Massachusetts biotech firm, one of several companies in the US and Europe currently using AI to make drug research and development less expensive and more efficient. Intelligent machines scour patient's genes for molecular fingerprints or biomarkers that can later be used to help measure a specific drug's impact and identify the patients in which such a drug is likely to be most useful.

Some companies such as Insilico Medicine Inc. in Baltimore, are forming research partnerships with universities and nonprofits or setting up AI services aimed at drug companies.
Based at Johns Hopkins University's Emerging Technology Centers, Insilico uses genomics, big data analysis and deep learning for in silico drug discovery. The company has drug discovery programs in cancer, amyotrophic lateral sclerosis and diabetes, as well as in age-related diseases such as sarcopenia, Parkinson's disease and Alzheimer's disease.

In January, GlaxoSmithKline PLC (GSK) and Lawrence Livermore National Laboratory in California announced a partnership to use AI for pharmaceutical R&D. The consortium is establishing itself in San Francisco and signing on further collaborators with the stated aim of using AI to slash development time from ten years down to one.

Now GSK is now partnering with Insilico Medicine to explore howInsilico's AI technology could aid the drug discovery process by identifying novel biological targets and pathways of interest.

"In our opinion, GSK is one of the most innovative science-led healthcare companies, which realized the potential of artificial intelligence early and has demonstrated its ability to partner with innovative startups in the field. We are delighted to collaborate with arguably, some of the world's best scientists on chronic diseases with unmet need."
— Alex Zhavoronkov, Ph.D., founder and CEO of Insilico Medicine.

The Insilico collaboration is GSK's second drug discovery deal of the summer based around AI. Earlier in July of this year they secured a deal with Exscientia, which automates drug discovery with its AI-enabled platform that could see the Scotland-based company rake in up to £33 million in research payments.

In Europe, scientists are getting ready to launch a similar initiative, which will include Johnson & Johnson 's Janssen Pharmaceuticals division, plus several other drug companies and academic researchers.

AI's broader role in biotech

But we have yet to pull out all the stops. Progress is retarded by a catch 22 : Financers of science don't like taking scientific risks, and scientists don't like taking financial risks. And like the space industry, the longevity industry is comprised of many converging technologies and the road ahead has many false avenues and therefore a presents a landscape of clear and present risk in the eyes of investors.

But moves are already underway to addressing both sides of the catch 22: removing financial risk by using AI to orchestrate global investment, and removing scientific risk by offering tools for machine learning, deep learning, and artificial intelligence to the companies that receive it.[65]

This would also have implications for the geographical distribution of funding. Professional investors in biotech have traditionally tended to stick to familiar comfort zones such the San Francisco Bay Area and Boston, MA. While European life science remains mired in a culture of risk aversion and Britain is strewn from north to south with cash-starved regenerative medical centres and expertise. But because machines have no comfort zones, we should not be surprised

if artificially intelligent investment results in a totally new and counterintuitive global distribution of funding for this industry. AI would not hesitate to exploit the talent and manpower of neglected regions, busting wide open the monopoly of traditional biotech hot spots, increasing the range and relevance of research, laying the groundwork necessary to raise regenerative medicine to the next levels.

An Undeclared War: Roadblocks in Geroscience and the Road Forward

In 2018, 'aging' remains an unnamed adversary in an undeclared war. For all intents and purposes it is mere abstraction in the eyes of regulatory authorities worldwide.

The World Health Organization (WHO), which sets the standards by which medical conditions are classified as specific diseases, subject to regulatory approval from specific nations, has never declared aging itself either a disease or any kind of target for biomedical intervention [61].

Any prospective therapy must aim to gain approval as a treatment for a particular recognised age-related disease or condition and this therefore leaves us with a difficulty. It is hard to argue to regulatory authorities that any age-related disease or infirmity already recognised is likely to be prevented by a given proposed therapeutic intervention in aging, even if aging were ostensibly retarded or reversed as a consequence. So much of the argument depends on incomplete knowledge of the links between aging and disease.

Unless an argument can be made based on shorter ramifications, geroscientific therapies cannot gain approval.

The result has been a series of proxy wars on this or that disease, while the empire of aging remains unmolested.

However there is emerging consensus in the geroscience community that aging can and should be classified as a distinct disease via the WHO's International Disease Classification (ICD) system. In a November 2015 a paper publish in Frontiers in Genetics made a carefully layered recommendation for the classification of aging as a disease in the 11th World Health Organization's (WHO) International Statistical Classification of Diseases and Related Health Problems (ICD-11) in 2018. [62] [63].

«Aging is a complex multifactorial process leading to loss of function and a very broad spectrum of diseases. While the notion of whether aging itself is a disease is usually disputed, classifying it as such will help shift the focus of biomedicine from treatment to prevention. Classifying aging as a disease with multiple 'non-garbage' ICD codes may help create business cases for large pharmaceutical companies to focus more R&D resources on this important field. Considering the unprecedented increases in life expectancy and the heavy burden of medical costs in the developed countries, maintaining the human body in the disease-free youthful state for as long as possible is not just an altruistic cause, but a pressing economic necessity», said Alex Zhavoronkov, PhD, CEO of Insilico Medicine, Inc.

But the expression of such logic is highly innovative and starkly at odds with existing popular and professional ethics.

It comes just four years after Colin Blakemore, formerly the Chief Executive of the British Medical Research Council (MRC), in the UK, appeared in Oxford's Sheldonian Theatre in a 2011 public ethical debate against Aubrey de Grey to defend the presence of aging in the human body. Although the event got some mainstream media converge, the sight of a former UK health chief defending medicine's eternal nemesis went entirely unremarked upon.

'The Debate of Ages', Sheldonian Theatre, Oxford. [88]

This lack of practical and ethical resolve among public and professionals is linked to the non-conceptual way in which aging is regarded by public and professionals. Years of silence from scientific authorities on the tractable nature of aging have allowed a near total absence of any popular conception of aging as something ultimately amenable to physical intervention.

Democratic demand for a war on cancer continues decades after its declaration because, despite it remaining unwon, a cure is still popularly conceived of as the removal or prevention of a tumour, and that very notion of the concrete and attainable objective continues to galvanise public demand for further research.

Whereas aging, despite being equally physical in nature to cancer, is still thought of as something mystically outside the realm of amenability, a habit of mind which makes itself immediately apparent in popular turns of phrase.

For example, a cancer patient may complain that his cancer is 'eating him alive', but a person left infirm by aging merely laments that 'time has taken its toll' on him. He does not complain that his cells are filled with junk or strewn with collagen crosslinks, which would be the equivalent verbal portrait of advanced biological age.

We have neither a declaration of war from the authorities nor an ability to conceive of the enemy among the public. The result has been inertia.

This inertia is further compounded by the fact that constituent technologies of the longevity industry, even those not known primarily for their anti-aging significance, are mired in regulation. Human gene therapy trials for example were been regulated down to a near-halt since since human trials produced their first death in 1999 in Arizona and another two in 2003 in France [64].

But the safety of the technology has improved dramatically in the past decade.

And in 2018, we are due see the first human clinical trials for heart failure treatment in several years [66].

Conclusion

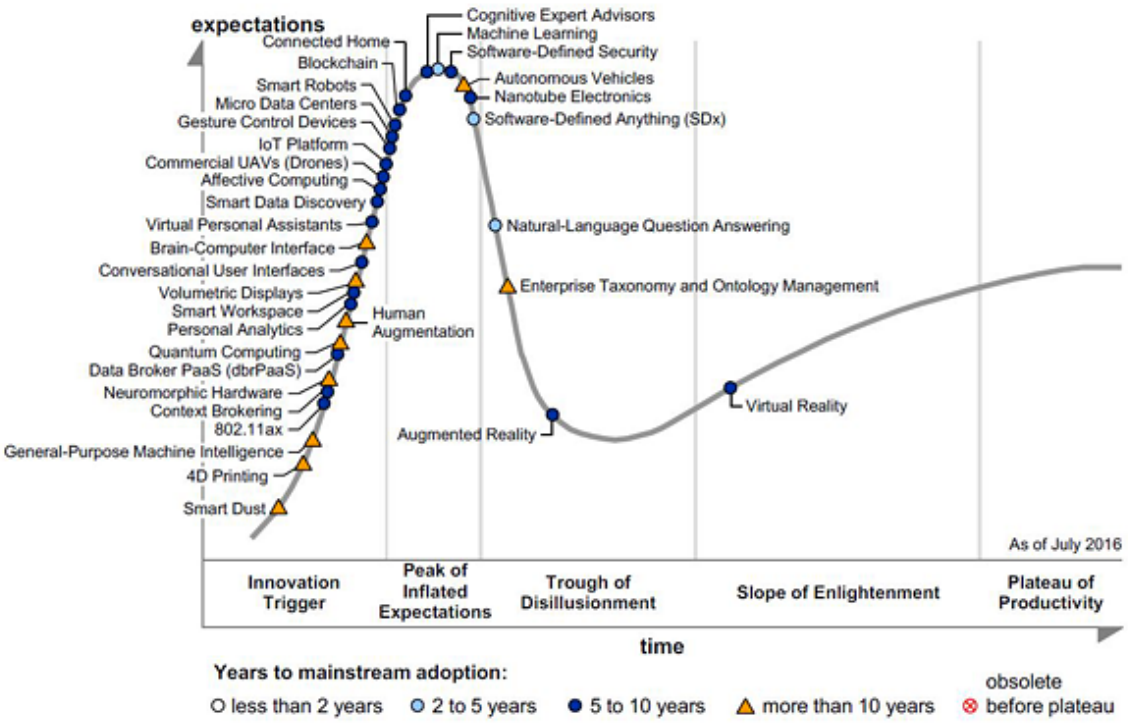
"If I have seen further than others it is by standing on the shoulders of giants"
~Isaac Newton

The rate of progress

Longevity is a simple metric, the simplest there is, being a single variable. But what is now its main inhibitor, aging, has a myriad of forms and causes, and a myriad of potential redresses, of which a balanced let alone detailed summary would be infeasible. As such this has necessarily been a rough sketch of uncharted waters.

But we are finally beginning to see an industry emerge from mankind's attempts to make sense of the biological chaos. This industry has the form of two parallel technologies: biomedical gerontology and rejuvenation biotechnology, built upon a foundation of knowledge mined by geroscience over decades. The progress of both has drawn the attention of the mainstream media, as well as entrepreneurs and policymakers seeking to bring anti-aging therapies closer to realisation.

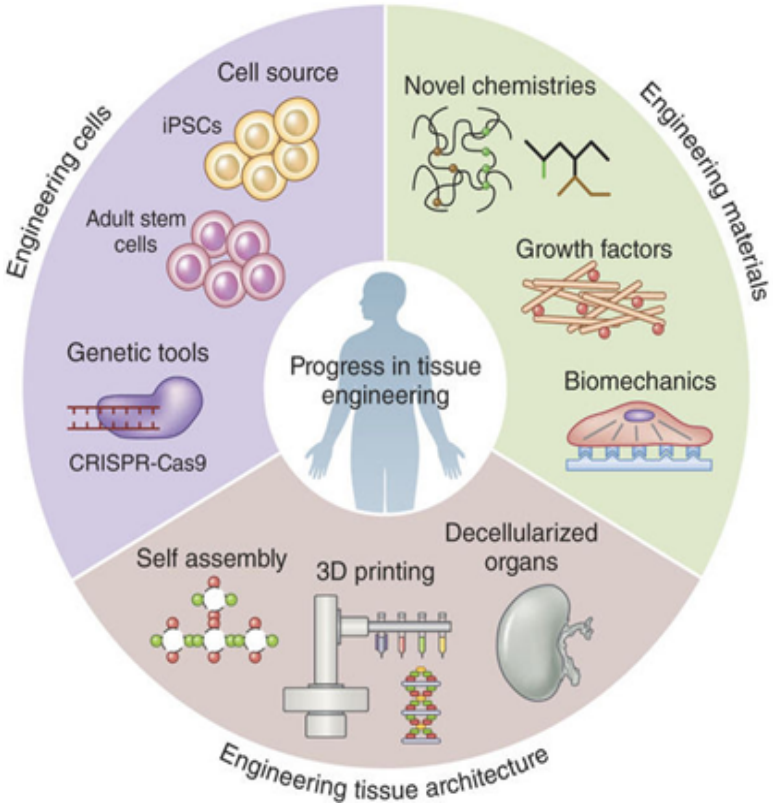
But no progress, no matter how disruptive, is made in an instant. Research creeps forward without fanfare, building on previous discoveries and forming trends. Even the CRISPR/Cas system, the plainest recent example of an unforeseen biotech breakthrough, was built atop years of endonuclease research.



Gartner Technology Hype Cycle [67]

Nonetheless a close look at the industry reveals which technological threads are advancing quickest:

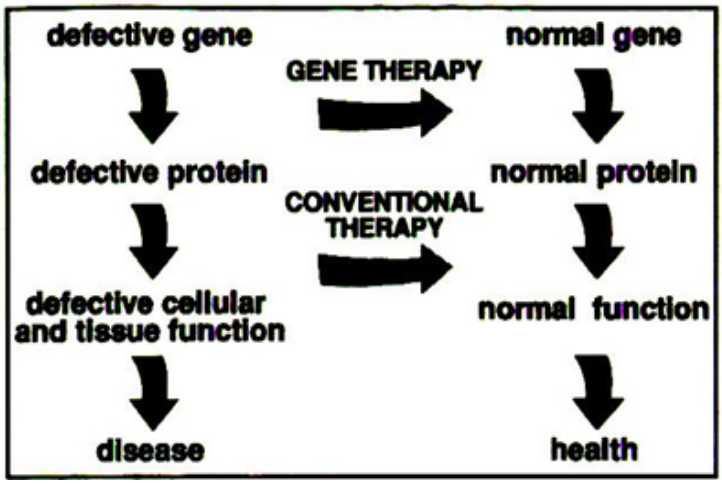
One is artificial intelligence. According to the US research and advisory firm Gartner, machine learning has reached the peak of the 'hype cycle' (which indicates when a technology is close to mainstream adoption) and will be fully embraced by the mainstream by 2020 [67]. There are clear indications of increased interest in machine learning technologies in longevity research, with many analytical agencies expecting AI technologies to enhance the precision of drug discovery and assemble fully personal therapies for patients based on their records. [68] [69]



Progress in tissue engineering

Also of interest is senolytics, the prospective class of pharmaceuticals that can remove senescent cells. Senolytic drug discovery has received a significant boost in terms of speed and public interest in recent years. Over 10 prospective senolytic drug candidates are being developed, and senolytics are expected to enter the market in less than a decade, and some, for example Dasatinib, a known anti-cancer medication, are already being used in healthcare.

The field of regenerative medicine has made a significant progress in the last decade, after a number of key enablers such as from iPSC technology and 3D printing of organic structures [70] It is the focus of several major longevity institutions. The Methuselah Foundation is particularly interested right now, and is establishing two major tissue engineering competitions under the New Organ campaign [71]. Such investments, combined with the technological advancements, ensure that progress in the application of regenerative medicine to aging remains a trend.



The difference between conventional and gene therapy [72]

Personalized medicine serves as an accelerating factor to all three, having been precipitated by a number of prerequisites: system biology, artificial intelligence technologies, and Big Data. The technology has the potential to transform the healthcare industry but in order to make its mark it would need to incorporate biomarker-based diagnostics for the efficient recognition of the hallmarks of aging and digital methods of prognostics based on bioinformatics and Big Data.

Last but not least we should keep an eye on gene therapy. Gene therapy is the most preventative of any technology discussed here as it goes to the root of pathology by striving to prevent harmful gene expression. Being the most effective way to treat genetic disorders, it has a wide range of possible applications in the healthcare system. And with the advent of the CRISPR/Cas systems, the accuracy and safety of gene interventions were raised to a new level. Gene therapies also have multiple uses in the longevity industry, from expressing telomerase in somatic adult somatic tissues [73] to emulating effects of mTOR inhibitors [74] in animal models. Although it is the prospect farthest from widespread implementation, it may ultimately prove the most influential, and there are already successful cases.

None of these technologies will reach fruition in time to avert the immediate crisis. Japan is already in the shadow of silver tsunami, and the rest of are sure to get wet. The danger is real, and technological threads outlined here -- both the short-term and the more speculative -- are the only flood defenses yet conceived of. And their implementation is a matter of political, financial and scientific will.

In Part 2 we look at the people and institutions involved in making it happen.

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