LONGEVITY TECHNOLOGY

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FORESIGHT INSTITUTE

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Foreword

Purpose of this report

Many people have a favorite method to pursue for extending healthspan and longevity. However, it is important to take a step back and understand the big picture. Instead of backing a single strategy, we can ask why everyone believes what they believe, what evidence do they have access to, and what information are they missing. This report is an initial stab at unifying the field of longevity to cover as many different avenues as possible. Some of the methods may be unconventional, or flat out wrong. If they are, we believe it is important to understand *why* they are wrong instead of simply dismissing them as unworthy of study.

As this is the first iteration of this report, there are many sections which are underdeveloped. We invite feedback and collaboration to populate this scaffold by refining the sections that currently exist as well as adding sections that may have been left out.

Each section in this report was included independent of any preexisting frameworks. To that end, some of these methods exist outside of the hallmarks/pillars or other such paradigms of categorizing aging. The categorization of this report focuses on organizing ideas by solutions rather than problems - more of a semantic difference and one which may or may not be better than the existing system.

This report is a research product of the Biotech and Health Extension Group sponsored by 100 Plus Capital
A group of scientists, entrepreneurs, funders, and institutional allies who cooperate to advance biotechnology to reverse aging, extend human healthspans, and improve cognition.

Foresight Institute

Foresight Institute is a 30+ year-strong San Francisco-based institute to advance crucial science and technology for the long-term flourishing of life. We believe that, in addition to directly addressing existential risks, one relatively neglected area for impact is to directly support differential technology development in areas that make great futures more likely.

Thank you for your interest in our work. Please contact us with feedback, questions, and suggestions.

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Longevity Value Proposition

What is the value of longevity?

While we all want to stay alive as long as possible, the actual value of longevity does not come from our selfish desires to stay out of the grave. Value is generated by production of goods and services - but one absolute requirement for such production is that the producer is alive.

A typical worker in the United States starts around the age of 20 and may retire at ~65. That is roughly 45 years of productivity, and we can assume this timespan of productivity correlates with healthspan. Once a person grows weak from aging, they are also typically unfit for work. Increasing healthspan therefore increases working time, and subsequently increases GDP. Conversely, increasing lifespan without increasing healthspan would likely be a value sink, taking up more time and resources to care for the unfit individual without gaining value back in return.

Assumptions:
- 45 year working span
- An increase in healthspan delays the age of retirement

For a worker that lives 100 years, a 10% lifespan increase means 10 more years of life. However, if that 10 years is a pure healthspan increase, their value generation increases by 22% (a 10 year increase into 45 working years). **A single longevity intervention that increases healthspan by 10 years nationally could increase the national GDP by 22%.**

The question now turns to how likely is it that we find that kind of intervention.

The idea risk is divided into three categories.

X : Experimental concept. The theory may be coherent, but is unclear whether it is even physically possible to accomplish this idea. It could turn into a black hole of investment.

M : Tedious effort but doable. The technology is tested and functional but requires a lot of funding and willpower to translate into real progress.

S : Safe concept. The technology is robust, possibly even decades old in maturity. Requires very little funding to translate into feasible results.

The impact of longevity strategies is divided into three categories.

A : Seismic breakthrough. 100%+ increase in lifespan and something which may redefine life as we know it. An invention along the lines of the internet, the phone, or electricity.

B : Major gains. Roughly 25-100% increase in lifespan. An invention or breakthrough which spawns an industry.

C : Minor gains. Roughly 0-25% increase in lifespan. Creates several companies. Avoiding smoking, avoiding obesity, exercising regularly fall into this category.

Breakthrough Technologies

List of next step technologies

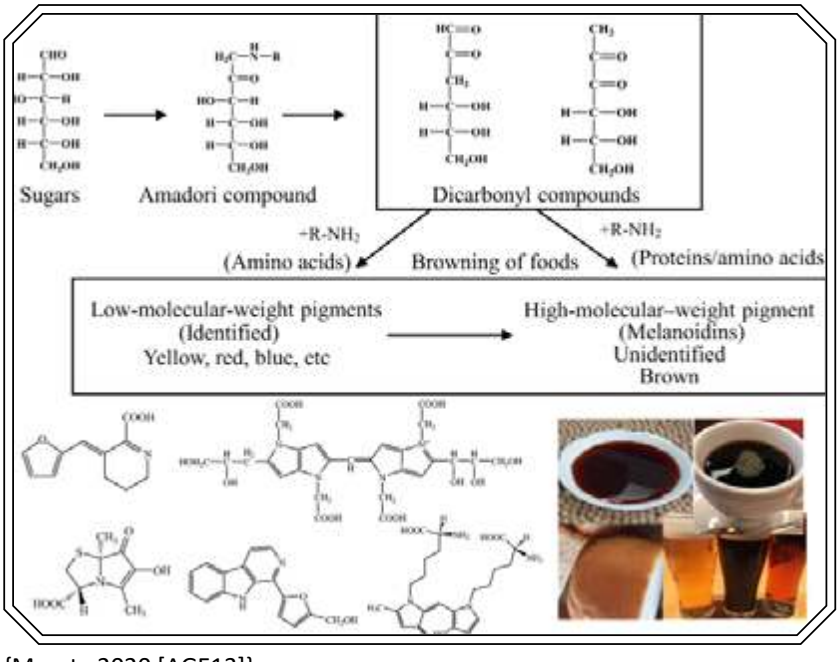
Advanced Glycation Endproducts

Introduction

Advanced glycation endproducts are created when sugar covalently binds to either protein, lipid, or nucleotides. This happens slowly under normal conditions but is accelerated in high heat. AGE's can form cross links between proteins, causing damage to the extracellular matrix which is implicated in arterial health and skin degradation. AGE's are also often very aesthetically attractive – the browning on bread and meat is attributed to advanced glycation endproducts.

The Maillard reaction - responsible for binding sugars with other molecules - can occur at room temperature, and certainly can occur without enzyme assistance within the body. It is thought that a major assisting factor are reactive oxygen species, which have chaotic free energy in the form of a highly reactive unpaired electron on their oxygen atom. There are two phases of the Maillard reaction, the first being a reversible reaction which leads to Schiff bases and Amadori products. Over the course of several months, these intermediate products slowly rearrange to become stable Advanced Glycation Endproducts which are non-reversible.

{Durango Herald}



{Murata 2020 [AGE13]}

Different sugars appear to have varying impacts on the production of AGE's. The most important to understand would probably be fructose, given its pervasive use in modern food. Comparison between the glycation of proteins using glucose and fructose have been carried out and shown that fructose creates alterations at an exponentially higher rate than glucose [AGE9]. Even more interesting, they were targeting albumin (although it was bovine albumin), which is related to blood aging vis a vis parabiosis experiments performed by Irina Conboy.

RAGE is a Receptor for Advanced Glycation Endproducts, named so because of its association with AGE's. This receptor seems to only cause inflammation when exposed to AGE's, without triggering any removal or degradation pathways. In 1999 it was hypothesized that the RAGE receptor is actually supposed to be detecting S100 proteins, and that it's association with AGE's is purely accidental due to its pattern recognition detection method [AGE10].

Advanced Glycation Endproducts

The Next Big Step - AGE Catalog

AGE's have been identified, but not categorized. It is likely that there are some specific types of AGE's which are harmful and other types which are beneficial. The next step is to develop a list of all types of AGE's which form in our food and in our bodies.

This is going to be difficult because AGE's are combinations of sugars with lipids, proteins, or nucleotides. For the sake of simplicity, lets assume protein implies amino acids and lipid implies free fatty acid. There are around 30 common free fatty acids, >20 amino acids, and 5 nucleotides. That's a total of 57 potential matching partners for the various sugars. With 20 common monosaccharides, that gives 1140 potential adducts, not including various permutations and cleavages of each combination. Add to this the possibility of involving multiple amino acids, or other lipid types such as phospholipids, and the list balloons out logarithmically.

A 'folding at home' style project to predict and simulate AGE formation may yield the data we are looking for here.

The current gold standard of AGE's is CML – carboxymethyl(lysine), which is derived from an oxidatively cleaved Fructose-Lysine adduct. Three different strains of thought are referenced by the prior statement – oxidative degradation, excess fructose toxicity, and excess lysine toxicity. CML is used as a proxy measurement for total AGE's but this is likely insufficient as a measuring device going forward, especially as we parse out the gradient of AGE's. Furthermore, free CML apparently has weak binding to RAGE [AGE12].

Anecdotally, the taste of different advanced glycation endproducts are not the same. Why does browning enhance the flavor of certain types of food while destroying the flavor of others? It implies that perhaps there are specific AGE's which are useful and good, while other types are toxic and inflammatory. Without a catalog there is no way to test this hypothesis.

Advanced Glycation Endproducts

Potential Impact - How will this affect us?

Idea Risk: M

Mapping out the microbiome metabolism network is technologically possible but extraordinarily tedious and time consuming.

Yield Potential: B/C

The potential impact here is limited. Diet optimization has been occurring via natural trial and error for hundreds of thousands of years of human evolution. It is unlikely that we will discover some new food schema that over-turns all food development up until this point, even if we have a deeper understanding of the nature of food.

Future Possibilities: B

The most impactful thing that could emerge from AGE research is if we discover that some types of AGE's are actually beneficial. The general paradigm could resemble that of reactive oxygen species - a damaging molecule thought to provoke aging but when looked at more closely has several key beneficial types which help the human body. There may be a Nitric Oxide equivalent of AGE's. The fact that there is a native receptor which specifically detects AGE's gives credence to that possibility. It could lead to a new class of drugs which may target aspects of our health which have been previously glossed over.

Furthermore, it is known that serum albumin is attacked via the maillard reaction to turn into AGE's [AGE9]. We know from recent experiments that replacing old human blood with a mix of plasma and albumin has regenerative effects. Is it possible that the detritus buildup explaining parabiotic regeneration interactions is rooted in advanced glycation endproducts forming from serum albumin, reducing albumin availability while simultaneously causing massive system-wide inflammation?

The AGE receptor is also implicated in other diseases, notably alzheimers via its interaction with amyloid beta. Perhaps some key element of this system is yet to be discovered which ties together several disparate phenomena and explains a large swath of human pathology.

Advanced Glycation Endproducts

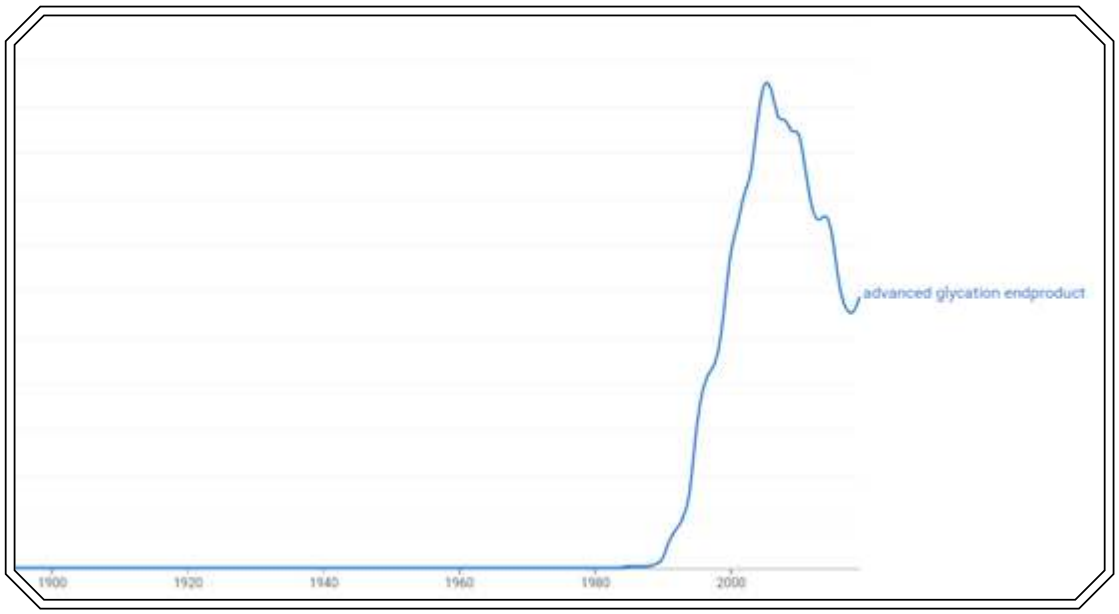
Timeline of Advanced Glycation Endproduct Research

1800

1912: Maillard reaction postulated [AGE1]
1925: Amadori products discovered [SOURCE UNAVAILABLE]
1953: Chemistry of browning reactions elucidated [AGE2]
1976: Hemoglobin AIc identified as AGE used to determine blood sugar level [AGE5]
1981: Maillard reaction postulated as a cause of aging [AGE6]
1989: Receptor for AGE's discovered [AGE3]
1989: CML, a type of AGE, shown to accumulate with age [AGE7]
1992: Receptor for AGE's cloned [AGE4]
1997: Dietary AGE's discovered to have significant impact [AGE8]
1999: RAGE likely detects S100 proteins [AGE10]
2003: RAGE mediates amyloid-B transport to brain [AGE11]

1900

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: N/A
Pillars of Aging: Metabolism

2000

Advanced Glycation Endproducts

Relevant Organizations: Who is working on this problem?

Diagnoptics
AGE Detection Company

AGE Scanner Mini
AGE Detection Device

Kapahi lab at Buck Institute
Glycation Research

Gugliucci lab at Touro University
Glycation Research

GlycanAge
Glycation Age Clock

Turner lab at MUSC
AGE Research

Taylor lab at Tufts
AGE Research

Haltiwanger lab at University of Georgia
Glycation Research

Ann Marie Schmidt at NYU
RAGE Research

Tilman Grune at University of Potsdam
Glycation Oxidation Research

Advanced Glycation Endproducts

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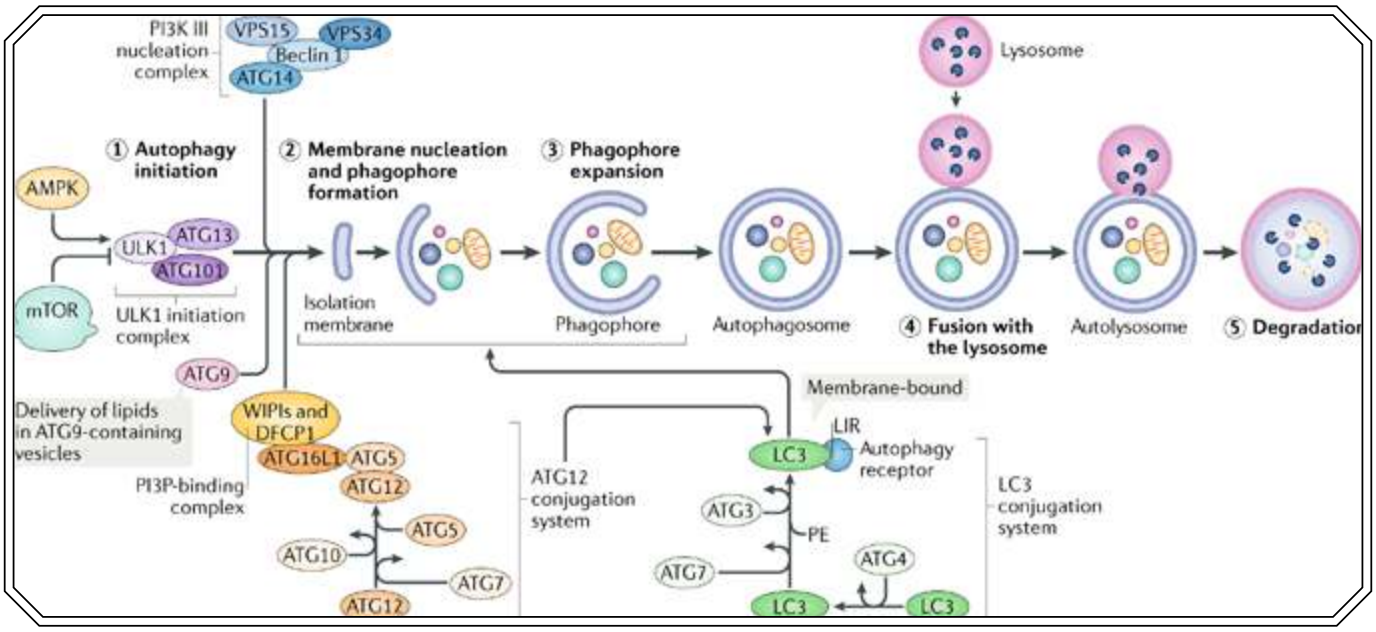
[AGE12] The Receptor for Advanced Glycation End Products (RAGE) specifically Recognizes Methylglyoxal-Derived AGEs. Shekhtman et. al. 2014.
[AGE13] Browning and pigmentation in food through the Maillard reaction. Murata. 2020.

Autophagy

Introduction

Like proteolysis, autophagy is a natural damage removal mechanism but instead of only breaking down individual damaged proteins it recycles large portions of the cell. Entire organelles can be digested and reconstituted via autophagy. The process involves lysosomal structures that encapsulate large portions of the cell and subject them to highly acidic environments, indiscriminately breaking down the structures within.

Autophagy seems to be the underlying mechanism for a variety of different longevity interventions. AMPK, mTOR (and by extension rapamycin and metformin), intermittent fasting, caloric restriction, exercise, protein restriction, and the heat shock reaction all converge on autophagy as the primary regeneration mechanism. It's also a buzzword for supplement effects, effective because autophagy is widely understood yet difficult to measure. By attaining better control over autophagy it may be possible to improve the repair of our cells to achieve dramatic lifespan extension.



{[AUTO17]}

The breakdown of autophagy can result in many different pathologies, such as the accumulation of lysosomes full of lipofuscin, or a buildup of crosslinked proteins like tau or amyloid-B. Loss of autophagic function is heavily associated with aging.

Autophagy

The Next Big Step - Measuring autophagy in vivo

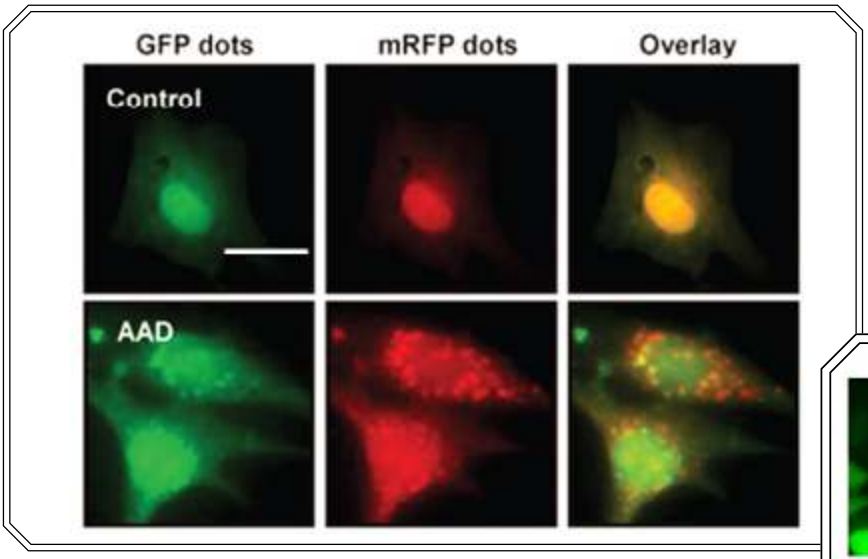
We need to measure autophagy in vivo in near real time. This is the biggest obstacle for autophagy research and for translating autophagy concepts into practical applications.

The current method for measuring autophagy is to detect LC3 proteins, a class of protein associated with the formation of an autophagosome, the vesicle structure initiated during cellular macroautophagy. These LC3 proteins are typically measured via western blotting or fluorescence. However, these only provide a single data point and require sacrifice of the sample tissue to aquire the information.

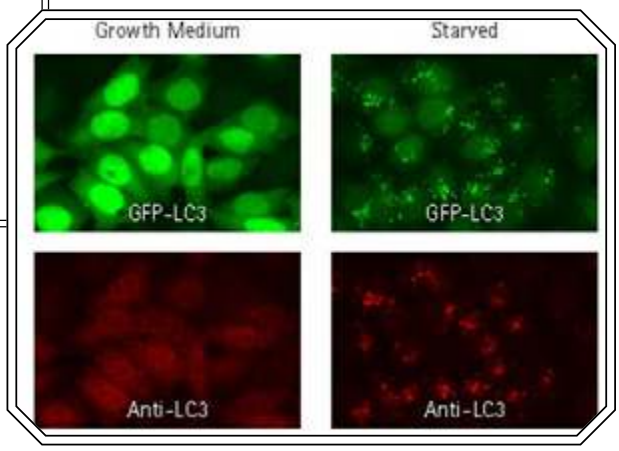
GFP has been investigated as a method of tracking LC3 proteins in vivo. Unfortunately, there are issues with expression differentials between GFP-LC3 and endogenous LC3 in various tissues, and it only really works well with organisms such as zebrafish which are transparent. Furthermore, GFP becomes quenched in the acidic environment of the interior of autophagosomes. This problem can be solved by using another probe - mRFP - which has red fluorescence. However, the original issue of usage limitations for transparent species remains. [AUTO15]

dKeima is a pH-sensitive probe which has two excitation states, allowing us to see whether it is in a heavily acidic environment such as an autophagosome. Again, this process requires visibility and therefore cannot be used on internal organs while the test subject is alive. [AUTO15]

LC3 remains the focal point of autophagy investigations, but no true in-vivo method of analyzing LC3 concentrations for living organisms exists.



{Genemedi}



{Sigma-Aldrich}

Autophagy

Potential Impact - How will this affect us?

Idea Risk: X

There is no way of measuring autophagy in vivo currently, not to the extent necessary for data mining. There is also no technology on the horizon which might make it possible.

Yield Potential: A

Measuring autophagy in vivo, reliably and in near real time, would open up an entire industry of therapy. Drugs, diets, behavior, and products could be correlated with increases or decreases of autophagy.

It is well known why a person would want to increase autophagy - to increase regeneration. But there are pragmatic reasons to decrease autophagy as well, in the case of sarcopenia and muscle degeneration disorders. The control of autophagy for people with such disorders would be akin to the control of blood sugar levels for diabetics. This one invention would affect several classes of disease and radically alter the landscape of medicine.

Roughly 10% of the world is afflicted by sarcopenia [AUTO16]. These people would directly benefit from monitoring autophagy rates.

Future Possibilities: B

Controlling autophagy over the course of a lifetime could yield extremely high dividends for lifespan extension. However, as a ballpark figure it would be unlikely to exceed 80-100% lifespan extension. Autophagy is an already naturally occurring process, and if it alone could modify lifespan by several orders of magnitude we would see greater lifespan diversity among people.

Autophagy

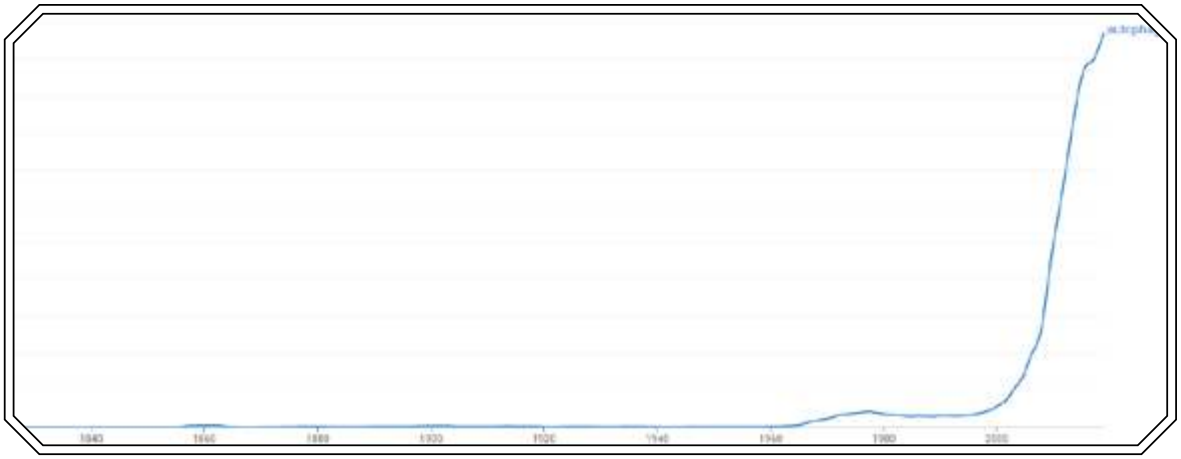
Timeline of Autophagy Research

1800

1836 – First proteolytic enzyme, pepsin, described [PTO7]
1942 – Protein turnover conceptualized [AUTO1]
1955 – Lysosomes discovered [PTO3]
1962 – Glucagon stimulates lysosome formation [AUTO3]
1963 – Autophagy coined [AUTO14]
1968 – Genetic control of protein degradation [AUTO2]
1968 – Autophagosome observed [AUTO4]
1980 – Amino acid inhibition of autophagy [AUTO6]
1982 – 3-Methyladenine inhibition of autophagy [AUTO5]
1993 – APG autophagy-related genes identified in yeast [AUTO8]
1995 – CVT autophagy-related genes identified in yeast [AUTO13]
1998 – TOR controls autophagy in yeast [AUTO10]
2005 – Mitophagy coined [AUTO9]
2008 – Ribophagy coined [AUTO12]
2009 – Lipophagy coined [AUTO11]

1900

Word Usage Over Time



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Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Loss of Proteostasis
Pillars of Aging: Proteostasis

2000

Autophagy

Relevant Organizations: Who is working on this problem?

Nordic Autophagy Society
Autophagy Advocacy

German Autophagy Association
Autophagy Advocacy

Biophytis
Metabolic Alteration of Autophagy

Samsara Therapeutics
Autophagy Therapy

Aeovian Pharmaceuticals
mTOR Therapy

Navitor Pharmaceuticals
mTOR Therapy

resTORbio
mTOR Therapy

Biosens
mTOR Therapy for sarcopenia

Rubinsztein lab at Cambridge
Autophagy Research

Davis Lab at MIT
Autophagy Research

Baehrecke Lab at UMass
Autophagy Research

Walker Lab at UCLA
Autophagy Research

Tooze Lab at Francis Crick Institute
Autophagy Research

Bratton Lab at MD Anderson Cancer Center
Autophagy Research

Sarkar Lab at Birmingham
Autophagy Research

Chauhan Lab in India
Autophagy Research

Autophagy

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Caloric Restriction

Introduction

Caloric restriction is one of the most common longevity methods around, but it appears to be one of the most commonly misunderstood concepts.

“Ad Libidum feeding” means allowing an animal unlimited access to food. Caloric restriction means restricting calories compared to ad libidum feeding. An obese person is an example of ad libidum feeding. What we consider a ‘normal’ weight is actually calorie restricted. If you only eat ~2000 calories a day, you are already restricting your intake.

When a morbidly obese person dies at 55, it doesn’t seem weird. It’s not shocking. I’m not standing here going “oh my goodness, however did that happen?!” That seems like a normal lifespan for someone who has been fat their whole life. And yet, the absolute maximum human lifespan is around 120 years old. That’s a difference of over 100%. When we compare the lifespan of the obese to the absolute maximum lifespan, we find the difference is remarkably similar to the lifespan increases observed in animal models of caloric restriction. It is my belief that humans have engaged in caloric restriction long before its benefits on lifespan were recorded in the annals of science.

Furthermore, the mechanism of caloric restriction appears to hinge on the retardation of the maturation process. That is, if maturation can be described as an arc, engaging in caloric restriction should only have an effect during the rise (early life), but not the fall (late life). The available data only partially agrees with this outlook though. While the longest lifespans are those that have early caloric restriction and late ad libidum feeding, there is still a difference between those that have early ad libidum and late restriction vs. whole life ad libidum feeding.

There is another aspect of caloric restriction which is what makes it relevant to damage prevention – a reduction in metabolic load in late life. Obesity is taxing on the soma and preventing obesity by limiting caloric intake reduces workload on organs like the pancreas and liver. Imagine the body is a car. An oil pump on a small sedan is not going to be as effective if placed into a semi-truck, but that is exactly what happens when you increase your body mass since organs do not grow along with your fat content. Higher body mass means more circulatory volume using the same sized organs, and that leads to a shift in workload. In this metaphor, the oil pump represents the human heart.

To summarize – there are two mechanisms for caloric restrictions impact on longevity. The first being a reduction in maturity speed during adolescence, and the second being the prevention of obesity at all stages of life.

Caloric Restriction

The Next Big Step - Ghrelin

This strategy appears to be a dead end. Ironically, caloric restriction is one of the best current methods for life extension - but we appear to already be using it correctly if we eat 3 meals a day. There may be a tie-in to the next step of autophagy here, namely to correlate caloric restriction regimens with autophagic flux if we could figure out how to measure autophay in vivo. Beyond that, there's not much else to be done. The deaths of calorie restriction proponents of the past decades have proven that it is not the panacea it was made out to be.

The pathway forward might involve ghrelin and subsequent research around it. Ghrelin acts like an alarm clock, inducing hunger pain in a rhythmic cycle to remind you to eat. Ghrelin also has metabolic effects which are tied to growth hormone release. Since its discovery over 30 years ago, a number of ghrelin mimetics and suppressors have been released to market.

Caloric Restriction

Potential Impact - How will this affect us?

Idea Risk: S

Caloric Restriction is the easiest therapy to do - simply stop eating so much.

Yield Potential: C

There are two major pathways for life extension via caloric restriction - slowing maturation and prevention of obesity.

We are already performing caloric restriction, and the benefits are known. By not eating ad libitum we prevent heart disease, diabetes, and a host of other problems. The major benefit is to simply not be fat. Avoiding obesity can extend life by up to 10 years [CAL6], but anecdotally, it isn't strange to see an extremely obese person die at 50 while seeing a normal weight person live to 100.

Slowing maturation via protein restriction may elongate life but likely comes with tradeoffs of fitness. Think about the ames dwarf mouse, except with humans.

Future Possibilities: C

Ghrelin is the only therapeutic currently linked to calorie restriction. It has been researched for 30 years, with multiple supplements and therapies spinning out of it. It has reached a commercial audience and doesn't appear to have a visible impact on life extension. Maybe there is something we have missed, some way of using it which is not yet known, but the likelihood at this point is low.

Furthermore, there are obvious tradeoffs for stunting the maturation process. Competition is still present and selective processes appear to be pushing development in a particular direction. Fully matured, shorter lived animals are likely going to out-compete longer lived, less matured animals.

Caloric Restriction

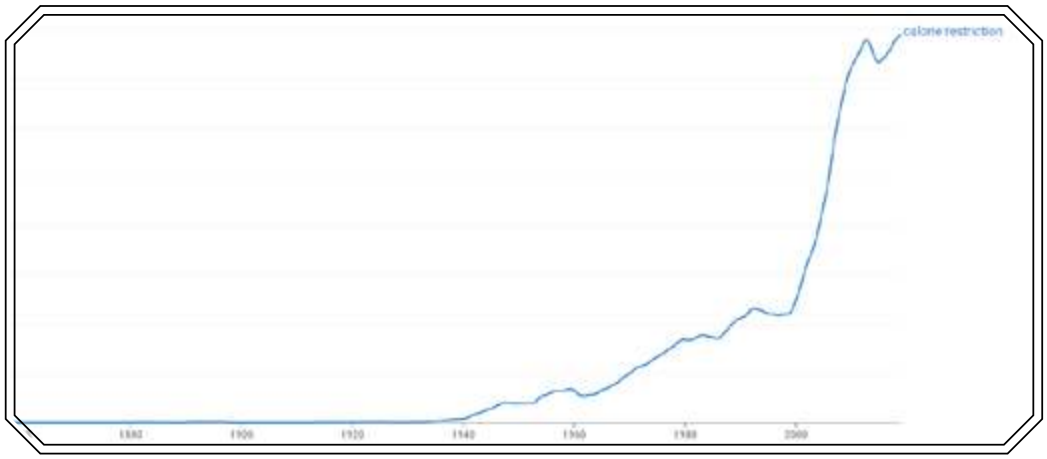
Timeline of Blood Replacement

1800

??? BC – origin of meal times [SOURCE UNAVAILABLE]
500 BC – Identification of obesity as a disorder [CAL5]
1724 – Essay on health detriment of obesity [CAL3]
1917 – Growth retardation extends lifespan in rats [CAL1]
1956 – IGF-1 discovered [SOURCE UNAVAILABLE]
1974 – Early restriction has more impact [CAL2]
1996 – Ghrelin receptor discovered [CAL4]
1999 – Ghrelin discovered [CAL7]

1900

Word Usage Over Time



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Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Deregulated Nutrient Sensing
Pillars of Aging: Metabolism

2000

Caloric Restriction

Relevant Organizations: Who is working on this problem?

Caloric Restriction Society
Caloric Restriction Advocacy

Caloric Restriction

Sources

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Crosslinked Proteins

Introduction

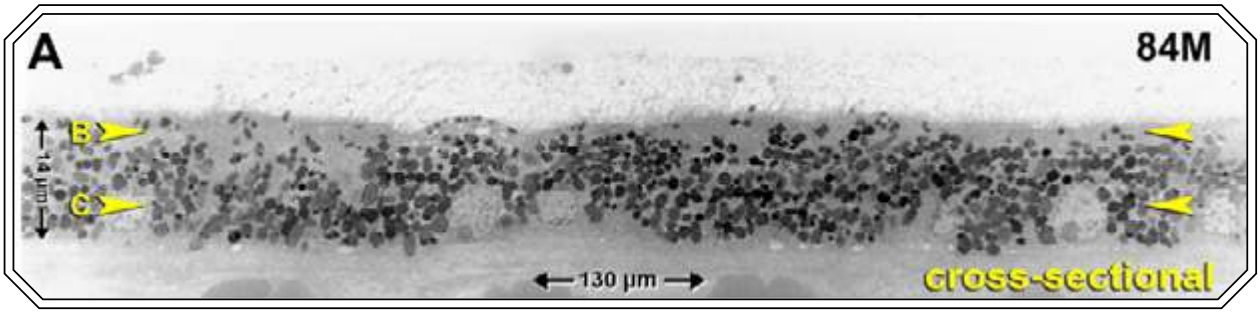
Proteins can be bound to each other via ionic or covalent interactions. This binding is referred to as crosslinking, and is sometimes deleterious to human health.

Alzheimers - Amyloid Beta and Tau

Amyloid Beta and Tau are proteins that aggregate in the brain, creating large chunks of material that cannot be broken down. Amyloid aggregates outside of the cells in the intercellular space, while tau forms tangles in the intracellular space. These aggregations are heavily associated with diseased neurons, although the debate on the nature of causality regarding these crosslinked proteins is still not settled.

Macular Degeneration - Lipofuscin

Lipofuscin is a mixture of oxidatively damaged lipids and other assorted molecules that have aggregated together. It appears capable of being broken down by autophagy but accumulates with age, presumably as a product of degrading autophagic efficiency.



{[CRP12]}

Arterial Stiffness - Glucosepane

A lysine-arginine covalently bonded adduct that appears in collagen structures in an age related fashion. Accumulation of glucosepane leads to arterial stiffening and a degradation of health.

Crosslinked Proteins

The Next Big Step - Break down lipofuscin in vivo

While lipofuscin has been identified over one hundred years ago, there are no reliable methods of breaking it down and removing it in vivo.

One recent development has been the use of beta-cyclodextrins as a method of binding and removing lipofuscin [CRP13].

This section needs more information.

Crosslinked Proteins

Potential Impact - How will this affect us?

Idea Risk: X

Some progress is being made but it is still not clear whether it is physically possible to degrade lipofuscin in vivo.

Yield Potential : A

Macular degeneration is directly linked to the accumulation of lipofuscin. Even though lipofuscin is a universal problem, most of the current medical attention seems to be centered around eye pathology. However, once a general solution is found it can be applied to much more than just the eye.

Future Possibilities: A

Breaking down protein aggregates is a fundamental requirement to stop the accumulation of damage that occurs with aging. It would be unwise to rely on natural stimulation of regenerative pathways like autophagy or proteolysis for this process. If we can get multiple robust solutions to protein crosslinking, a large chunk of the deleterious effects of aging can be taken care of.

Crosslinked Proteins

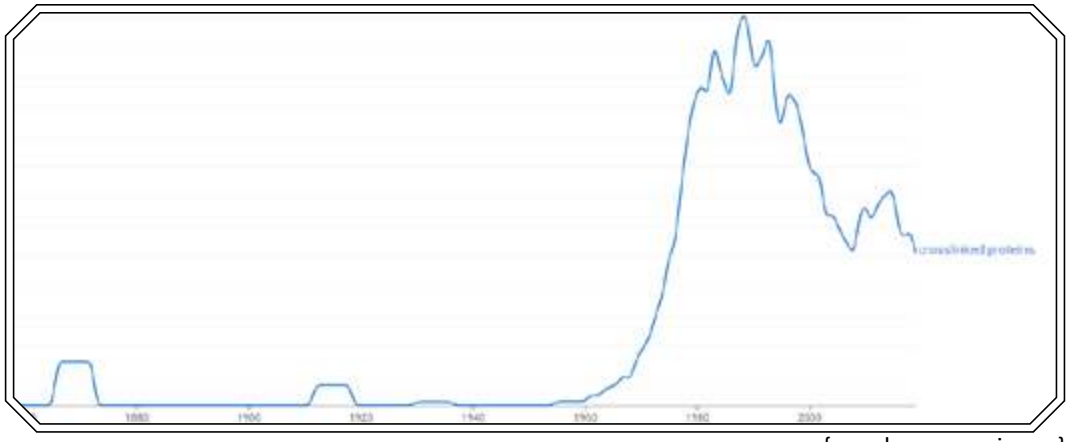
Timeline of Crosslinked Protein Research

1800

1832 – Earliest concept of crosslinking, vulcanization of rubber [SOURCE UNAVAILABLE]
1842 – Description of autofluorescent material in neurons [SOURCE UNAVAILABLE]
1886 – Association of autofluorescent material with age [CRP9]
1887 – Observation of accumulation of particles in marine worms [SOURCE UNAVAILABLE]
1900 – Clinkers of metabolism theory of aging [SOURCE UNAVAILABLE]
1907 – Alzheimer's disease identified [CRP1]
1912 – Lipofuscin coined [SOURCE UNAVAILABLE]
1952 – Cholesterol deposition in arteries attributed to crosslinking [CRP7]
1955 – Crosslinking theory of aging [CRP8]
1959 – Lipofuscin accumulates linearly with age [CRP10]
1964 – Plaques and tangles observed [CRP2]
1984 – Amyloid-beta associated with Alzheimer's disease [CRP3]
1984 – Lipofuscin formation tied to oxidative damage [CRP11]
1985 – Tau protein associated with Alzheimer's disease [CRP4]
1987 – Amyloid precursor protein identified [CRP5]
1995 – In vivo measurement of lipofuscin [CRP12]

1900

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Loss of Proteostasis
Pillars of Aging: Proteostasis

2000

Crosslinked Proteins

Relevant Organizations: Who is working on this problem?

Revel Pharmaceuticals
Crosslink Degradation

Rodriguez-Boulan Lab at Cornell
Lipofuscin Degradation Research

Lakkaraju Lab at UC San Francisco
Retinal Lipofuscin Research

Sparrow Lab at Columbia
Retinal Lipofuscin Research

ADRC at Columbia
Alzheimers Research

Stern Lab at Boston University
Alzheimers Research

Spiegel Lab at Yale
Glucosapane Research

Kodiak
Diabetic Retinopathy Treatment

Crosslinked Proteins

Sources

[CRP1] An english translation of alzheimers 1907 paper Uber eine eigenartige erkankung der hirnrinde. Stelzmann, Schnitzlein, Murtagh. 1907. {1995}
[CRP2] Ultrastructural studies in Alzheimer's presenile dementia. Terry, Gonatas, Weiss. 1964.
[CRP3] Alzheimers disease and Downs syndrome – sharing of a unique cerebrovascular amyloid fibril protein. Glenner, Wong. 1984.
[CRP4] Mise en evidence immunologique de la proteine tau au niveau des lesions de degenerescence neurofibrillaire de la maladie d'Alzheimer. Brion, Passareiro, Nunez, Flament-Durand. 1985.
[CRP5] The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Kang et. al. 1987.
[CRP6] Visualizing melanosomes, lipofuscin, and melanolipofuscin in human retinal pigment epithelium using serial block face scanning electron microscopy. Curcio et. al. 2017.
[CRP7] Cross Linking – key to aging? Bjorksten. 1955. {1957}
[CRP8] A mechanism of cholesterol deposition on arterial walls. Bjorksten. 1952.
[CRP9] Beitrage zur kenntniss der nervenzellen in den peripheren ganglien. Koneff. 1886.
[CRP10] Rate and magnitude of age pigment accumulation in the human myocardium. Strehler, Mark, Mildvan, Gee. 1959.
[CRP11] In vivo measurement of lipofuscin in Stargardt's disease – fundus flavimaculatus. Delori et. al. 1995.
[CRP12] Influence of oxygen tension, pro-oxidants and antioxidants on the formation of lipid peroxidation products (lipofuscin) in individual cultured human glial cells. Thaw, Collins, Brunk. 1984.
[CRP13] Beta cyclodextrins bind stabilize and remove lipofuscin bisretinoids from retinal pigment epithelium. Rodriguez-Boulan et. al. 2014.

Extracellular Matrix

Introduction

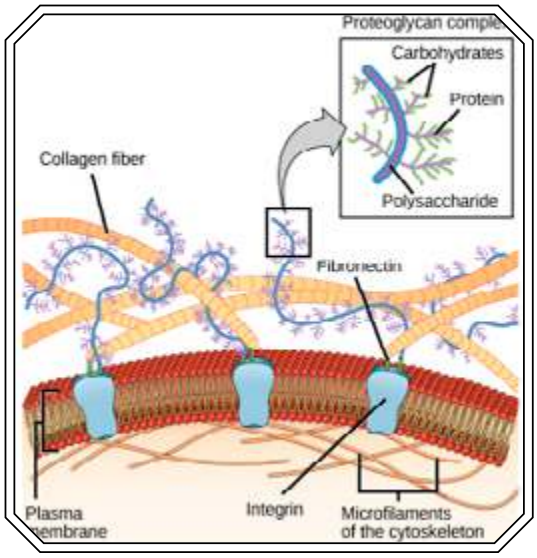
The extracellular matrix is a mix of proteins and sugars which bond together to form an intricate web in between the cells of our body. As the extracellular matrix ages, it gets damaged in various ways. Crosslinks form between molecules which shouldn't be linked, or pieces of it may dissolve away and fail to get replaced. The degradation of the extracellular matrix is seen most prominently in the wrinkling of skin of old people - caused by the destruction of elastin.

Elastin

Elastin is found in all connective tissues as well as blood vessels. It is an elastic molecule which can stretch and contract, hence the name. Elastase breaks down elastin and is produced in the pancreas. It has been known for at least a hundred years that bacteria such as pseudomonas - associated with pneumonia - produce elastase. Human pancreatic elastase is inhibited by low levels of human serum while bacterial elastase is not. The current concensus is that bacterial elastase and other similar enzymes degrade the extracellular matrix of the lungs, leading to the symptoms seen in pneumonia. Other pathologies associated with degrading or missing elastin are hernias and diverticulitis.

Collagen

Roughly one third of the body protein mass is actually made up of collagen. While abundant, it is susceptible to all sorts of damage such as oxidative stress, UV radiation, chemical stress, and disease. Collagen is naturally modified with crosslinks to connect it to glycans and elastin, but can be damaged with abherrant crosslinks forming glucosepane - an advanced glycation endproduct.



{Khan Academy}

Glycoproteins

Proteins modified with sugars are called glycoproteins. Fibronectin and laminin are a few of the glycoproteins involved in the extracellular matrix structure.

Degradation

Various enzymes are capable of degrading the extracellular matrix. Enzymes such as matrix metalloproteinase and elastase target specific elements within the ECM and break them apart. Some pathogenic bacteria are only dangerous due to excretion of these enzymes which damage our ECM.

Extracellular Matrix

The Next Big Step - Rebuilding ECM

When collagen was first discovered, it was assumed to be unchanging over the course of an organisms lifetime. Subsequent studies have overturned that assumption, revealing shorter and shorter half-life times of collagen by using new and improved measurement techniques.

The next big thing for the extracellular matrix is to discover to what extent natural regeneration occurs, and how to rebuild it with interventions.

Collagen induction therapy uses small needles to poke hundreds of holes in the skin, causing light physical damage. While slightly grotesque in practice, the physical stress is supposed to cause ECM rebuilding.

Collagen replacement therapy - simple direct injection of collagen. To what extent the new collagen is integrated into the ECM is up for debate.

Platelet Rich Plasma therapy supposedly stimulates collagen growth.

Extracellular Matrix

Potential Impact - How will this affect us?

Idea Risk: X

While there are some early promising methods for regenerating skin ECM, the majority of the ECM is located in connective tissue all over the body. There is no known way of attempting to selectively remove or regenerate these portions nor is there any technology on the horizon promising to do so.

Yield Potential: A

Williams syndrome is characterized by a lack of elastin gene ELN. Pneumonia is lethal due to elastases produced by bacteria. Understanding and quickly regenerating elastin could help mitigate death by pneumonia.

Collagen is the most common protein in the human body. Understanding the ECM and solving issues of ECM degradation has the largest impact by mass on our health.

Future Possibilities: A

Beyond simply repairing the ECM - is there any way to improve it? The constraints of using proteins and sugar to build extracellular scaffolding.

Extracellular Matrix

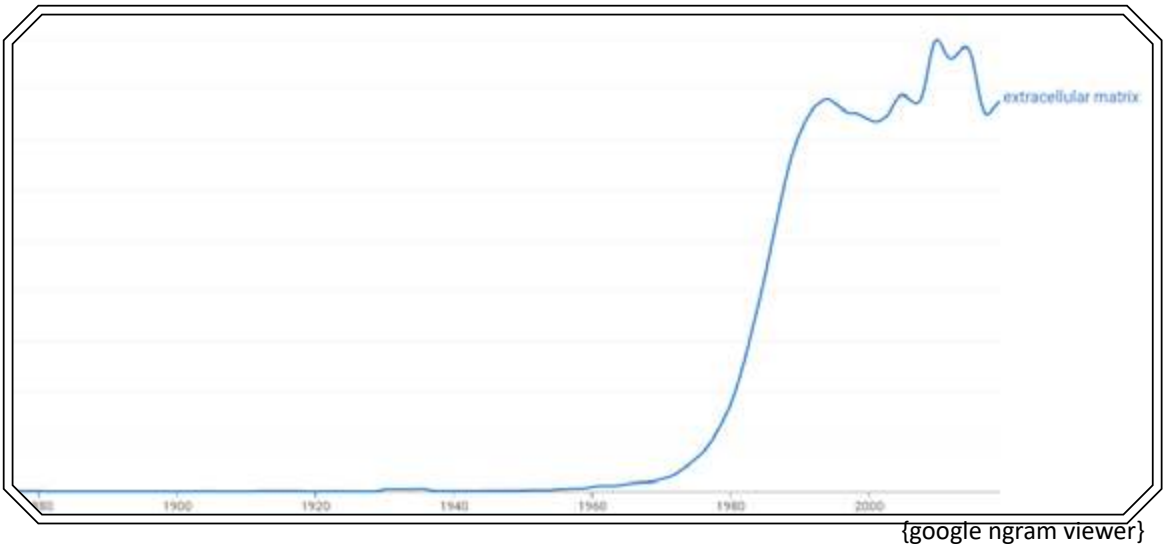
Timeline of Extracellular Matrix Research

1800

1844 - Elastin isolated [ECM1]
1894 - Collagen isolated [ECM1]
1903 - Pseudomonas extracellular elastase [ECM7]
1950 - Collagen assumed to be static over lifetime [ECM9]
1958 - Lysyl Oxidase [ECM4]
1962 - Matrix metalloproteinase [ECM3]
1973 - Fibronectin [ECM6]
1979 - Laminin [ECM5]
1992 - Collagen half life in rats is 45 days to 250 days [ECM10]
2015 - Adipocytes prevent fibrosis in burn wounds [ECM13]
2016 - Murine skin collagen VII half life is ~30 days [ECM11]

1900

Word Usage Over Time



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Relevant categorization

2000

Trifecta: Accumulation of Damage
Hallmarks of Aging: Loss of Proteostasis
Pillars of Aging: Macromolecular Damage

Extracellular Matrix

Relevant Organizations: Who is working on this problem?

Hynes Lab at MIT
Cancer ECM Research

Hansen Lab at University of Colorado
ECM Research

Duer Lab at Cambridge
ECM Aging Research

Sagi Lab at Weizmann Institute
ECM Research

Neu Lab at University of Colorado
ECM Research

Calve Lab at University of Colorado
Musculoskeletal ECM Resarch

Niklason Lab at Yale
Porcine ECM Research

Weaver Lab at UCSF
Cancer ECM Research

ScarTec
Scar Tissue Inhibition

Extracellular Matrix

Sources

[ECM1] Chemical studies of elastin mucoid and other proteids in elastic tissue. Richards and Gies. 1902.
[ECM2] The Role of the Elastase of Pseudomonas aeruginosa in Experimental Infection. Mull and Callahan. 1964.
[ECM3] Collagenolytic activity in amphibian tissues a tissue culture assay. Lapiere and Gross. 1962.
[ECM4] The cross-linking of collagen and elastin - enzymatic conversion of lysine in peptide linkage to allysine by an extract from bone. Martin and Pinnell. 1958.
[ECM5] Laminin - a glycoprotein from basement membranes. Timpl et. al. 1979.
[ECM6] Cell surface proteins and malignant transformation. Hynes. 1976.
[ECM7] Bacterial elastase I Isolation purification and properties. Cohen and Mandl. 1960.
[ECM9] The relative metabolic inertia of tendon collagen in the rat. Slack et. al. 1950.
[ECM10] Turnover rates of different collagen types measured by isotope ratio mass spectrometry. Robins et. al. 1992.
[ECM11] Collagen VII Half-Life at the Dermal-Epidermal Junction Zone: Implications for Mechanisms and Therapy of Genodermatoses. Nystrom et. al. 2016.
[ECM12] Mechanical properties of the collagen network in human articular cartilage as measured by osmotic stress technique. Maroudas. 1998.
[ECM13] Wound Healing Immediately Post-Thermal Injury Is Improved by fat and adipose derived stem cell isografts. Levi et. al. 2015.

Gene Repair

Introduction

DNA repair comes in multiple flavors – base excision repair, nucleotide excision repair, mismatch repair, double strand repair, and translesion synthesis. DNA repair is a nexus of convergence for many longevity mechanisms including sirtuins, FOXO, IGF-1, TERT, and HSF-1. Better and more efficient DNA repair is associated with longer lifespans and robust stress resistance.

Base vs. Nucleotide excision repair

Base repair changes the nucleotide plus the phosphate backbone, while nucleotide repair only swaps out the nucleotide. Nucleotide repair appears to be more common and robust.

Double Strand repair

Typically refers to Nonhomologous End Joining when referenced in human contexts. Repairs DNA that has been split across both strands. NHEJ is error prone and used frequently - approximately 10 double stranded breaks occur in human cells per cell per day (need citation here). Pervasive NHEJ is also one of the reasons that telomere loops need to exist at the ends of chromosomes.

Werner Syndrome

One of the disorders related to gene repair failure is Werner Syndrome. Discovered over a century ago [DNA10], Werner Syndrome is notable for displaying symptoms that appear to mimic rapid aging.

Gene Repair

The Next Big Step - Improve DNA repair machinery

Incremental improvements to DNA repair machinery are likely possible with current technology, although it would be very difficult. We have access to a library of mammalian species that have extremely good DNA repair capabilities - all we need to do is translate those mechanisms to humans. Either some kind of overexpression or upregulation using genes, proteins, mRNA, or other known style of altering cell behavior.

Gene Repair

Potential Impact - How will this affect us?

Idea Risk: M

Although it should be within reach, altering the DNA repair machinery will be a tedious process of trial and error as we discover why our mechanisms are shaped the way they are. The presence and expression of our current method of repairing DNA are like this for a reason, and it's likely we don't yet fully understand the consequences of altering it.

Yield Potential: A

Several pathologies could be solved by fixing DNA repair machinery. Anything involving cellular senescence, neurodegeneration, cancer, or central nervous system troubles likely has some causal relationship to DNA repair.

Future Possibilities: A

DNA damage creates the largest cascade of troubles at the cellular level. Epigenetic tags, RNA, protein, and downstream signaling molecules all get thrown out of alignment when DNA fails. This is clearly an important aspect of the aging process and accumulation of damage over time.

Gene Repair

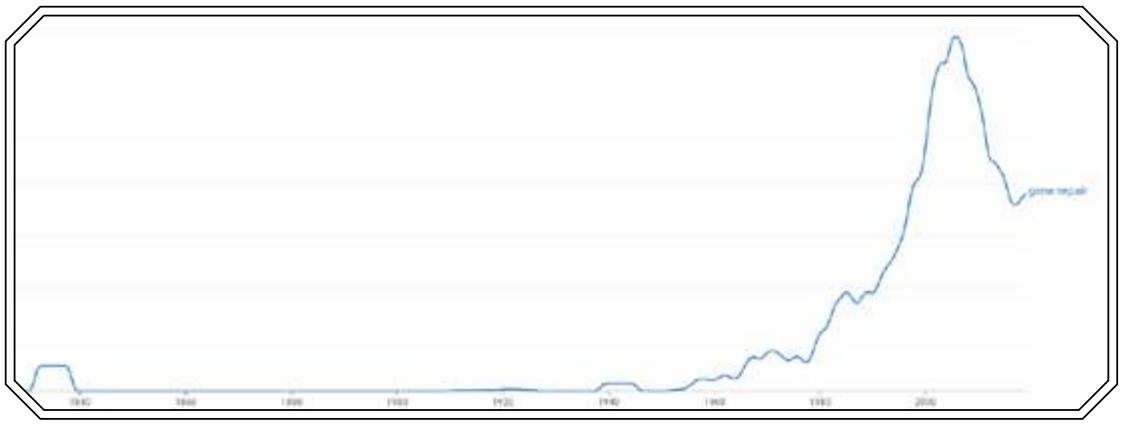
Timeline of Gene Repair Development

1800

1904 – Werner's syndrome defined [DNA10]
1949 – Discovery of enzymatic photoreactivation [DNA1]
1958 – Postulation that DNA damage is the cause of aging [DNA4]
1963 – Discovery of excision repair [DNA2]
1968 – Defective DNA repair associated with cancer [DNA3]
1997 – Werner syndrome protein identified as DNA helicase [DNA6]
2003 – Werner syndrome associated with poor DNA repair [DNA5]

1900

Word Usage Over Time



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Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Genomic Instability
Pillars of Aging: Macromolecular Damage

2000

Gene Repair

Relevant Organizations: Who is working on this problem?

Wyss Institute
Gene Therapy

Ames Lab
Prior DNA Damage Research

Gorbunova Lab at University of Rochester
DNA Repair Aging Research

Lieber Lab at University of Southern California
DNA Repair Aging Research

Gene Repair

Sources

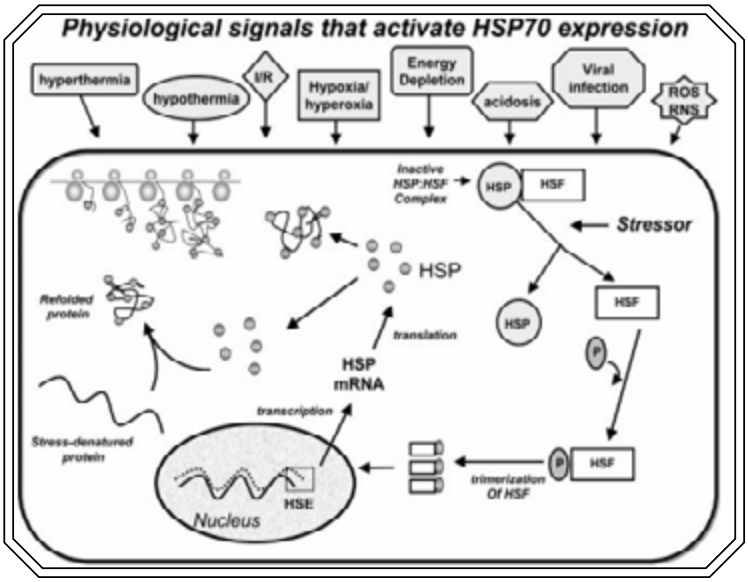
[DNA1] Photoreactivation of ultraviolet-irradiated escherichia coli with special reference to the dose-reduction principle and to ultraviolet-induced mutation. Kelner. 1949.
[DNA2] The disappearance of thymine dimers from DNA – an error-correcting mechanism. Setlow, Carrier. 1963.
[DNA3] Defective repair replication of DNA in xeroderma pigmentosum. Cleaver. 1968.
[DNA4] On the nature of the aging process. Szilard. 1958.
[DNA5] WRN, the protein deficient in werner syndrome, plays a critical structural role in optimizing DNA repair. Chen et. al. 2003.
[DNA6] The werner syndrome protein is a DNA helicase. Gray et. al. 1997.
[DNA7] Werner's syndrome and human aging. Salk, Fujiwara, Martin. 1982.
[DNA8] SIRT6 is responsible for more efficient DNA double-strand break repair in long-lived species. Gorbunova et. al. 2019.
[DNA9] A method for detecting abasic sites in living cells Age-dependent changes in base excision repair. Ames et. al. 1999.
[DNA10] On cataract in conjunction with scleroderma. Werner. 1904.
[DNA11] Werner Syndrome as a model of human aging. Monnat et. al. 2018.
[DNA12] Ageing, repetivite genomes and DNA damage. Karanjawala and Lieber. 2004.

Heat Shock Response

Introduction

The heat shock response is a protein based response to thermal damage. Heat causes motion, which leads to denaturing of proteins via breaking of weak atomic bond. To prevent heat damage, chaperone proteins activate during heat stress and attach to the denaturing proteins, stabilizing them and preventing unfolding. It also helps transit proteins for degradation or removal from the cell.

The heat shock response is triggered by heat [HSR1], oxidative stress, oxygen deprivation, heavy metals [HSR6], and amino acid analogues. It has become clear over the years that the heat shock response is actually a generalized stress response mediating cellular repair and stabilization. As such, it is a powerful catch-all tool which deserves as much attention as autophagy.



{[HSR3]}

The relative lack of attention given to the heat shock response in the field of aging is bizarre. Here is a generalized regenerative pathway that has hormetic properties and is activated by a wide array of insults - honestly it's difficult to find a more ideal candidate for targeted drugs or therapies. Upregulation of soluble HSP70 is typically used to measure the response, and is cheap and quick to perform.

Heat Shock Response

The Next Big Step - Routine heat shock triggers

The heat shock response has been studied extensively, yet we do not have extensive information about how to apply it to our daily lives. The consensus is that heat stroke, saunas, and sunburns trigger the response. What about showers, hot tubs, and sunbathing with sunscreen? What about highly acidic foods?

We need accurate and tested information about the thresholds required to trigger the heat shock response during routine behaviors that are commonplace in our daily lives. If a sauna has the capacity to trigger a heat shock reaction, standing in the shower under similar temperature water should also be able to trigger the reaction.

How long, and how how, should a shower be in order to trigger the heat shock response?

Develop a profile of heat shock induction from a list of heat stresses using a diverse array of gender, weight, athleticism, etc. Determine which factors are important. Hone in on critical factors and redo the experiment with greater precision. Build an array of heat shock effects for various body types.

Heat Shock Response

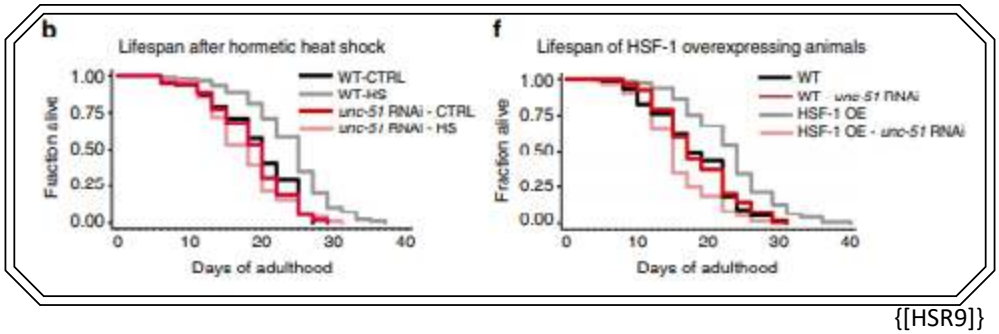
Potential Impact - How will this affect us?

Idea Risk: S

Heat shock response triggers are known and well documented, but not thoroughly tested in a civilian environment. It should be cheap and easy to figure out some ways of translating old knowledge about heat shock into behavioral and diet changes.

Yield Potential: C

A meta-analysis of lifespan studies using heat shock for life extension found no overall impact on lifespan [HSR8]. However, they admitted that there were inconsistencies with how the heat shock response was applied in the various experiments selected. If we assume that time, duration, and rhythmicity of the reaction can influence the outcome we may look to the high end of the successful experiments for a ballpark of what the heat shock reaction is capable of achieving.



{[HSR9]}

The above graph is one of the best I could find - maximum lifespan was increased roughly 20-30%. This was for c. elegans worms. I could not find any heat shock response lifespan studies for mammals - only for drosophila, c. elegans, and a few species of beetles.

Future Possibilities: B

Based on the lifespan analysis available to us the effect of the heat shock response is relatively small in comparison to some other life extension options. With practice and optimization maybe it can reach 50% extension, but the potential seems limited.

Heat Shock Response

Timeline of Heat Shock Response Research

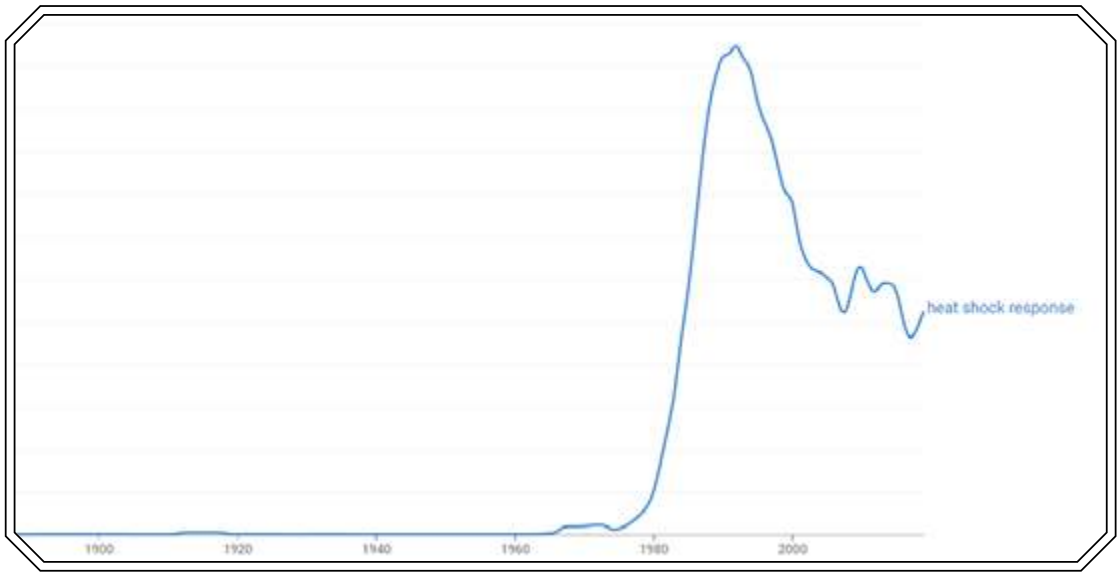
1800

1900

2000

1952 – Puffs in drosophila chromosome associated with RNA synthesis [SOURCE UNAVAILABLE]
1962 – Heat induced chromosome puffs observed in drosophila DNA [HSR1]
1974 – Heat induced puffs associated with protein production [HSR2]
1980 – Heavy metals induces heat shock reaction [HSR6]
1984 – HSF1 identified as master regulator [HSR10]
2000 – HSF1 overexpressed in cancer [HSR11]

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Loss of Proteostasis
Pillars of Aging: Adaptation to Stress

Heat Shock Response

Relevant Organizations: Who is working on this problem?

Wyss Institute
Gene Therapy

Rattan Lab at Aarhus University
Heat Shock Aging Research

Tytell Lab at Wake Forest
Heat Shock Research

Karras Laboratory at MD Anderson Cancer Center
Heat Shock Research

Morimoto Lab at Rice University
Heat Shock Research

Sistonen Lab at Abo Akademi
Heat Shock Research

Mivechi Lab at Augusta University
Heat Shock Research

Heat Shock Response

Sources

[HSR1] A new puffing pattern induced by temperature shock and DNP in drosophila. Ritossa. 1962.
[HSR2] Protein synthesis in salivary glands of drosophila melanogaster – relation to chromosome puffs. Tissieres, Mitchell, Tracy. 1974.
[HSR3] Heat shock proteins - modifying factors in physiological stress responses and acquired thermotolerance. Kregel. 2002.
[HSR4] Heat Shock Proteins - molecular chaperones in cardiovascular biology and disease. McMillan and Benjamin. 2012.
[HSR5] HSF1 mediated stress response of heavy metals. Riegel. 2018.
[HSR6] Transition series metals and sulfhydryl reagents induce the synthesis of four proteins in eukaryotic cells. Jackson et. al. 1980.
[HSR7] Induction of heat shock proteins for protection against oxidative stress. Greensmith and Kalmar. 2009.
[HSR8] Life extension after heat shock exposure - assessing meta-analytic evidence for hormesis. Nakagawa et. al. 2013.
[HSR9] Hormetic heat stress and HSF-1 induce autophagy to improve survival and proteostasis in C elegans. Hansen et. al. 2017.
[HSR10] A drosophila RNA polymerase II transcription factor contains a promotor-region-specific DNA-binding activit. Topol and Parker. 1984.
[HSF11] A novel association between the human heat shock transcription factor 1 and prostate adenocarcinoma. Roy-Burman et. al. 2000.

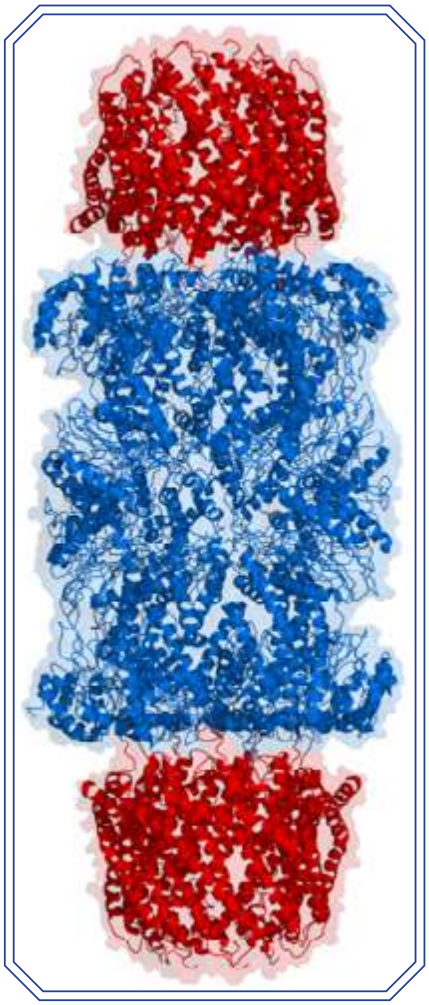
Proteolysis

Introduction

Proteolysis is a natural repair mechanism by which the cell breaks down misfolded or damaged proteins and reconstitutes them. The process works by tagging proteins with ubiquitin, marking them for degradation, then activating proteolysis machinery which chews up the protein into its amino acid components.

Proteasome

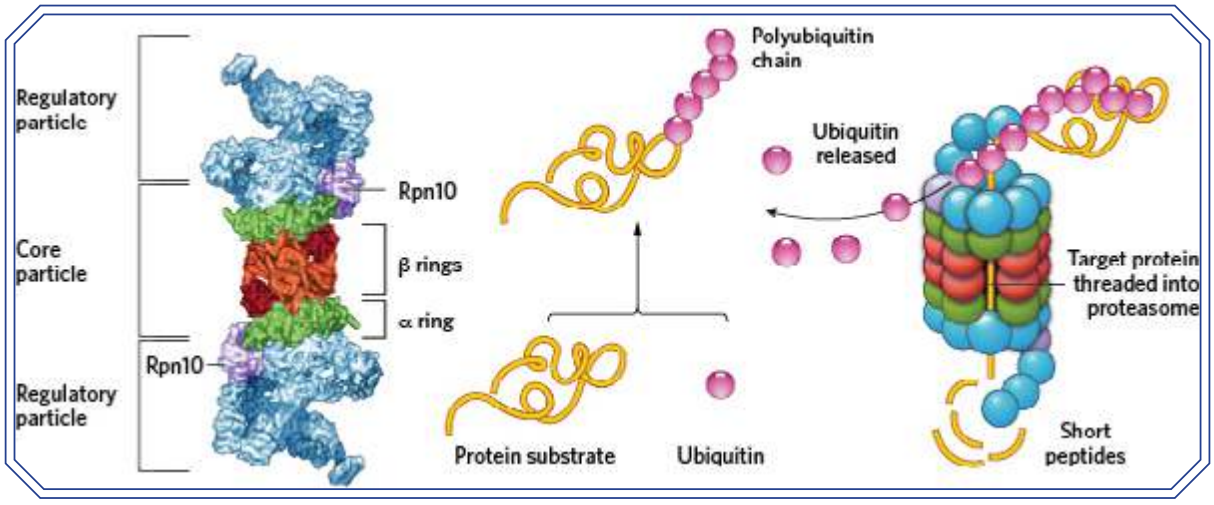
The proteasome is the workhorse of the proteolytic system. Unlike the process of autophagy, proteasomes target individual proteins for degradation. If autophagy is a grinder, a proteasome is a scalpel.



{Wikipedia}

Ubiquitin

The process of ubiquitination is most commonly associated with proteolysis, although it has a multifunction purpose. Ubiquitin gets attached to proteins in a step wise fashion, forming chains that are used for signaling purposes. Typically, ubiquitinated proteins are marked for degradation by the proteasome.



{TheScientist}

Proteolysis

The Next Big Step - PROTAC (Proteolysis Targeting Chimeras)

Proteolysis targeting chimeras are complex molecules that manipulate the cell into ubiquitinizing specific proteins. They consist of a E3 ligase binding domain and a targeting domain. The targeting domain is built to attach to a protein of interest, a protein in the cell which you want to get rid of. The E3 ligase binding domain then recruits the natural ubiquitin machinery, which starts to ubiquitinize the protein. Eventually the protein is targeted for degradation and the PROTAC detaches and moves on to the next target.

There are multiple advantages to using PROTACs. The first is that it actually destroys the targeted protein, instead of just inhibiting it. The second is that it uses the native protein degradation pathways, reducing the potential for side effects by introducing weird small molecule inhibitors into a cell. The highly specific nature of PROTACs can target previously undruggable pathways.

PROTACs are different from other levels of control in that they target the end of the protein production pathway. Gene knockout prevents proteins from being created, but it is a permanent feature. PROTAC control is reversible. You can remove a protein from a system, measure the impact, then allow it to return.

Proteolysis

Potential Impact - How will this affect us?

Idea Risk: M

PROTAC development is well underway but they are still expensive and the whole field is in its infancy. The technology appears to work but is still gated behind money and expertise.

Immediate Impact: B

PROTAC development is well under way, with several companies already beginning to spring up. Cancer appears to be the primary target for the immediate future.

Future Possibilities: A

The proteolytic system can target any protein, including pathogenic proteins and signal cascade proteins. Beyond simply preventing or curing diseases, core cellular functions can be completely remodeled. Imagine degrading chromatin remodeling proteins, or inhibitors of chromatin remodeling proteins, in a systemic manner.

The reversible nature of PROTACs could also open up faster pathways for understanding the function of proteins. In the context of research, it is much faster to remove proteins temporarily and observe changes instead of creating an entire gene knockout line of mice.

Proteolysis

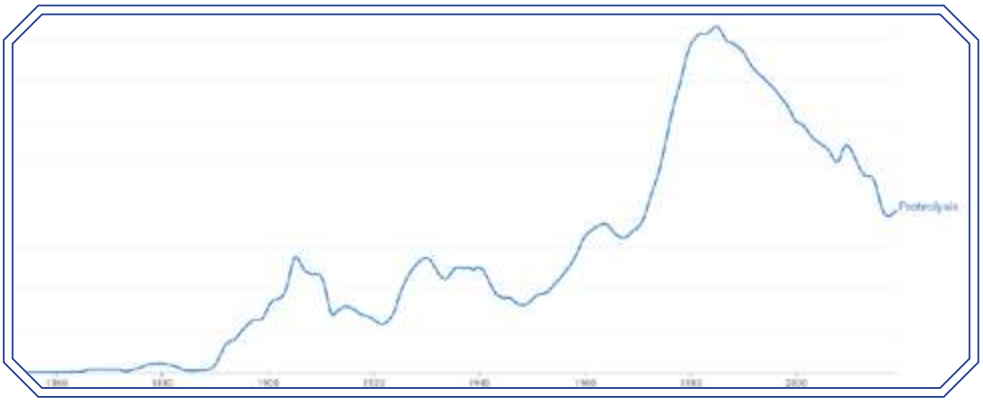
Timeline of Proteolysis Research

1800

1700 – Observation that papaya extract degrades protein [SOURCE UNAVAILABLE]
1836 – First proteolytic enzyme, pepsin, described [PTO7]
1891 – Intracellular proteolysis investigated [SOURCE UNAVAILABLE]
1908 – 'Wear and tear quota' for proteins [SOURCE UNAVAILABLE]
1931 – Pepsin crystallized [PTO4]
1939 – All proteins perceived as metabolically labile [SOURCE UNAVAILABLE]
1942 – Protein turnover [AUTO1]
1955 – Lysosomes discovered [PTO3]
1975 – Ubiquitin discovered [PTO6]
1978 – Ubiquitin-based proteolytic system hypothesized [PTO2]
1988 – Unfolded protein response discovered [PTO1]
1988 – Proteasome identified [PTO5]
2001 – PROTAC described [PTO9]

Word Usage Over Time

1900



{google ngram viewer}

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Loss of Proteostasis
Pillars of Aging: Proteostasis

2000

Proteolysis

Relevant Organizations: Who is working on this problem?

Munch Lab at IBC
Proteolysis Research

Mayor-Ruiz Lab at IRB Barcelona
Targeted Protein Degradation Research

PMAP (defunct)

MEROPS database of peptidases
Database of proteolysis proteins

International Proteolysis Society
Proteolysis Association

Vilchez Lab at CECAD
Proteostasis Research

Zhou Lab at University of Florida
PROTAC Research

Proteolysis

Sources

[PTO1] The presence of malfolded proteins in the endoplasmic reticulum signals the induction of glucose-regulated proteins. Kozutsumi et. al. 1988.
[PTO2] A heat stable polypeptide component of an ATP-dependent proteolytic system from reticulocytes. Ciehanover, Hod, Hershko. 1978.
[PTO3] Tissue fractionation studies. Duve et. al. 1955.
[PTO4] Crystalline pepsin. Northrop. 1931.
[PTO5] Identity of the 19S prosome particle with the large multifunctional protease complex of mammalian cells (the proteasome). Arrigo, Tanaka, Goldberg, Welch. 1988.
[PTO6] Isolation of a polypeptide that has lymphocyte-differentiating properties and is probably represented universally in living cells. Goldstein et. al. 1975.
[PTO7] Mikroskopische Untersuchungen über die Uebereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen. Schwann. 1839.
[PTO9] Protacs - chimeric molecules that target proteins to the skp1-cullin-F box complex for ubiquitination and degradation. Deshaies et. al. 2001.

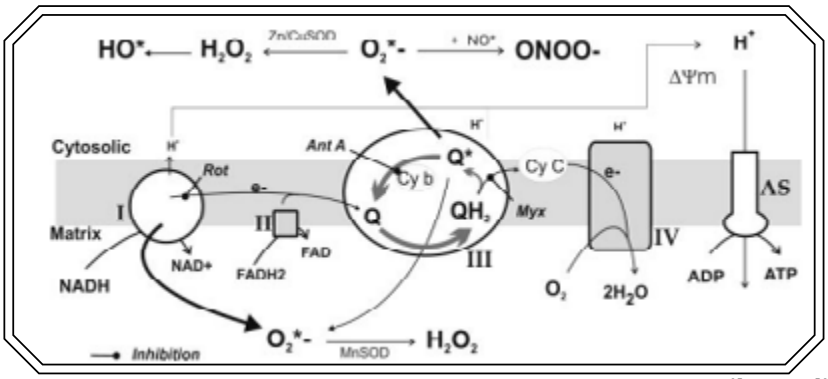
Reactive Oxygen Species

Introduction

Reactive Oxygen Species (ROS) are oxygen atoms that have unpaired electrons, making them prone to covalently bonding with random surrounding hydrogen atoms. By stealing hydrogen from key molecules such as proteins, DNA, or lipids, these ROS can end up causing mutations or degrading the cells internal components. Human respiration involves O2 being turned into CO2 by the electron transport chain. ROS are produced naturally in the body as a product of an imperfect respiration system that allows oxygen to escape the electron transport chain without becoming fully saturated.

If ROS are the primary cause of damage accumulation over time, then attenuating the effect of ROS could theoretically yield biological immortality. However, ROS such as Nitric Oxide have been discovered to be key signaling molecules. There are also multiple pathways for the cell to fix ROS damage. In C elegans, deletion of SOD-2 increases lifespan and also leads to higher oxidative stress, which runs counter to the ROS theory of aging. However, the impact of that evidence on ROS theory is difficult to assess given c. elegans unique dauer life phase attribute and the growing trend of unrepeatable biological experiments.

The core concept of ROS theory and why it is so interesting is that it is a product of mitochondrial oxidation. Mitochondria were enveloped – some might say domesticated – by eukaryotes very early on in earths history. Metaphorically they are akin to overclocking a CPU. ROS theory of aging implies that this overclocking is the reason for accumulating damage, and the fundamental reason for why we age is that biological competition favors the short term boost of mitochondrial efficiency over long term stability.



{[ROS14]}

Reactive Oxygen Species

The Next Big Step - Biologically Immortal Cell Database

Single celled eukaryotes have been dealing with ROS damage since the dawn of mitochondrial integration, so why aren't they being studied for ways of regenerating in the presence of ROS damage? The problem of ROS damage and mitochondrial regeneration has been solved since the dawn of eukaryotes.

I propose we build a database of several cell types - single celled prokaryotes, single celled eukaryotes, clothed germlines, and somatic eukaryotes. We compare these cells with each other and see if patterns emerge based on mitochondrial presence as well as whether the cell is capable of being immortal.

At the very least, we can eliminate mitochondria from the aging conversation so we can focus on more real issues.

Reactive Oxygen Species

Potential Impact - How will this affect us?

Idea Risk: X

Building a database of cells is doable but tedious - however the next step, translating the single celled eukaryotic regeneration mechanisms to humans is completely unknown.

Yield Potential: A

Reactive oxygen species damage is so prevalent it constitutes a major theory of aging. Solving this problem would eliminate a major source of damage and the supposed root cause of things like lipofuscin, arterial hardening, and lipid peroxidation.

Lifespan studies are conflicting, and there is currently no consensus on whether ROS increases or decreases lifespan or to what extent.

Future Possibilities: A

Difficult to say. I think the methodology used to solve the mitochondrial/ROS problem could be applied to many other aging problems as well. It might lead to a cascade of progress.

Reactive Oxygen Species

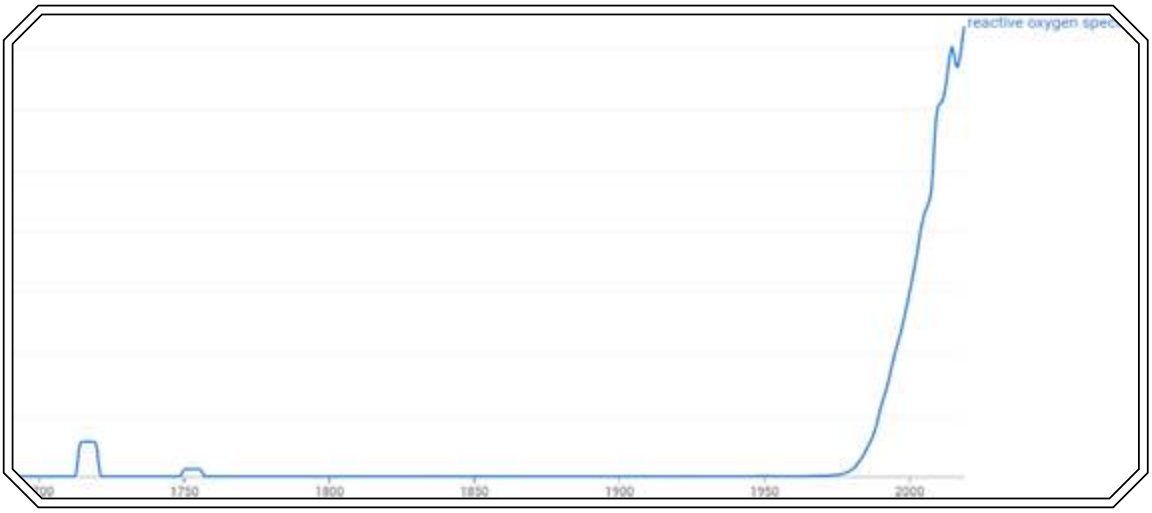
Timeline of ROS

1800

1768 – Nitric Oxide accidentally discovered [SOURCE UNAVAILABLE]
1878 – Oxygen toxicity observed in animals [ROS1]
1888 – Glutathione discovered [SOURCE UNAVAILABLE]
1900 – Organic free radicals discovered [ROS2]
1939 – Superoxide dismutase isolated [SOURCE UNAVAILABLE]
1956 – Free Radical theory of aging proposed [ROS3]
1957 – Selenium recognized as essential trace element [ROS4]
1964 – Thioredoxin discovered [ROS5]
1966 – Selenium counteracts mercury poisoning [ROS6]
1969 – Superoxide Dismutase identified [ROS7]
1973 – Glutathione peroxidase is a selenoenzyme [ROS8]
1977 – Selenocysteine discovered [ROS9]
1984 – Selenium unequal tissue sequestration in selenium-deprived rats [ROS10]
2008 – Mercury toxicity attributed to selenium sequestration [ROS11]
2009 – Deletion of SOD-2 in c elegans increases lifespan [ROS12]
2012 – ROS production in parrots and quail similar despite 5x difference in lifespan [ROS13]

1900

Word Usage Over Time



{google ngram viewer}

2000

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Mitochondrial Dysfunction
Pillars of Aging: Macromolecular Damage

Reactive Oxygen Species

Relevant Organizations: Who is working on this problem?

Rea Lab at University of Washington
Mitochondria Aging Research

Haigis Lab at Harvard
Mitochondria Aging Research

Loeb Lab at University of Washington
Mitochondria Aging Research

Poyton Lab at University of Colorado
ROS Aging Research

Jacob Lab at University of Michigan
ROS Aging Research

Baur Lab at University of Pennsylvania
ROS Aging Research

Cai Lab at UC Los Angeles
ROS Biology Research

Mitrix
Mitochondrial Transfusion

Reactive Oxygen Species

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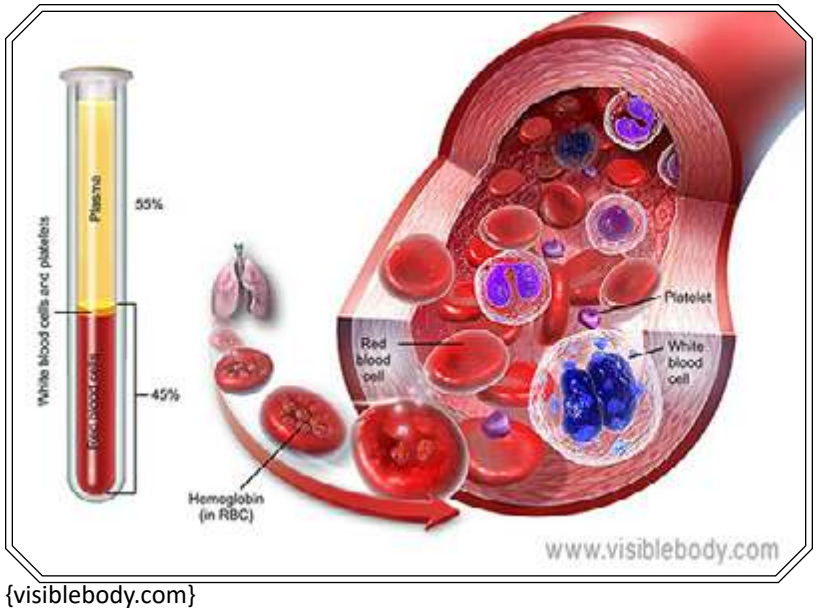
Blood Replacement

Introduction

Blood transfusions are an easy way of replacing a large component of the human body, and have been carried out successfully since 1818, unfortunately the original source of the first blood transfusion could not be located [BL1]. Blood was the first cryogenically stored and reimplanted component, being frozen for treatments since at least 1964 [BL3].

One current pursuit of biological immortality involves getting blood from a young person and transfusing it to an older person, with an assumption of regenerative effects based on experiments involving parabiosis [BL4]. Parabiosis is defined as the linking of blood vessels between two organisms so they share blood. When performed between mice this parabiosis procedure leads to rejuvenation of the old mouse and faster aging of the young mouse. While the current schema requires blood donation by the young, there is the possibility of growing blood artificially from either a foreign source or from the persons own stem cells which will ameliorate the moral issue of using young blood. Lab grown blood has been successfully transfused into a human in 2011 [BL5].

Development of blood replacement is still ongoing. The foremost expert on this would be Irina Conboy, who's experiments on mice have pioneered the current understanding of parabiosis. The latest consensus appears to be that there is some kind of detritus in old blood which can be diluted or removed to create regeneration. Young blood doesn't have anything particularly special about it. By removing old blood and replacing it with serum and albumin protein, rejuvenation occurs.



{visiblebody.com}


{zymo}

At the intersection of cryonics and parabiosis is the prospect of frozen blood being stored for long periods of time in order to donate young, or rather detritus-free, blood to your future self. Currently we have the technology to freeze and store blood but extremely long storage has not been well tested. The original inventor of frozen blood claimed it could last up to 30 years but this has not been verified in practice yet. The technology to do this is robust, relatively cheap, widely tested and available nationwide, the only issue is bureaucratic red tape. Blood donor centers are typically not allowed to store blood for personal use.

Blood Replacement

The Next Big Step - Blood Dilution

Blood dilution trials in humans seem to be the next step. Good information about parabiotic regeneration and the nature of old vs. young blood has been acquired from rodents. We have the technology to safely test these theories in people. The methods are used every day for blood donation and blood storage, and should be relatively cheap and straightforward to conduct human trials.

Going beyond simple blood dilution trials, there are several potential avenues for blood replacement.

- Blood donation
Blood given by a matching donor. Potential issues with compatibility and contamination.

- Self donation w/ cryonics
Freezing your own blood and storing it cryogenically for future transfusion back into your body. This option solves the compatibility problem but current long term cryogenic storage of blood is hampered by a lack of an ideal cryoprotectant.

- Lab grown blood
Blood grown from a patients stem cells differentiated into blood cells in vitro. This was first accomplished in 2017 by Sugimura lab. Has not been scaled up yet.

- Synthetic blood
Blood mimetics which function like blood. Advantageous due to the possibility of mass production, but no working material has been created so far.

Blood Replacement

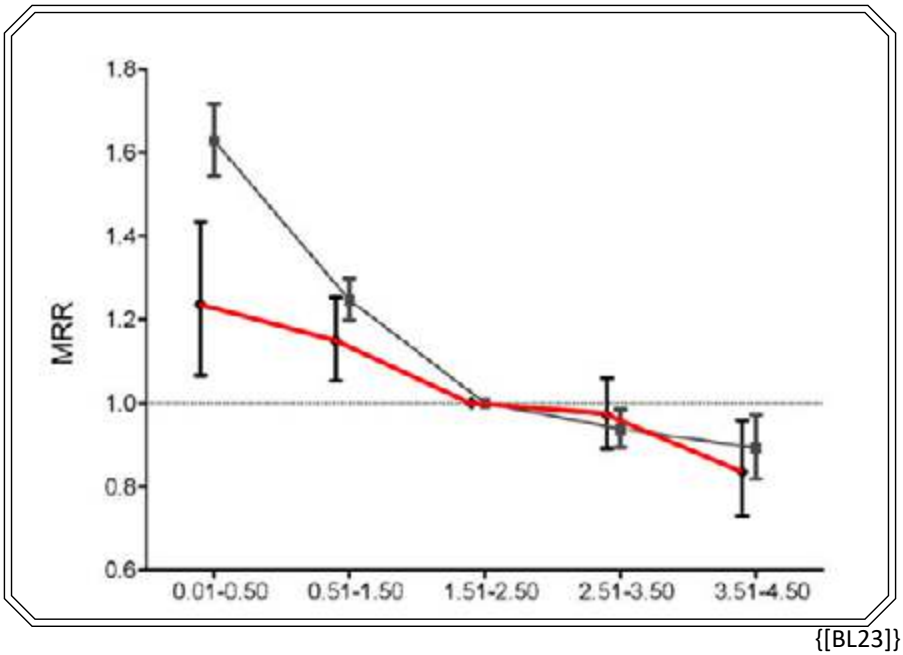
Potential Impact - How will this affect us?

Idea Risk: S

The technology for handling blood has been around for decades and it is possible to start human trials immediately.

Yield Potential: C

Operating under the assumption that old blood contains detritus, and that dilution/removal is doing most of the heavy lifting, we actually have a body of data that can act as a proxy for blood replacement impact. Blood donors are a group of people who are basically performing this therapy on themselves already. Based on data from a 2015 study taking into account the healthy donor effect, we see a significant reduction of mortality rate.



{[BL23]}

The red line in the above graph shows the corrected data set that takes into account the healthy donor effect - that mostly well-off people are giving blood. Higher frequency donors are to the right, lower frequency donors are to the left. MRR (mortality ratio) of 1.0 was arbitrarily set to the 1.5-2.5 donor level, it does not represent non-donor mortality. What we see here is a roughly 30% decrease (from 1.2 to .8) of mortality probability for the highest frequency blood donors as compared to infrequent blood donors.

Future Possibilities: B

This mortality study gives us a rough estimate of the impact of blood replacement therapy. With development and resources, and the will to push this methodology to new limits, we could see drastically better results. This is data from people who are not attempting to regenerate themselves but who are simply being kind to strangers. It wouldn't be unreasonable to suggest lifespan increases of 50%+ if we completely figure out blood replacement.

Blood Replacement

Timeline of Blood Replacement

1800

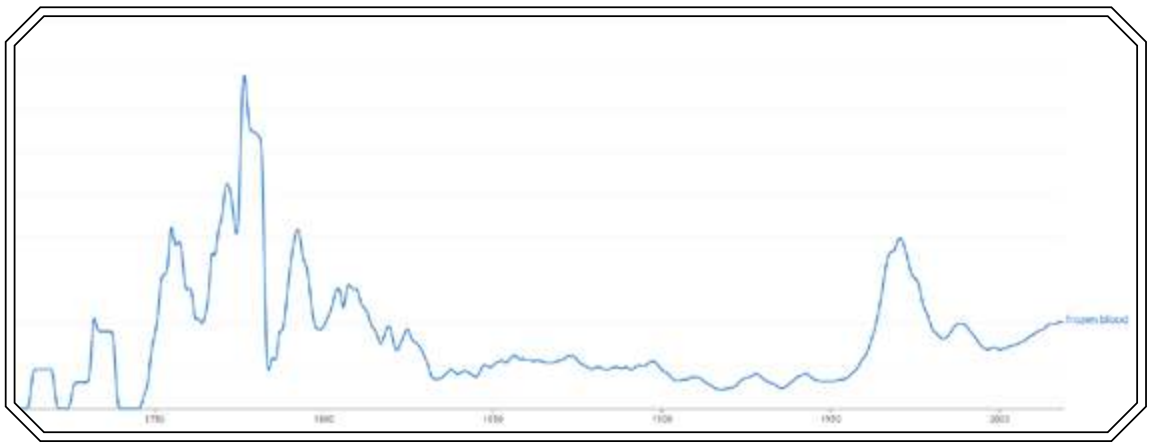
1628: Blood circulation discovered, first blood transfusion attempt [BL2]
1665: Successful dog blood transfusion [BL6]
1818: Successful human blood transfusion [BL6]
1840: Hemoglobin discovered [BL8]
1840: Hemophilia treated [BL7]
1863: Surgical animal grafting [BL9]
1878: First artificial blood replacement attempted (bovine milk) [BL10]
1900: Blood types discovered [BL11]
1908: Parabiosis terminology established [BL12 - SOURCE UNAVAILABLE ONLINE]
1914: Blood anticoagulant used in successful transfusion [BL13]
1914: Plasmaphaeresis [BL17]
1932: Blood bank established [BL14]
1940: Rhesus antigens discovered in humans [BL15]
1964: Frozen Blood [BL3]
1972: Apheresis machine built [BL18]
1972: Effects of parabiosis on lifespan investigated [BL19]
1979: Fluosol-DA perfluorochemical blood substitute tested [SOURCE UNAVAILABLE]

1900

1990: Recombinant hemoglobin from e.coli [BL16]
2011: Lab grown artificial blood transfusion [BL5]
2015: Blood donor mortality study [BL22]
2016: Old blood inhibits tissues [BL20]
2020: Regeneration via dilution of old blood [BL21]

2000

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Stem cell exhaustion
Pillars of Aging: Stem cells and regeneration

Blood Replacement

Relevant Organizations: Who is working on this problem?

Sugimura Lab at University of Hong Kong
Blood Engineering Lab - stem cells

Artificial Cells Research Centre at McGill University
Artificial Blood

Red Cross Blood
Blood Donation

American Red Cross Research
Frozen Blood Research

Alkahest
Plasma replacement therapy

Young Blood Institute
Plasma replacement therapy

Naval Blood Research Laboratory (defunct)
Blood preservation research

Conboy Lab at UC Berkeley
Parabiosis Research

Nugenics Research
Plasma replacement therapy

Blood Replacement

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[BL3] Frozen Blood. Huggins. 1964.
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[BL5] Proof of principle for transfusion of in vitro-generated red blood cells. Giarratana et. al. 2011.
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[BL23] Blood donation and blood donor mortality after adjustment for a healthy donor effect. Hjalgrim et. al. 2015.

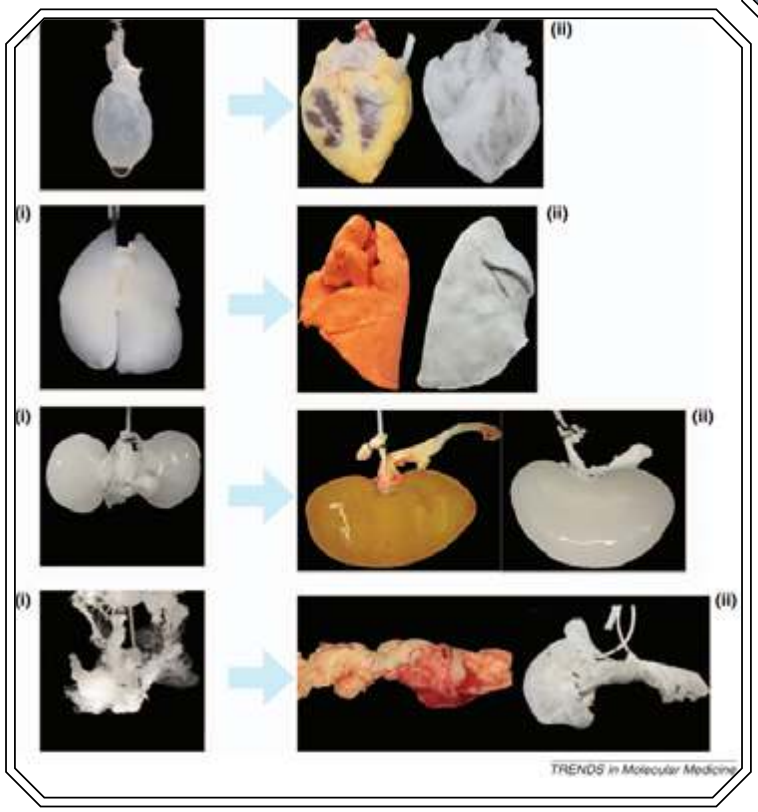
Organic Organ Replacement

Introduction

The human body is made up of organ systems. When any one of these organ systems fails, it can cause the whole organism to die. The purpose of organ replacement is to renew the organ systems of the body by replacing them with equivalent yet younger organs. Such organs could be sourced from either organ donors or be grown in a laboratory, or even be bioprinted using stem cells directly from the patient.

The current best replacements come from organ donors. A vast network of hospitals and legal institutions provides the backbone for the organ donor system here in the US. In other countries, organ donation is... less regulated. There is a moral imperative to make sure that organs are sourced from willing participants who have agreed to donate them in the event of untimely death. Because of this, the wait lines for things like hearts and lungs are very long. The immune system further complicates the situation - organ traits must match the recipient otherwise there will be rejection and organ failure.

{NIH Medline Plus}



{[ORG21]}

A more recent solution which removes moral issues from organ replacement is to grow organs directly from a patients own stem cells. The more mature and reliable process involves building decomposable scaffolds of organs and impregnating them with the correct progenitor cells. The cells eventually dissolve the scaffold and form themselves into functional organs. A bladder created this way was transplanted successfully into a patient in 2006.

The next evolution of this method is to print organs using 3D printers. Many companies are developing bioprinters with extreme resolution, able to lay down patterns of multiple cell types.

Organic Organ Replacement

The Next Big Step - Vascularization

The companies producing printed organs at this point in time are doing mostly flat, tissue-like versions of organs. The reason is that the vasculature - the blood vessels - cannot be printed correctly yet. Printed biomaterial must get its oxygen from diffusion which limits its thickness to about the size of a human thumbnail. Multiple companies have started out with a goal of printing organs only to pivot to tissue engineering because they could not solve this problem. The technical hurdle is the structure of the capillaries, which are 8-10 microns wide but comprised of cells in the 50+ microns range. The cells are structurally elongated, which makes direct printing of the capillaries not possible with current technology.

Investigated solutions

Electrospinning creates sub-micron filaments that can be used as scaffolding for capillaries but the fibers cannot be controlled [ORG16]. They end up as a random thickly-layered mat which creates suboptimal vascular networks and makes seeding the scaffold difficult.

Capillary beds can be induced to form near larger, directly printed vessels via in vitro angiogenesis [ORG20]. The process has not been mastered yet.

Stereolithography and photolithography can be used to deposit thin films onto a surface and build organs layer by layer. These are time consuming and tedious technologies to wield.

Most of the current organ construction efforts are hoping that building such small capillaries will not actually be necessary.

Organic Organ Replacement

Potential Impact - How will this affect us?

Idea Risk: X

Without a solution to the vasculature problem, organ production is limited and expensive. It is unknown whether it is possible to reliably grow capillaries. Theoretically, signs point to it being possible. Practically, we do not know.

Yield Assessment: A

Heart transplants: 3500 at $1.6 million each = $5.6 billion
Liver transplants: 8200 at $900,000 each = $7.38 billion
Kidney transplants: 22000 at $450,000 each = $9.9 billion
Single lung transplants: 800 at $930,000 each = $744 million
Double lung transplants: 2000 at $1.3 million each = $2.6 billion
Cornea transplants: 53,000 at $32000 each = $1.7 billion

In 2020 there were approximately 40,000 organ transplants performed (corneal transplants not included). There are over 100,000 people currently on the waiting list for organ transplants. Taking the major categories into account and extrapolating the data, we're looking at roughly $65 billion per year for critical need patients. Ideally, organ printing would lower the cost of organ transplants so maybe that turns into $40 or $50 billion.

Life expectancy of patients receiving an organ transplant is in the +5-10 year range. There is a general assumption that printed or scaffold manufactured organs would perform better than a homologous transplant, so perhaps +10-25 years may be an optimistic estimate.

It is likely that there are more patients which would like an organ transplant but do not go through the hassle of the medical system in order to put themselves on an unreliable waiting list for a lottery ticket at life. Perhaps 10x the number of current patients would like to replace an organ but are not in critical need. The potential market for them is $650 billion per year.

Future Possibilities: A

Beyond the current paradigm of organ transplants is the potential industry of external or designer organs. Conceptually, external organs would be fitted outside the body with appropriate septas for blood circulation. Think about medtronics artificial pancreas except not artificial. Such organs could act as backups for, say, heart failure or lung failure. Imagine swapping out organs as if you were changing clothes. Designer organs are another interesting concept - organs which do not currently exist in the human body. Development would be difficult but it would enable a new stage of human existence which has never been seen before. Imagine humanizing and printing the Hunter's organ from an electric eel and placing it into a human forearm.

Designer organs and external organs can only be pioneered by those with the manufacturing capacity to produce organs.

Organic Organ Replacement

Timeline of Organ Replacement Research

1800

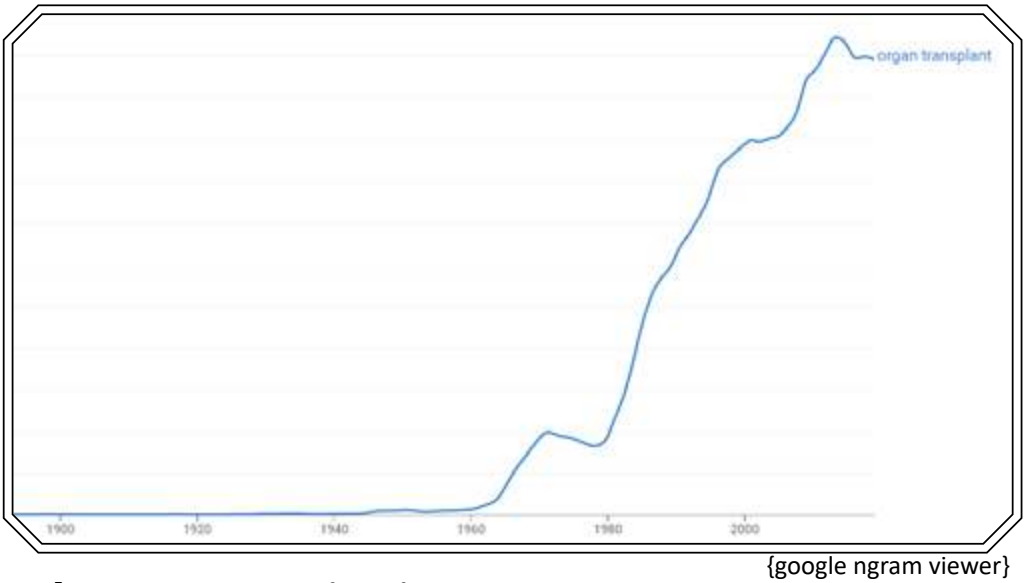
1597 – Skin autograft [ORG1]
1667 – Xenotransfusion [ORG15]
1871 – Skin graft [ORG2]
1896 – Blood vessel suturing
1905 – Xenotransplantation [SOURCE UNAVAILABLE]
1949 – Tissue bank [SOURCE UNAVAILABLE]
1950 – Kidney transplant [ORG4]
1951 – Skin grafting and the immune system [ORG17]
1963 – Lung transplant [ORG5]
1964 – Heart transplant (chimp to human) [ORG6]
1966 – Pancreas transplant [SOURCE UNAVAILABLE]
1967 – Successful liver transplant [ORG7]
1967 – Heart transplant (human to human) [ORG8]
1971 – Cryopreserved skin allograft [ORG9]
1980 – Angiogenesis in vitro [ORG19]
1987 – University of Wisconson organ preservation solution [ORG18]
1999 – Bioengineered bladder replacement [ORG11]
2004 – Electrospinning investigated in context of vasculature scaffolds [ORG16]

1900

2005 – Ovarian transplant [ORG12]
2005 – Bioengineered trachea [ORG13]
2008 – First baby born from transplanted ovary
2010 – Full face transplant [ORG14]

2000

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: N/A
Pillars of Aging: Macromolecular Damage

Organic Organ Replacement

Relevant Organizations: Who is working on this problem?

Wake Forest Institute of Regenerative Medicine
Tissue/Organ engineering lab

Organovo
Tissue Engineering Company

Organogenesis
Tissue Engineering Company

Miller Lab at Rice University
Organ engineering lab

The Ott Lab for Organ Engineering at Harvard
Organ engineering lab

Badylak lab at University of Pittsburgh
Organ engineering lab

Wyss Institute at Harvard
Organ engineering lab

Tissue Engineering and Organ Fabrication Laboratory at Massachusetts General Hospital
Organ engineering lab

Carnagie Mellon Bioengineered Organs Initiative
Organ engineering lab

Allevi Bioprinting
Bioprinting Company

Cellink
Bioprinting Company

3D Bioprinting Solutions
Bioprinting Company

Bioprinting World Map
List of 3D bioprinting companies

Organ Preservation Alliance
Association for organ storage

New Organ Alliance
Association for organ storage

Scientific Registry of Transplant Recipients
Database of hospitals capable of transplantation

United Network for Organ Sharing
Organ donation and transplantation organization

Organic Organ Replacement

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[ORG21] Organ engineering based on decellularized matrix scaffolds. Ott and Song. 2011.

Microbiome

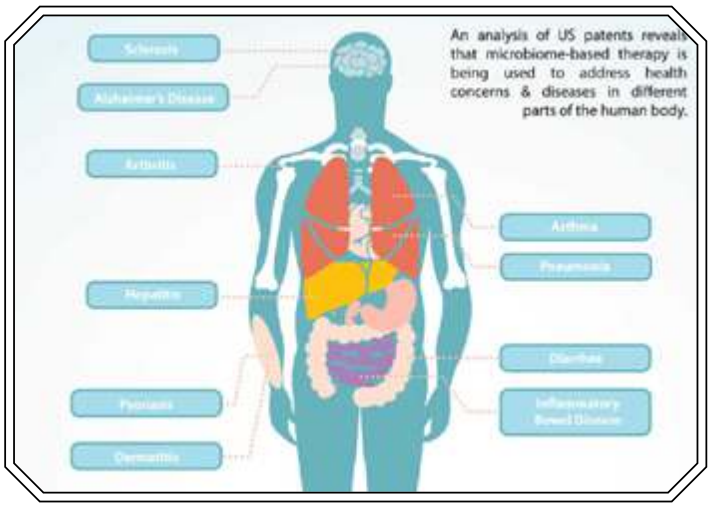
Introduction

The microbiome refers to the population of bacteria, fungi, and viruses that occupy the human body. While not strictly part of the human body, they do participate in metabolic functions and are a vital and necessary component of the soma. The microbiome is important enough to create evolutionary pressure that modifies development of the human body in disparate and critical ways. It has recently been reported that human breastmilk contains oligosaccharides that are indigestible by humans – their presence is strictly to foment a desirable bacterial population in human infants [MB1]. It has been hypothesized that the appendix was related to the microbiome since 1986 [MB2]. The current prevailing theory is that it helps restore the microbiome in the event of rapid discharge [MB3].

Microbiome Control

Bacterial/fungal populations can be controlled through diet, antibiotics, bacteriophages, and indirect control via changing the human immune system. The immune system automatically targets and destroys specific bacterial populations in the gut, mouth, and other places. Diet and drug use shifts microbiome population by creating starvation or nutrient abundance. Bacteriophages can target specific bacterial strains for removal. Alterations in microbiome populations are correlated with aging, although direction of causality is not clear.

{Sigma Aldrich}



{Parola Analytics}

Diseases associated with the microbiome

obesity [MB17]
+ diabetes
inflammatory bowel disease (IBD) [MB16]
nonalcoholic fatty liver disease (NAFLD) [MB19]
+ hepatocellular carcinoma
metabolic syndrome [MB22]
asthma [MB21]
atherosclerosis [MB18]
cirrhosis [MB20]

There are currently over 600 bacterial genera commonly associated with the human microbiome [MB13]. If we accept that any human organ is basically a mass of cells with common traits, the microbiome can be seen as a set of 500 organs that may or may not exist in any particular individual. Imagine attempting to manage the health of a person when you don't even know what organs they possess.

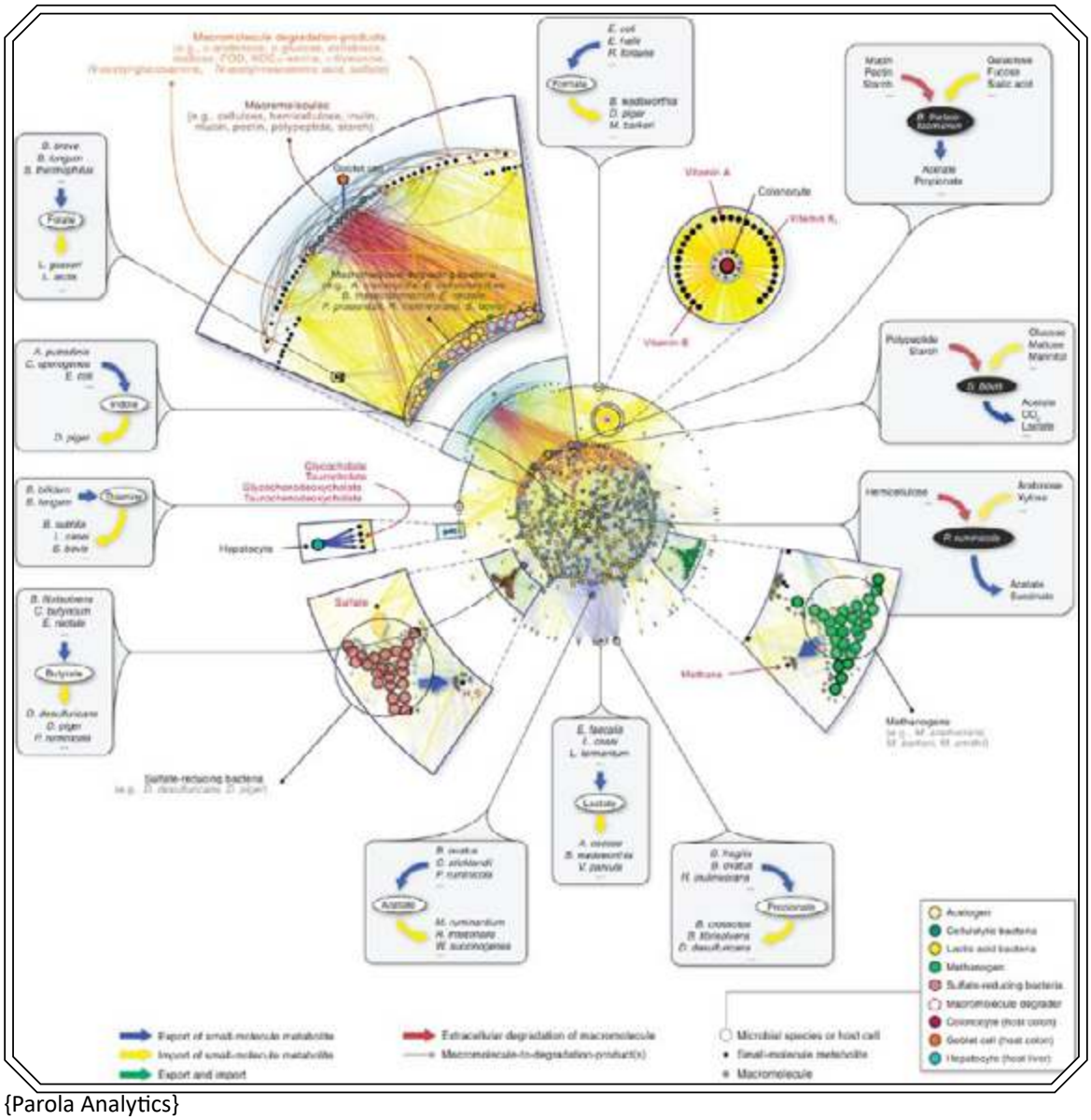
Microbiome

The Next Big Step - Microbiome Metabolic Map

The microbiome is essentially a network of up to 500 organs all with various interconnectivity. Even if we know the full list of species in a specific persons microbiome, we do not know what that means in terms of inputs and outputs. We need a map of the linked metabolism that emerges from the genetic information we get by sequencing an entire microbiome.

This is going to be tedious and grueling work, and likely expensive. Several attempts are already underway, and just by looking at the resulting data we can see that it is overwhelmingly complex.

But this is a necessary step toward controlling the microbiome. If I have 200 species, I need to know what to eat in order to raise or lower any one specific species and how that will affect the rest of my microbiome. I also need to know what metabolic activity is occurring to the food I already eat due to the species present in my gut.



{Parola Analytics}

Microbiome

Potential Impact - How will this affect us?

Idea Risk: M

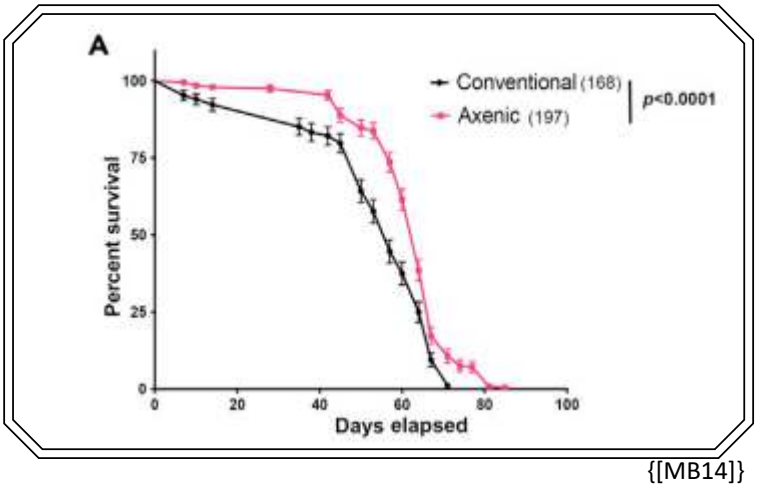
We have the technology to sift through the microbiome and map it, but it will be tedious.

Yield Potential: B/C

The microbiome is one of the last black boxes in the human metabolic system. We may uncover the root of several diseases by understanding it - maybe even cure things like IBS, heartburn, nonalcoholic fatty liver disease, and nonconformant forms of obesity.

Notably, the big success with the microbiome was the discovery of heliobacter pylori, leading to the treatment and elimination of stomach ulcers. This then cascaded into a reduced rate of cancer, as stomach ulcers created conditions which led to cancer. It is likely several forms of intestinal and rectal cancer could be avoided by obtaining control over the microbiome.

There is some lifespan data for flies grown with and without a microbiome. The general magnitude of impact is likely around 15% lifespan extension, possibly up to 50% with extreme advances in the field.



{[MB14]}

Future Possibilities: B

Imagine a world where someone gives you diet advice, and you could tell if it will work for you based on your microbiome data. How about knowing whether a drug will work or fizzle out because of the specific species of microbes in your gut.

The techniques applied to map the human microbiome metabolic network can be applied elsewhere as well. Imagine mapping cow or termite microbiome networks to discover the energetically ideal way to break down cellulose and lignin, opening up new avenues for food or fuel.

Within the body of human society, wastewater digesters are the de-facto stomach and intestine. How about using microbiome mapping techniques to better fine-tune wastewater digesters, increasing efficiency of waste management and reclaimed methane energy.

Microbiome

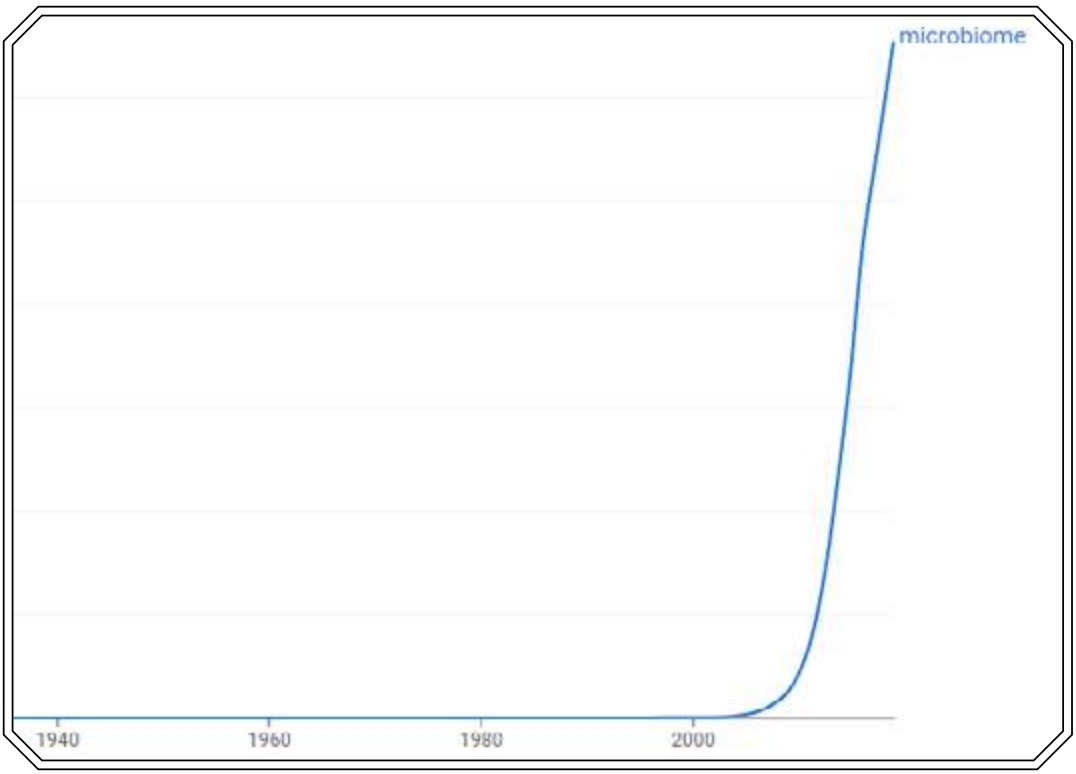
Timeline of Microbiome Research

1800

1671 – Discovery of bacteria [MB11]
1985 – Heliobacter pylori linked to ulcers [MB12]
1986 – Appendix hypothesized to be used for bacterial storage [MB2]
1988 – Microbiome defined [MB4]
2008 – Human Microbiome Project [MB5]
2010 – 3.3 million non-redundant genes in microbiome categorized [MB10]

Word Usage Over Time

1900



{google ngram viewer}

Relevant categorization

Trifecta: Antagonistic Pleiotropy
Hallmarks of Aging: N/A
Pillars of Aging: N/A

2000

Microbiome

Relevant Organizations: Who is working on this problem?

Viome
Microbiome testing company

Cosmos ID
Microbiome testing company

The Microsetta Initiative
Microbiome testing & identification research

Microba
Microbiome testing company

Edward Giniger
Microbiome Research

BioPharma List
Microbiome company list

Pan-Jun Kim lab
Microbiome metabolic map

Goodman lab
Microbiome drug metabolism

International human microbiome consortium congress
Conference of microbiome research

Chang Lab at University of Chicago
Microbiome research

Microbiome Research at University of Texas
Microbiome Research

Jackson Lab
Microbiome Research

Microbiome Research at Yale
Microbiome Research

Gilbert Lab at UCSD
Microbiome Research

Microbiome Research at Cedars Sinai
Microbiome Research

Turnbaugh Lab at UCSF
Microbiome Research

Sonnenburg Lab at Stanford
Microbiome Research

Phage Directory
Bacteriophage Research

Microbiome

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[MB9] Barley b-glucans-containing food enhances probiotic performances of beneficial bacteria. Arena et. al. 2014.
[MB10] A human gut microbial gene catalogue established by metagenomic sequencing. Qin et. al. 2010.
[MB11] Microscopiorum. Leeuwenhoek. 1687.
[MB12] Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Marshall, Warren. 1985.
[MB13] Biodiversity and functional genomics in the human microbiome. Huttenhower et. al. 2012.
[MB14] Common features of aging fail to occur in drosophila raised without a bacterial microbiome. Giniger et. al. 2021.
[MB15] The human microbiota in health and disease. Li et. al. 2017.
[MB16] The microbiome and inflammatory bowel disease. Quigley et. al. 2019.
[MB17] Human gut microbes associated with obesity. Gordon et. al. 2006.
[MB18] Role of gut microbiota in atherosclerosis. Backhed and Jonsson. 2016.
[MB19] The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). Gerard and Safari. 2019.
[MB20] The microbiome in cirrhosis and its complications. Bajaj and Acharya. 2019.
[MB21] The role of the microbiome in asthma the gut-lung axis. Esposito et. al. 2018.
[MB22] Links between metabolic syndrome and the microbiome. Gildner. 2020.

Stem Cells

Introduction

Stem cells are cells which have the ability to differentiate into multiple (pluripotent) or any (totipotent) differentiated cells in the human body. Most adult stem cells exist in creche pockets dotting the body and are responsible for natural regeneration, such as skin and liver cell turnover. Adult stem cells are often only pluripotent, they can differentiate into multiple cell types for the surrounding tissue but cannot differentiate into cells for other organs. New types of stem cells continue to be discovered, such as oocyte stem cells which have overturned a long held belief that women are born with all the eggs they will ever carry [STEM10].

The current theoretical immortality pathway for stem cells is as follows – cells are harvested from the body, then 'deprogrammed' into becoming pluripotent embryonic stem cells (essentially totipotent for the purposes of antiaging) via a mix of signaling molecules such as Oct4, Nanog, and Sox2. The cells are then culture expanded outside the body, creating a large pool of raw regenerative material. The cells then get injected back into the body at specific sites, replacing old aged cells and rejuvenating the body. Assuming all the steps work as theorized, this is a viable pathway to immortality as it has the ability to heal every part of the soma.

This field has become so massive it is difficult to summarize what exactly is going on.

Stem Cells

The Next Big Step - Mesenchymal Stem Cells

Mesenchymal stem cell usage is hot right now, but it feels overplayed. Why does it require medical tourism, how come people are giving anecdotal evidence instead of measurable results. Not sure what the next step is beyond “seeing a therapy actually work with full FDA approval and oversight”. [STEM15]

Need to speak with industry insiders for more information about what technology is currently on the horizon.

Stem Cells

Potential Impact - How will this affect us?

Idea Risk: M

Stem cells are expensive and difficult to work with but the reasons for that are largely bureaucratic.

Yield Potential: A

Stem cells are being applied toward cancer, heart disease, parkinsons, multiple sclerosis, alzheimers, amyotrophic lateral sclerosis, diabetes, ocular disease, and dental disease [STEM14].

Future Possibilities: A

Stem cells are the progenitor cells of the body and of the organism as a whole. Understanding the nature of stem cell regeneration likely will lead to understanding the nature of aging, life, and death.

Stem Cells

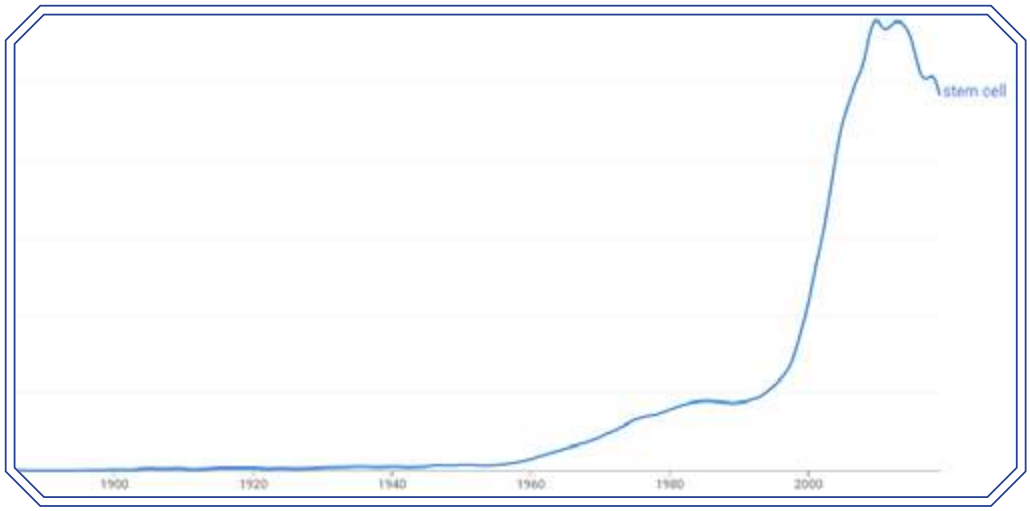
Timeline of Stem Cell Research

1800

1855: Cancer hypothesized to have stem cell origin [STEM12]
1879: “Stemmzelle” terminology [STEM1]
1898: Stem cells linked to regeneration [STEM11]
1954: Differentiation heirarchy in mice teratomas observed [STEM3]
1959: First successful transplantation of bone marrow (stem cells) [STEM5]
1963: Self renewing mouse bone marrow cells documented [SOURCE UNAVAILABLE]
1978: Stem cells discovered in human cord blood [STEM8]
1981: First in vitro stem cell line developed from mice [STEM6]
1997: Cloned lamb from stem cells [STEM4]
1998: First human embryonic stem cell lines [STEM2]
2011: FDA approval of hematopoietic progenitor cord cell therapy [STEM13]
2018: Human lung inside mice partially regenerated via stem cells [STEM9]

Word Usage Over Time

1900



{google ngram viewer}

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Stem Cell Exhaustion
Pillars of Aging: Stem Cells and Regeneration

2000

Stem Cells

Relevant Organizations: Who is working on this problem?

Biopharm list
List of stem cell companies

Stem Cell Institute
Unregulated stem cell therapy

Regenexx
Stem Cell Therapy

Centagen
Unregulated Stem Cell Therapy

Ascendance Bio (defunct)

AgeX Therapeutics
Stem cell therapy

Stanford Stem Cell Institute
Stem Cell Research

Harvard Stem Cell Institute
Stem Cell Research

Columbia Stem Cell Initiative
Stem Cell Research

NCATS Stem Cell Translation Lab
Stem Cell Research

Broad Stem Cell Research at UCLA
Stem Cell Research

ReNeuron
Stem Cell Company

Rando Lab at Stanford
Stem Cell Aging Research

UseAnja
Stem Cell Cord Blood Banking

Bone Therapeutics
Bone Stem Cell Therapy

Endogena
Stem Cell Therapy for Eyes

Treefrog Therapeutics
Stem Cell Therapy

Stem Cells

Sources

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[STEM3] Spontaneous testicular teratomas in an inbred strain of mice. Stevens, Little. 1954.
[STEM4] Viable offspring derived from fetal and adult mammalian cells. Wilmut, Schnieke, McWhir, Kind, Campbell. 1997.
[STEM5] Supralethal whole body irradiation and isologous marrow transplantation in man. Thomas et. al. 1959.
[STEM6] Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. Martin. 1981.
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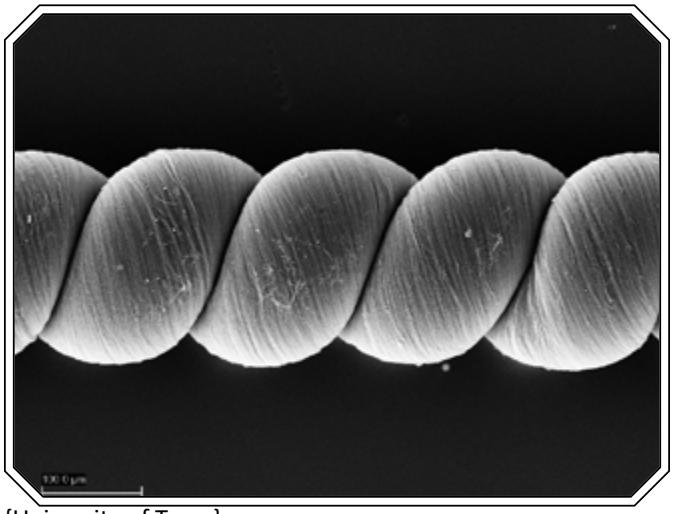
[STEM9] Regeneration of the lung alveolus by an evolutionarily conserved epithelial progenitor. Zacharias et. al. 2018.
[STEM10] Germline stem cells and follicular renewal in the postnatal mammalian ovary. Johnson et. al. 2004.
[STEM11] Experimental studies of the regeneration of planaria maculata. Morgan. 1898.
[STEM12] Archiv fur pathologische anatomie und physiologie und fur klinische medicin. Virchow. 1855.
[STEM13] Acknowledgment Letter, January 28, 2011 – Hemacord
[STEM14] Current state of stem cell-based therapies an overview. Aly. 2020.
[STEM15] The pros and cons of mesenchymal stem cell-based therapies. Majka et. al. 2019.

Artificial Muscle

Introduction

Skeletal muscle accounts for 30-40% of body mass [MUS7]. Being able to create an artificial replacement for muscle takes us a long way toward cybernetic bodies, which is one pathway for countering the aging process. The artificial muscles in development today use a variety of mechanisms and power sources in an attempt to get them compact enough and strong enough to function like normal muscles.

One category of artificial muscle design is to use small threads of smart materials which twist when electric current or heat are applied to them. The twisting motion reduces the length of the thread, leading to contraction. A large variety of exotic and common materials have been tested for this type of muscle, ranging from carbon nanotubes to fishing line. High strengths and rapid contraction are have been touted as the advantages to these types of muscles, although repeated use may result in a degradation in strength and control.

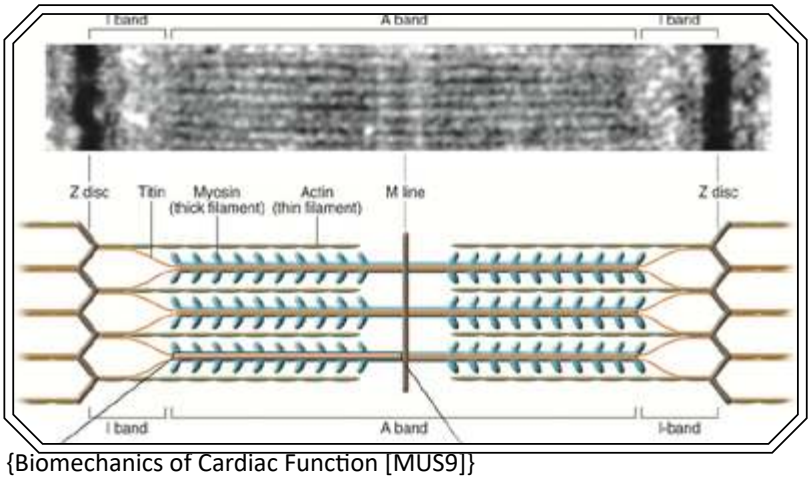


{University of Texas}

{McKibbon}

The McKibbon muscle was one of the earliest artificial muscle designs. It uses simple pneumatics to generate contraction via pressure. The mechanism is simple to understand and relatively cheap. These designs are bulky and prone to degradation from constant use. They have issues with control due to pneumatic pump accuracy and the chaotic nature of the bladder expansion. Furthermore, the contraction distance is severely limited from the geometry of the bladder. An evolved version of this design involves internal folding structures surrounded by pressurized fluid.

Currently there are no designs which attempt to use the actual mechanism that myosin proteins use for real human muscle. The diagram to the right illustrates how myosins work - essentially they pull two protein threads past each other in order to create contraction. Releasing the threads allows the muscles to extend - and control of both steps is done via electric signals propagated through nerve cells.



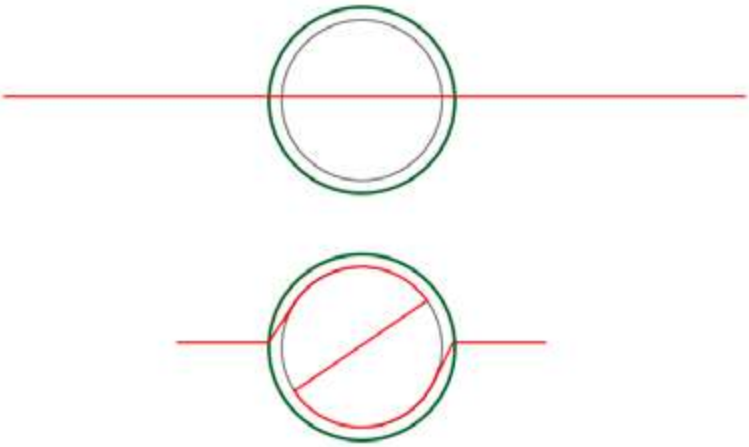
{Biomechanics of Cardiac Function [MUS9]}

Artificial Muscle

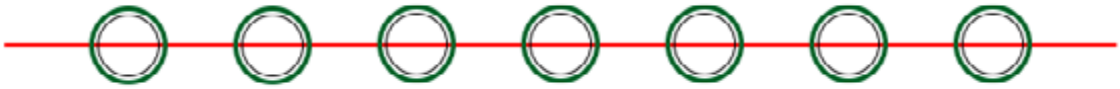
The Next Big Step - Thread Action

None of the current artificial muscle designs mimic the system in place in our normal muscles. The biggest advantage of the myosin which governs human muscle is the scale - it is absolutely tiny and relies on molecular forces to operate. It should be possible to design a muscle at a macro scale which operates on the same principles as proof of concept, then miniaturize it with

One way the thread pulling mechanism might be used is via a reel mechanism. In order to contract the thread, we can weave it through a bearing with a hole cut through the center. By rotating the inner bearing, the two points of these threads are pulled past each other, contracting the steel thread. Rotation would be modulated by some kind of motor housed within the inner cylinder, acting on the outer cylinder.



This device allows for in-line thread contraction simply by spinning the inner wheel, which pulls the steel thread past itself as it wraps around the cylinder. In order to relax the muscle, you only need to stop powering the reels and allow them to spin back to the normal position. The outer wheel does not need to be mounted to anything other than the thread itself. This mechanism is limited by the spin rate and radius of the bearing. Increasing the number of bearings lets you reduce the size of the bearing, while simultaneously increasing the speed of contraction. With enough bearings on a single thread, the size can get down into the micro or nano scale and contraction speeds (assuming you can control all reels at once) would be extremely fast. A further advantage of this particular mechanism is that there is no contraction limit, the inner rotor can continue pulling until the entire length of the cable is consumed in the reel.



This is just one suggestion for using thread action to create an artificial muscle. Mechanically, there are many options of how to do this. Pragmatically, nanoconstruction needs to be a thing prior to attempting to use this to replace human muscle. These reels need to be built extremely small and use ambient power, maybe by being embedded in a gel which can be electrified to actuate all of them at once.

Regardless of the actual design, we need to have a muscle mechanism option which more accurately uses the mechanism present in real human muscle rather than bladders or twisted string.

Artificial Muscle

Potential Impact - How will this affect us?

Idea Risk: S

Proving out the concept for artificial muscle based on true muscle design should be relatively cheap and straightforward.

Yield Potential: A

Prosthetics is the most direct, impactful use for artificial muscle. Making prosthetics which more accurately mimic human motion would directly improve the lives of an estimated 2 million people who have lost limbs in the US. The global market is estimated at $2.7 billion for 2024.

Future Possibilities: A

Even with the development of artificial muscles, a cybernetic body seems far away. However, building true artificial muscles is a necessary step on that road. Beyond cybernetics, artificial muscles will likely be scaleable for use in non-human machines like robotic arms and shipping infrastructure. Artificial muscle also paves the way to mechs, gundams, tachikoma, and all sorts of bizarre robotic inventions we haven't imagined yet.

Artificial Muscle

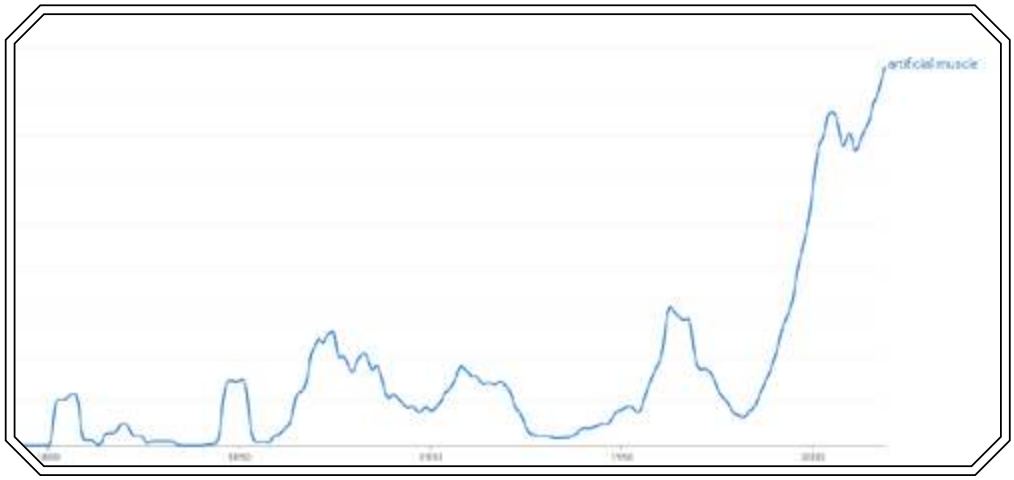
Timeline of Artificial Muscle

1800

1880 – Electroactive Polymer [MUS1]
1932 – Elastic gold-cadmium alloy [MUS3]
1947 – Sliding thread theory of muscle contraction [MUS5]
1969 – Piezoelectric effect in polarized PVDF [MUS2]
2014 – Heat activated muscle from fishing line [MUS4]
2017 – Heat activated silicone/ethanol [SOURCE UNAVAILABLE]
2018 – HASEL hydraulic muscle [MUS6]

1900

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Loss of Proteostasis
Pillars of Aging: Proteostasis

2000

Artificial Muscle

Relevant Organizations: Who is working on this problem?

Wyss Institute
Artificial Muscle Research

Artificial Muscle Research Initiative UMaine
Artificial Muscle Research

UCSD Robotics Lab
Muscle Mimetics Research

Center for Artificial Muscles - Zurich
Artificial Muscle Research

Artificial Muscle

Sources

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[MUS2] Piezoelectric effect in polarized poly (vinylidene fluoride). Fukada, Takashita. 1969.
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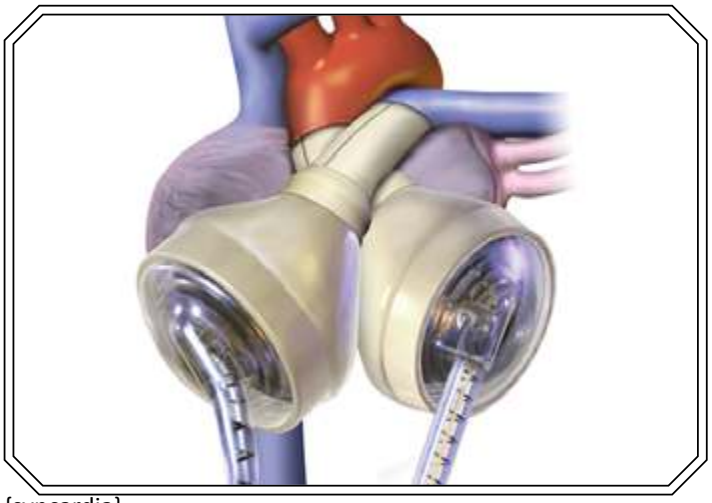
[MUS8] Limb loss and preservation registry. https://www.llpregistry.org/
[MUS9] Biomechanics of cardiac function. Han and Voorhees. 2015.

Artificial Organs

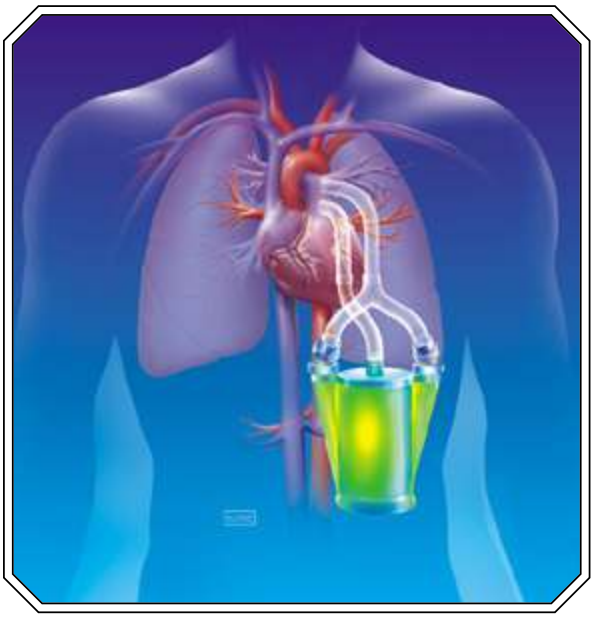
Introduction

Artificial organs are devices made of plastic, metal, or composites which take on the function of organs in the human body. The distinct advantage of building organs instead of growing them is that they are easier to produce than grown or bioprinted organs.

The heart is one of the slowest regenerating organs in the body, with approximately 1% turnover per year. The reason for this is that it is difficult to regenerate an organ which is always active. This makes the heart a critical weak point and it's no surprise that in this age of medical technology heart disease is the leading cause of death globally. Artificial hearts have been in development for around a hundred years.



{syncardia}



{inlander.com}

Artificial lungs have developed from external steel behemoths used to fight polio to small rollable devices the size of a backpack. These lungs are built like dialysis machines, except with the intention of purging carbon dioxide instead of toxins. Early development is underway for the liver, spleen, kidney, and stomach as well.

In terms of true artificial organs, the artificial pancreas is furthest along in development. Unlike the heart, current artificial pancreatic devices are made with the intent of being used permanently. Commercialization is well underway, with multiple iterations already developed by Medtronic and alternative devices available from other companies as well. These devices are getting better every year as testing and usage reveal opportunities for improvement.

{Medical News Today}

The promise of using metal and plastic in place of flesh is hampered by the simplicity of the devices we are able to create. Often these artificial organs can only perform one or two specific functions of an organ, when the reality of our biology is that all our organs are complex multifunctional machines.

Artificial Organs

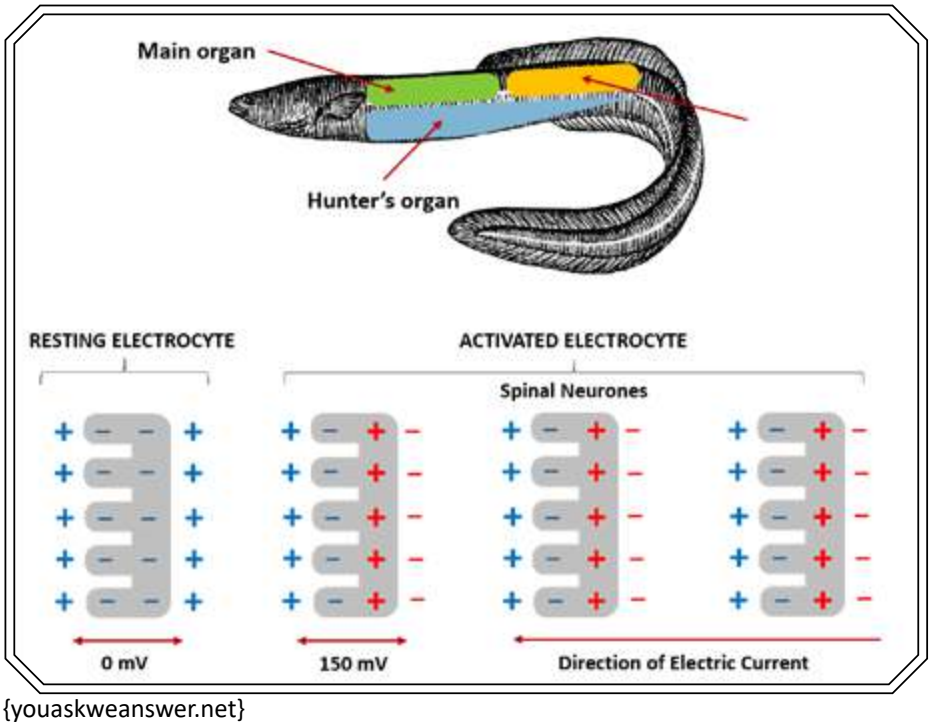
The Next Big Step - Bioelectrical Power Supply

While a number of artificial organ designs have emerged over the years, none are currently fully implantable although just recently the kidney has made some progress. All designs seem to require some kind of external logistical backpack or device which powers the device. The power requirement creates size issues and requires tubes or wires to exit the body, necessitating skin septa which are vulnerable to infection and inflammation. Fully implantable designs of hearts or lungs have come up here and there, but the companies making artificial organs always pivot away from them after several years.

It is clear that the major difficulty of implantability is power. Artificial organs use electricity for power. The human body generally uses sugar as its energy storage and distribution system. The power required for continuously running a large pump or diaphragm goes beyond the current battery technology.

Creating artificial organs with the ability to use blood sugar as an energy source would be a massive step forward for artificial organ development. Eliminating the need for external power also solves the septa problem. This is the next big step, and with this one invention the entire industry of artificial organs would be taken to the next level.

The trillion dollar question is how to accomplish this task. For inspiration, we might want to look at the electric eel, which uses disc-stack capacitor cells to convert chemical energy into electrical energy, releasing a massive charge into the surrounding water to stun its prey. Current attempts to produce biobatteries or “sugar batteries” are in the microwatt range. In comparison, an electric eel can produce >400 watts of power. For our purposes we may want to instead create lower amperage, sustained power in order to run an internal artificial heart or pancreas. Work on this has been ongoing since 2017 [ARO12].



{youaskweanswer.net}

Artificial Organs

Potential Impact - How will this affect us?

Idea Risk: X

While we can watch an eel shock an alligator to death in front of our eyes, our ability to copy that mechanism is not very clear. We are at the early stages of designing cells that can even stay alive on their own, much less a fully functioning humanized cellular capacitor.

Yield Assessment: A

Affordable, reliable, self-contained artificial hearts would outright solve heart disease. Solving heart disease would eliminate the number one cause of death worldwide. It's difficult to imagine a more pressing issue, apart from going back in time and curing malaria.

Artificial organs have the potential to eliminate 4 of the top 10 causes of death in the United States [ARO11]. Heart disease, chronic lower respiratory disease, diabetes, and kidney disease could be directly solved by artificial organ replacement. It is likely that artificial organs could drastically reduce two more causes - influenza and cancer mortality - since influenza often kills via lung inflammation and cancer shuts down specific organ functions.

Future Possibilities: A

If the various artificial organ projects all get to completion, it gets us a long way toward cybernetic humans. Imagine having a heart attack and simply pressing a button to switch to your auxiliary heart. It may also be possible to take the performance of our organs to absurd extremes - lungs with prefilters so we don't have a problem breathing in heavy smoke, a liver which can process alcohol so efficiently you don't get a hangover, or kidneys which don't get kidney stones.

The potential for bioelectrical power opens another fascinating realm of possibility. Imagine plugging your phone into your arm to charge it. Think about how useful innate electrical production could be in a survival situation. Bioelectrical power doesn't need to be limited to just powering organs.

Artificial Organs

Timeline of Artificial Organs

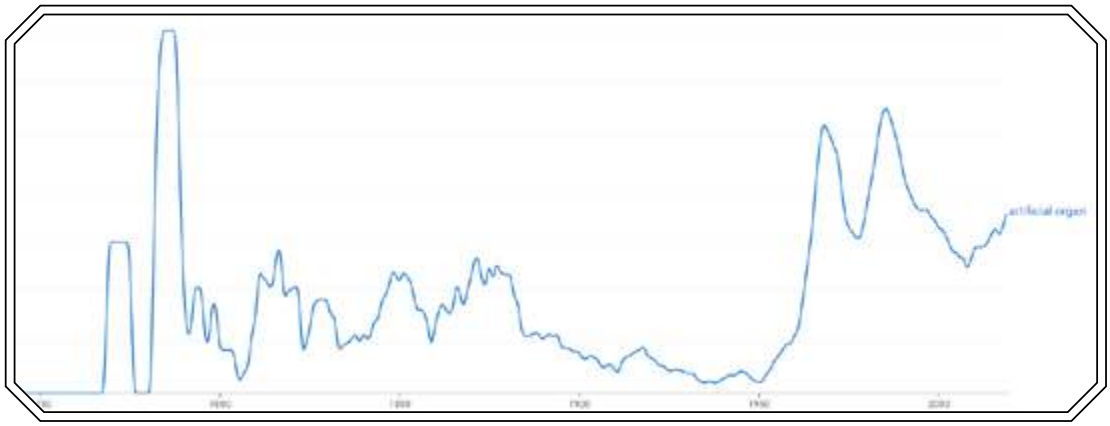
1800

1832 – Negative pressure ventilator [SOURCE UNAVAILABLE]
1929 – Iron Lung [ARO4]
1937 – First artificial heart transplanted to dog [SOURCE UNAVAILABLE]
1952 – First artificial heart machine used on human [SOURCE UNAVAILABLE]
1953 – Extracorporeal membrane oxygenation [SOURCE UNAVAILABLE]
1963 – Controlled glucose monitoring [ARO8]
1964 – Artificial heart program by National Institute of Health [SOURCE UNAVAILABLE]
1966 – First ventricular assist device implant [SOURCE UNAVAILABLE]
1969 – First clinical use of total artificial heart [ARO1]
1974 – Biostator commercial device [ARO9]
1982 – Wearable pancreas [ARO10]
1992 – Intravascular Oxygenator [ARO5]
1993 – SynCardia heart [SOURCE UNAVAILABLE]
1996 – Phoenix-7 heart [SOURCE UNAVAILABLE]
2000 – Pumpless extracorporeal lung assist [ARO6]
2001 – Abiomed AbioCor heart [SOURCE UNAVAILABLE]
2005 – Magscrew heart [SOURCE UNAVAILABLE]

1900

2008 – Impella heart pump [SOURCE UNAVAILABLE]
2014 – Artificial Spleen [ARO3]
2016 – Minimed 670 approved by FDA [SOURCE UNAVAILABLE]
2017 – Soft artificial heart [ARO2]
2017 – Wearable artificial lung [ARO7]

Word Usage Over Time



{google ngram viewer}

2000

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: N/A
Pillars of Aging: N/A

Artificial Organs

Relevant Organizations: Who is working on this problem?

UCSF Artificial Kidney Project
Artificial Kidney Research

Wearable Artificial Organs
Artificial Kidney Company

ALung Hemolung
Artificial Lung Company

Abiomed
Oxy-1 external lung system

MC3
Artificial Heart and Lung Company

Syncardia
Artificial Heart Company

Bivacor
Artificial Heart Company

Mayo Clinic Nyberg Lab
Artificial Liver Research

Medtronic
Artificial Pancreas

Mayer Lab at Adolphe Merkle Institute
Bioelectrical power

Kerzenmacher Lab
Bioelectrical power

Artificial Organs

Sources

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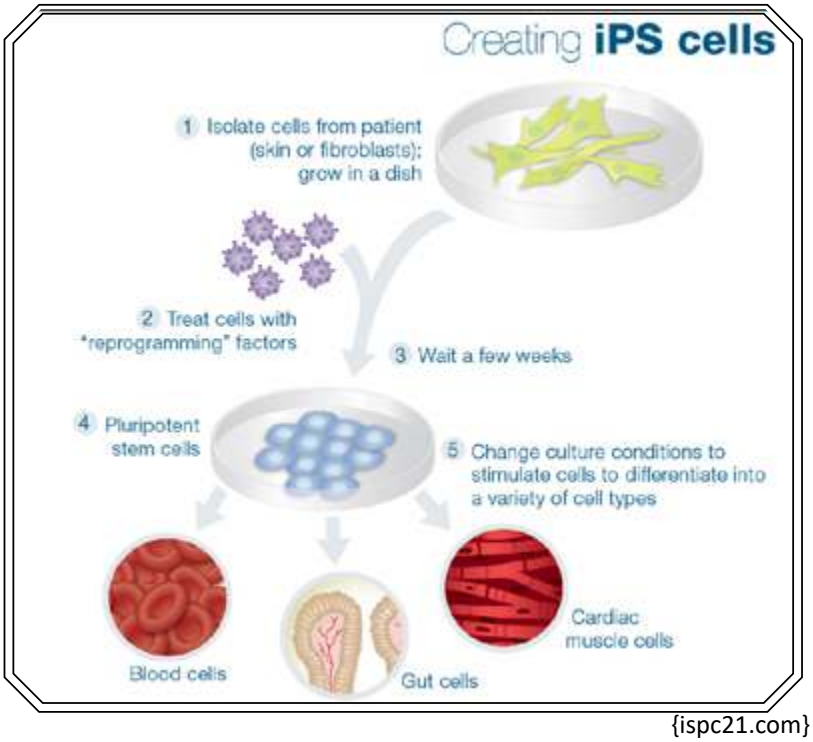
[ARO2] A soft total artificial heart – first concept evaluation on a hybrid mock circulation. Cohrs et. al. 2017.
[ARO3] An extracorporeal blood-cleansing device for sepsis therapy. Ingber et. al. 2014.
[ARO4] An apparatus for the prolonged administration of artificial respiration. Drinker, Shaw. 1929.
[ARO5] Intravascular Oxygenator A new alternative method for augmenting blood gas transfer in patients with acute respiratory failure. Mortensen. 1992.
[ARO6] Pumpless extracorporeal lung assist and adult respiratory distress syndrome. Reng et. al. 2000.
[ARO7] In vitro and in vivo evaluation of a novel integrated wearable artificial lung. Madhani et. al. 2017.
[ARO8] Automation control of blood sugar a servomechanism for glucose monitoring and control. Kadish. 1963.
[ARO9] The artificial beta cell – a continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system). Pfeiffer, Thum, Clemens. 1974.
[ARO10] Wearable artificial endocrine pancreas with needle-type glucose sensor. Shichiri et. al. 1982.
[ARO11] Mortality in the United States, 2019. Arias et. al. 2019.
[ARO12] An electric eel inspired soft power source from stacked hydrogels. Mayer et. al. 2017.

Cellular Reprogramming

Introduction

Human beings start out as a single cell and grow into an organism comprised of many billions of cells. During this growth many cells silence portions of their genome permanently in a process known as differentiation. Epigenetic markers such as methylation and acetylation are used to control gene expression and turn a totipotent cell into a heart, muscle, or brain cell.

One interesting method of tackling cellular regeneration is to simply deprogram the cell back to its original state. A method to do this was discovered in 2006 by Shinya Yamanaka [CDP1]. Four transcription factors - Oct3/4, Sox2, c-Myc, and Klf4 - were introduced to mouse adult fibroblasts and turned them back into pluripotent stem cells. Since then, other combinations of factors have been used to either dedifferentiate or transdifferentiate cells between various states. This process can be used to invoke the innate potential for regeneration that the germline possesses and repurpose it to reverse cellular aging.



{ispc21.com}

While cellular reprogramming involves epigenetics, the process of reprogramming covers a slightly different domain. This section specifically covers dedifferentiation, redifferentiation, and transdiffferentiation processes.

One of the downsides for cellular reprogramming using transcription factors is the potential for tumorigenesis. The reprogramming currently available is like a quick hack - it clearly works but we do not understand the differentiation process enough to account for all the edge cases that arise when reprogramming large batches of cells.

Cellular Reprogramming

The Next Big Step - Targeted Reprogramming

Blanket reprogramming of cells is clearly a terrible idea. Turning your entire body back into stem cells would kill you - what we want is to target specific senescent or damaged cells and induce dedifferentiation and regeneration. This is the bottleneck for cellular reprogramming.

The options currently available are:

Lentiviruses

Sendai-virus

Plasmids

Minicircles

Transposons

mRNA

miRNA

Cellular Reprogramming

Potential Impact - How will this affect us?

Idea Risk: M

The problem of cell targeting has been around for a while. There are many solutions but the question is which one will work, and is it efficient enough to justify the effort.

Yield Assessment: A

Reprogramming currently has a high risk of cancer. However, the intimate relationship between cell reprogramming and cancer is also likely it's most valuable asset. By fully understanding the nature of this phenomena, a pathway opens up to curing most cancer as well as targeting diseases of senescence.

Future Possibilities: A

Mastering the differentiation process forwards and backwards means total control over regeneration at the cellular level. It's a catch-all solution with tremendous potential for solving most of the problems of aging.

Cellular Reprogramming

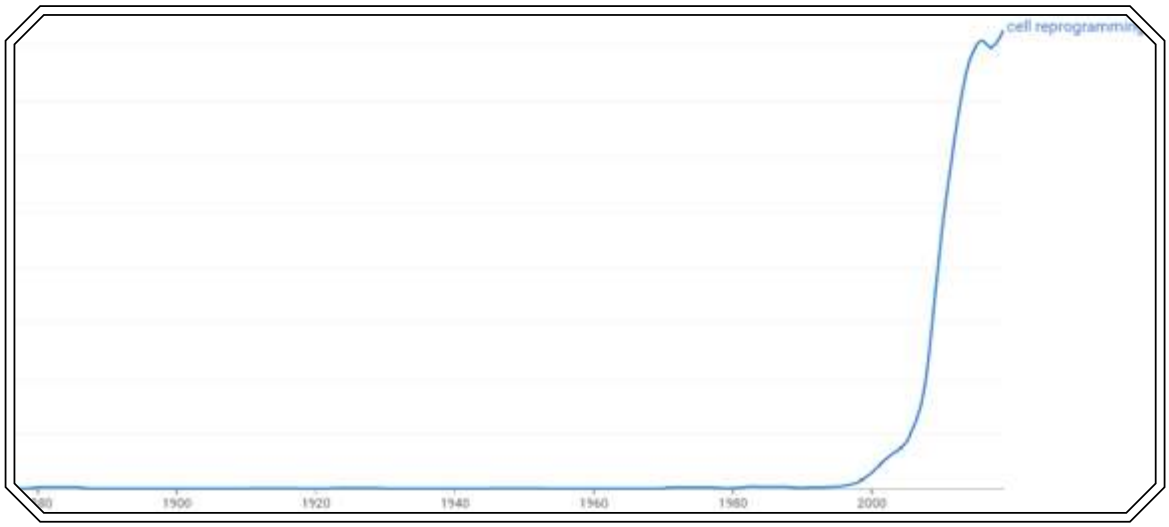
Timeline of Organ Replacement Research

1800

2006 - Yamanaka factors discovered [CDP1]
2007 - Human induced pluripotent stem cells [CDP3]
2008 - Neural stem cells to iPSC [CDP4]

1900

Word Usage Over Time



{google ngram viewer}

2000

Relevant categorization

Trifecta: Antagonistic Pleiotropy
Hallmarks of Aging: Genomic Instability
Pillars of Aging: Stem Cells and Regeneration

Cellular Reprogramming

Relevant Organizations: Who is working on this problem?

Turn Biotechnologies
Yamanaka Reprogramming

Youth Bio Therapeutics
Yamanaka Reprogramming

Cellular Reprogramming

Sources

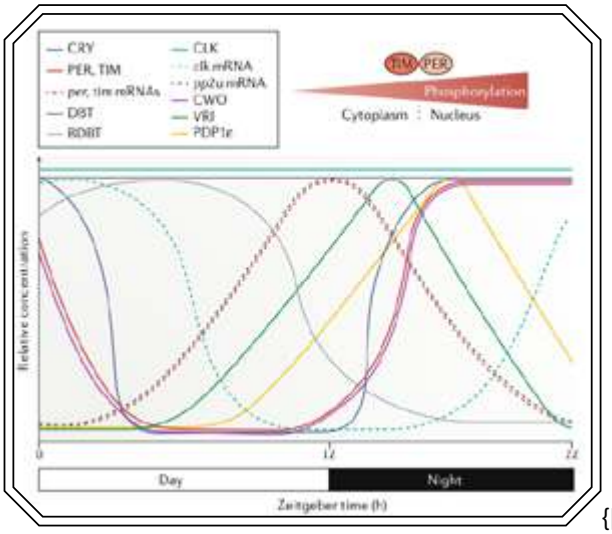
[CDP1] Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Takahashi and Yamanaka. 2006.
[CDP2] Sox2 and Oct-3/4: A Versatile Pair of Master Regulators that Orchestrate the Self-renewal and Pluripotency of Embryonic Stem Cells by Functioning as Molecular Rheostats. Rizzino. 2009.
[CDP3] Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Yamanaka et. al. 2007.
[CDP4] Pluripotent stem cells induced from adult neural stem cells by reprogramming with two factors. Scholer et. al. 2008.

Circadian Rhythm

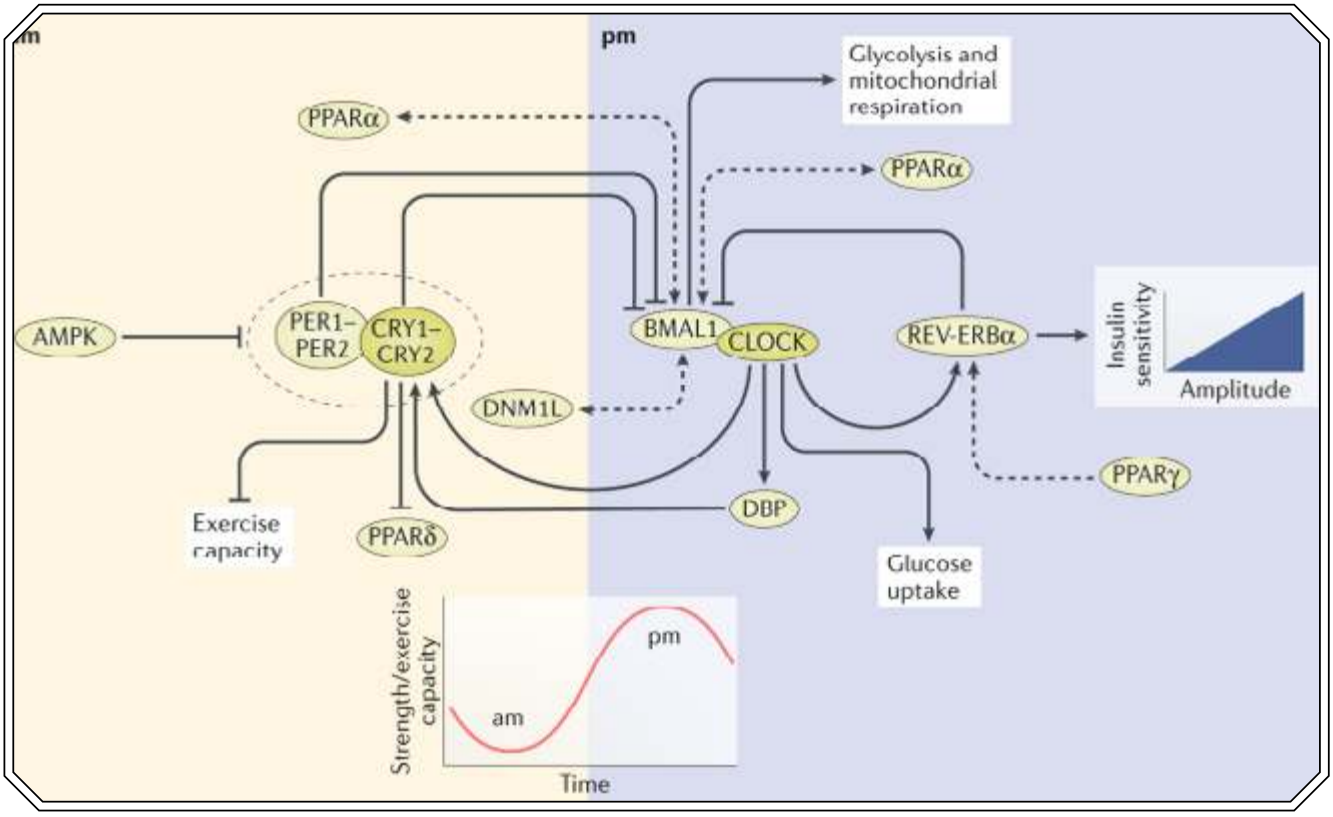
Introduction

Circadian rhythm refers to the daily biological cycles our bodies are entrained to. It is responsible for regulating blood pressure, sleep, body temperature, hormones, and metabolism. The most important and well known component of circadian rhythm is sleep, which in turn controls the regeneration cycle. As people age, their circadian rhythm becomes misaligned not just in relation to the environment but also between individual organs. This leads to a general breakdown in homeostasis which can create a death spiral.

The core genes associated with the actual circadian clock mechanism are CLOCK, CRY, PER, BMAL, REV-ERB, and ROR. These genes encode proteins which take part in self-regulating feedback loops.



{[CIRC22]}



{[CIRC17]}

Circadian Rhythm

The Next Big Step - Verify peripheral mechanisms

There is conflicting information as to what proteins and genes are actually associated with the circadian clock. The core appears well understood, but the peripheral mechanisms are not well understood and/or lack robust evidence.

Complicating the matter is that there appears to be at several high-level control schema for the circadian rhythm. There is the suprachiasmatic nucleus, which regulates the circadian rhythm via hormones. There is also organ-specific circadian rhythm which can operate independently of the SCN. Furthermore, testosterone and estrogen levels can affect daily rhythms. Testosterone also declines with age.

Sirtuins play a role in the circadian clock - which isn't as weird as it sounds. The CLOCK protein has a histone acetyl transferase. Methyltransferase proteins are also involved in the process - the entire process seems to be deeply intertwined with epigenetic modification. Here we have a rhythmic acetylation/methylation mechanism that can malfunction and is also capable of being organ or tissue specific. It breaks down over time and is associated with aging. To what degree is this associated with methylation clocks?

Food also entrains the circadian rhythm. This has been evident almost since the circadian clock had been established. However, relatively recently in 2001 food entrainment was linked to NAD+ metabolism [CIRC20].

There are various degrees of confidence for all of these associations and the conclusions they imply. What is clear is that understanding the extent to which the circadian clock interacts with other systems is a pressing question and one which, when fully elucidated, will yield tremendous results.

Circadian Rhythm

Potential Impact - How will this affect us?

Idea Risk: M

The field of biology has been piecing together molecular mechanisms of cell function for many decades. However, the process is costly and slow, and many mistakes are made along the way. The circadian rhythm appears to be hooked into most cellular processes and as such will require a lot of effort to map out its affect on the body.

Yield Potential: A

Correctly identifying and understanding the complete circadian mechanism could lead to a new solution for sleep that does not create the sort of side effects seen in current sleeping pills. It was estimated that the cost of hypnotics to Medicare in 2015 was ~$31 billion [CIRC18]. Benzodiazepines, a type of sleeping pill, is associated with ~50% increased risk of contracting pneumonia and pneumonia death [CIRC19]. By improving or possibly eliminating sleeping medications we may save vast amounts of lives and resources. It would overturn an entire industry and probably alter the way we sleep.

Future Possibilities: A

Our normal circadian cycle is based on a completely arbitrary condition - the speed at which our planet rotates relative to the sun. Because of this, our sleep/wake cycle is entrained to 24 hours, but we have no way of knowing how efficient this is for regeneration. The regenerative cycle occurs during sleep, but who is to say that a 8 hour regenerative cycle and 16 hour wake cycle is the best for longevity? How do diurnal animals differ from nocturnal animals in terms of regeneration? Radically altering the circadian rhythm may produce a massive life extension effect - but it first requires that we understand the mechanism completely.

Circadian Rhythm

Timeline of Circadian Rhythm Research

1800

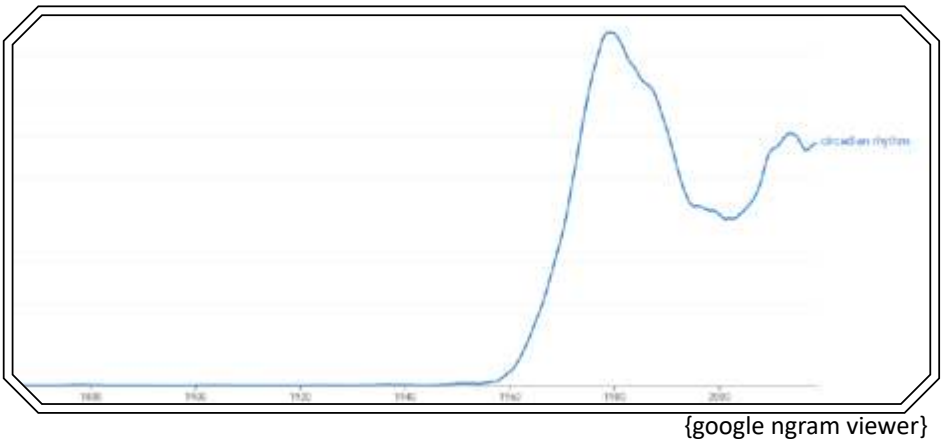
350BC – Androsthenes describes diurnal leaf movements [SOURCE UNAVAILABLE]
1729 – First record of circadian oscillation [CIRC1]
1832 – Chloral Hydrate discovered [CIRC12]
1864 – Barbituates synthesized
1896 – Experiments on sleep
1918 – 24 hour pattern observed even in absence of light and temperature changes
1951 – Methaqualone synthesized [SOURCE UNAVAILABLE]
1954 – Glutethimide synthesized [CIRC13]
1955 – Benzodiazepine synthesized [CIRC14]
1959 – Circadian coined [SOURCE UNAVAILABLE]
1965 – Food associated with circadian entrainment [CIRC21]
1971 – Period gene discovered [CIRC2]
1973 – Frequency gene discovered [CIRC6]
1978 – National Institute on Aging initiative targeting sleep changes and aging
1984 – Zolpidem [CIRC15]
1989 – Rev-erb alpha discovered [CIRC9]
1994 – Timeless gene discovered [CIRC7]
1994 – ROR alpha discovered [CIRC10]

1900

1994 – Clock gene discovered [CIRC5]
1996 – Cryptochrome gene discovered [CIRC8]
1997 – BMAL1 (ARNTL) gene discovered [CIRC11]
2001 – Food circadian entrainment linked to NAD+ [CIRC20]
2003 – Ramelteon [CIRC16]
2013 – Glymphatic system discovered [CIRC4]
2013 – Glymphatic system associated with sleep cycle [CIRC3]

2000

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Antagonistic Pleiotropy
Hallmarks of Aging: Altered Intercellular Communication
Pillars of Aging: N/A

Circadian Rhythm

Relevant Organizations: Who is working on this problem?

Center for Circadian Biology UCSD
Circadian Research Hub

Lipton Lab at Harvard
Circadian Rhythm Research

Refinetti Lab
Circadian Rhythm Research

Circadian Lab at Stanford
Circadian Rhythm Research

Sleep and Chronobiology Lab at Boulder
Chronobiology Research

Colwell Lab at UCLA
Circadian Rhythm Research

Sehgal Lab at UPenn
Circadian Rhythm and Aging Research

Wallace Mendelson
Sleeping Pill History

Schmitt Lab at University of Wyoming
Circadian Rhythm Research

Hastings Lab at Cambridge
Circadian Rhythm Research

Circadian Rhythm

Sources

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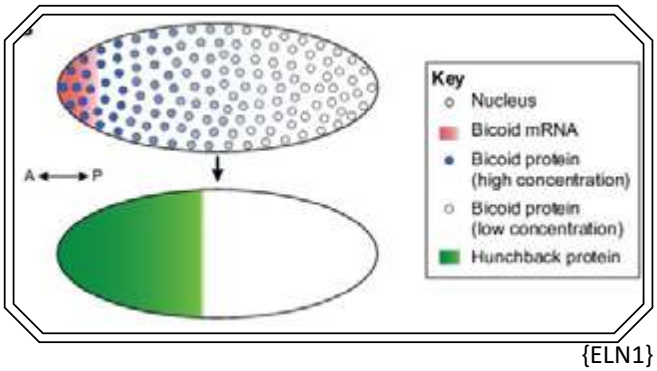
[CIRC2] Clock mutants of drosophila melanogaster. Konopka, Benzer. 1971.
[CIRC3] Sleep drives metabolite clearance from the adult brain. Xie et. al. 2013.
[CIRC4] Garbage truck of the brain. Nedergaard. 2013.
[CIRC5] Mutagenesis and mapping of a mouse gene, clock, essential for circadian behavior. Vitaterna et. al. 1994.
[CIRC6] Isolation of circadian clock mutants of neurospora crassa. Feldman, Hoyle. 1973.
[CIRC7] Loss of circadian behavioral rhythms and per RNA oscillations in the drosophila mutant timeless. Sehgal, Price, Man, Young. 1994.
[CIRC8] Similarity among the drosophila 6-4 photolyase, a human photoylase homolog, and the DNA photoylase-blue-light photoreceptor family. Todo et. al. 1996.
[CIRC9] A novel member of the thyroid-steroid hormone receptor family is encoded by the opposite strand of the rat c-erbAa transcriptional unit. Lazar, Hodin, Darling, Chin. 1989.
[CIRC10] Isoform-specific amino-terminal domains dictate DNA-binding properties of RORa, a novel family of orphan hormone nuclear receptors. Giguere et. al. 1994.
[CIRC11] Characterization of a subset of the basic-helix-loop-helix-PAS superfamily that interacts with components of the dioxin signaling pathway. Hogenesch et. al. 1997.
[CIRC12] Ueber die Zersetzung des Alkohols durch Chlor. Liebig. 1832.
[CIRC13] 3-Disubstituted Dioxopiperidines and the Manufacture thereof. Tagmann and Hoffmann. 1954.
[CIRC14] Quinazoline 3-Oxide Structure of Compounds Previously Described in the Literature as 3.1.4-Benzoxadiazepines. Sternbach et. al. 1959.
[CIRC15] Pharmacological profile of the imidazopyridine zolpidem at benzodiazepine receptors and electrocorticogram in rats. Langer et. al. 1985.
[CIRC16] The sleep-promoting action of ramelteon in freely moving cats. Miyamoto et. al. 2004.
[CIRC17] Circadian rhythms and exercise - resetting the clock in metabolic disease. Zierath and Gabriel. 2019.
[CIRC18] What do hypnotics cost hospitals and healthcare? Kripke. 2017.
[CIRC19] The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. Myles et. al. 2013.
[CIRC20] Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. McKnight et. al. 2001.
[CIRC21] Rats anticipation of diurnal and a-diurnal feeding. Stokes and Bolles. 1965.
[CIRC22] Molecular mechanisms and physiological importance of circadian rhythms. Axelrod et. al. 2019.

Electrodynamic Morphology

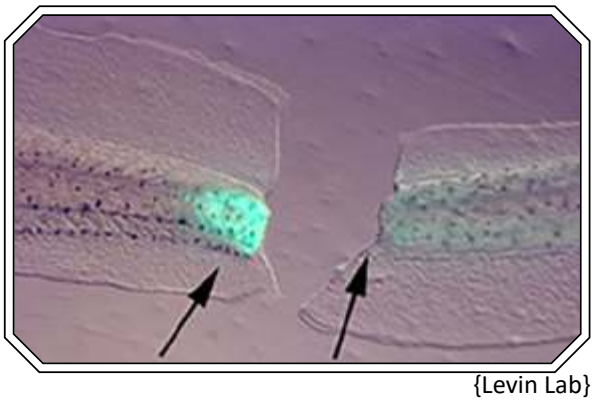
Introduction

Hormones are signaling molecules that travel through the bloodstream or other fluid portions of the body to direct cell activity at a distance. Another method of directing cell activity occurs via the bodies innate electrical signaling network.

Most cells are capable of sending and receiving electrical signals to their neighbors. These signals are modified as they cascade through cells, creating electrical gradients which can dictate cell behavior and gene expression. The electrical signaling network is thought to be responsible for developmental behavior in a wide array of species.



{ELN1}



{Levin Lab}

Above left: Morphogen gradient created by hormones. Above right: Electrical gradient created via electric signals.

This field is simultaneously old and yet relatively new. The electro-dynamic theory of life dates back to 1935 [ELG2] and yet comparatively little has been done with biological electrical signal gradients since then. The lab of Michael Levin appears to be the only lab working on this theory. Their progress controlling the morphology of planarians and frogs is interesting.

Electrodynamic Morphology

The Next Big Step - Bioelectric Map of Human Body

The general principle of electric gradients in living systems has been tested and validated. However, we do not understand the nature of these gradients in the human body. A map needs to be built describing the ideal electrical state of various tissues and organs. With that map we can then test electrical states and figure out deviations from the ideal then attempt to treat the problem.

Electrodynamic Morphology

Potential Impact - How will this affect us?

Idea Risk: X

It is unknown how a bioelectric map would be developed.

Yield Potential: B

The near term potential is likely limited by our ability to generate and measure electric fields in vivo.

Future Possibilities: A

In the long term, this technology plus an understanding of morphogens may lead to complete limb/organ regeneration and maybe even a solution to the vascularization problem of organ production.

Electrodynamic Morphology

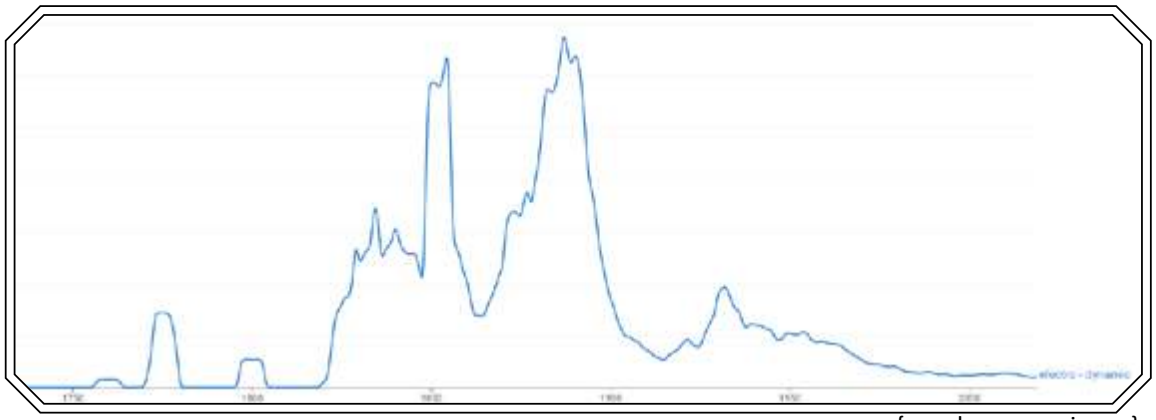
Timeline of Electrodynamics

1800

1935 - Electrodynamic theory of life [ELG2]
1952 - Morphogens postulated [ELG5]

1900

Word Usage Over Time



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Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Altered Intercellular Communication
Pillars of Aging: N/A

2000

Electrodynamic Morphology

Relevant Organizations: Who is working on this problem?

Levin Lab at Tufts University
Electrical signal network research

Zhao Lab at UC Davis
Electrical signals & wound healing

Bates Lab at University of Colorado
Ion channel influence on morphology

Harris Lab at Harvard Medical School
Ion channel influence on morphology

Electrodynamic Morphology

Sources

[ELG1] Studies of morphogens keep calm and carry on. Iber and Stathopoulos. 2013.
[ELG2] The electro-dynamic theory of life. Northrop and Burr. 1935.
[ELG3] Morphological coordination: a common ancestral function unifying neural and non-neural signaling. Levin et. al. 2020.
[ELG4] Bioelectric signaling: Reprogrammable circuits underlying embryogenesis, regeneration, and cancer. Levin. 2021.
[ELG5] The chemical basis of morphogenesis. Turing. 1952.

Epigenetics

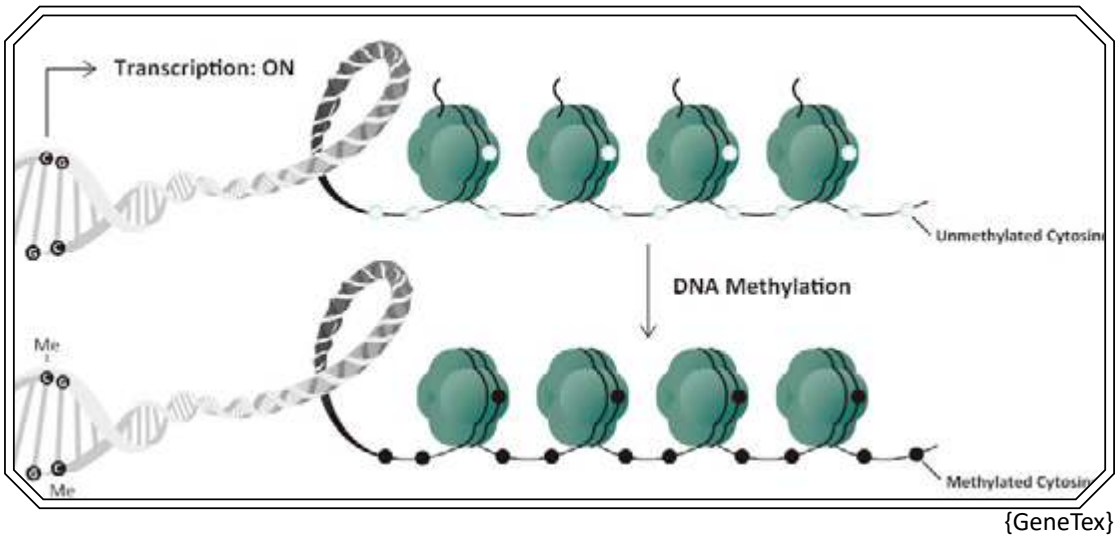
Introduction

The epigenome is the term referring to modifications to DNA which do not directly alter the nucleic acids. The main purpose of making these modifications is to turn various genes on or off, thereby altering cell function. This mechanism is present in both single and multicellular life, although the purposes differ. In single celled organisms, epigenetic modifications are used for DNA repair and to temporarily silence genes such as acid resistance. In multicellular organisms, these modifications can be permanent and are used to differentiate cells into specialized roles.

Methylation

DNA can be modified by attaching methyl groups to cytosine. This methylation of the nucleic bases C and A can alter expression of genes without changing the underlying DNA code. Histones, core proteins around which DNA is wrapped, can also be methylated. Methylation is associated with aging. If we can somehow control methylation regulation, it may be possible to slow down the aging process by stabilizing gene expression. Unlikely to yield biological immortality by itself, but control of methylation seems to imply control over DNA expression and DNA repair which has potential ramifications far beyond the gene.

Methylation potentially falls into every major category of aging philosophy. It could be a programmed death mechanism, where some kind of evolutionary pressure created a self-destruct mechanism to modify the regulation of methylation and slowly kill ourselves off. It could be antagonistic pleiotropy, where after a certain time the methylation process simply stops being useful yet continues to act because of a loss of reproductive selective pressure. It could also simply be a product of accumulating damage from the environment altering methylation sequences in random patterns. In prokaryotes, methylation is used for DNA repair.



{GeneTex}

Acetylation

The second major category of epigenetics associated with aging is acetylation. The concept of using sirtuins to alter the aging process was based on acetylation and de-acetylation of histones. Histones are small spheres used to organize DNA - by altering acetylation states of these spheres it is possible to silence sections of the genome.

Epigenetics

The Next Big Step - Mechanistic Understanding of Methylation Clocks

The current methylation clocks are useful for predicting biological age but have no therapeutic value.

By breaking apart the clock aggregations into smaller components, it may be possible to derive the underlying mechanisms for why methylation is so closely correlated with age. Once we know how these clocks are driven it may be possible to develop therapies targeting the root cause.

A good place to start would be the circadian rhythm. It drives rhythmic epigenetic alterations and is degraded/altered with age.

Epigenetics

Potential Impact - How will this affect us?

Idea Risk: X

While there are some ideas floating around, there is no clear frontrunner for the mechanism behind methylation clock progression.

Yield Potential: B

If we can find and target the underlying cause of age-related methylation changes, we may be able to strike a serious blow against aging. Unfortunately there's not much evidence for the scale of change we could effect by doing so. Once we start modifying clock speed and seeing lifespan alterations, we'll know roughly how much impact epigenetic control can have.

Future Possibilities: A

Control over methylation and acetylation means control over gene silencing. It may evolve into the ability to silence aberrant genes or give us another pathway for reprogramming cells from one type to another.

Epigenetics

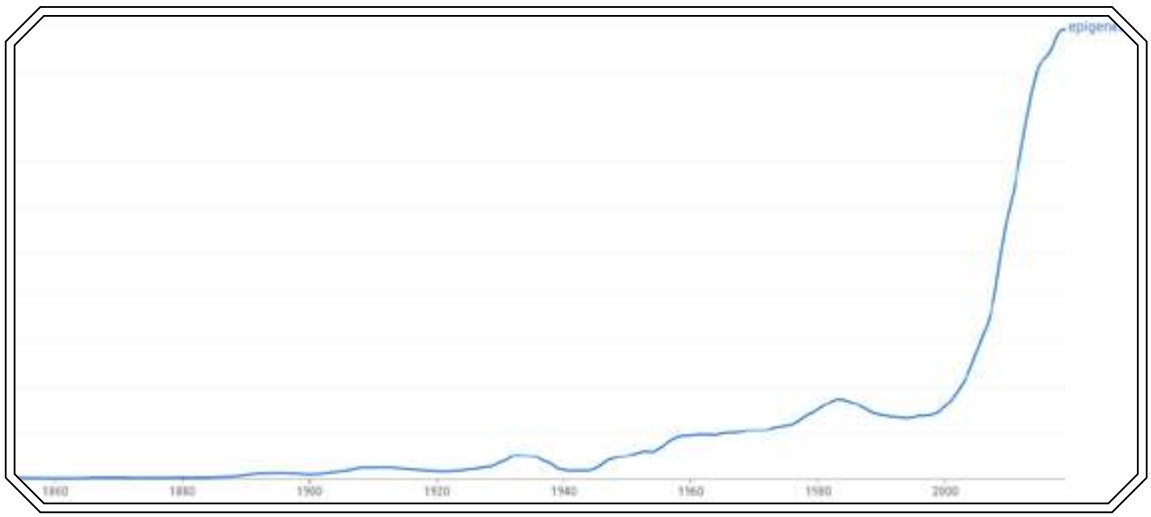
Timeline of Epigenetic Research

1800

1906 – NAD+ discovered [SOURCE UNAVAILABLE]
1938 – Vitamin precursors of NAD+ discovered [MET9]
1942 – Epigenetics [MET1]
1964 – Methylation and acetylation of histones [MET2]
1965 – Methylation of bacterial DNA [MET7]
1977 – Ethionine inhibits DNA methylation [MET3]
1980 – 5-azacytosine inhibits DNA methylation [MET4]
1982 – DNA methylation of adenine for DNA repair in prokaryotes [MET5]
1987 – Sirtuins discovered in yeast [MET10]
1992 – Bisulfite detection of methylation [MET6]
2000 – Sir2 discovered to be NAD+ dependent [MET11]
2013 – Methylation clock associated with chronological age [MET8]

1900

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Programmed Aging
Hallmarks of Aging: Epigenetic Alterations
Pillars of Aging: Epigenetics

2000

Epigenetics

Relevant Organizations: Who is working on this problem?

Levine lab at Yale
Epigenetic Clock Research

Horvath lab at Yale
Epigenetic Clock Research

Berger Lab at UPenn
Epigenetic Aging Research

Allard Lab at UC Los Angeles
Epigenetic Aging Research

Ideker Lab at UC San Diego
Epigenetic Aging Research

Baccarelli Lab at Columbia
Epigenetic Aging Research

Richards lab at Cornell
Epigenetics Research

Selker lab at University of Oregon
Epigenetics Research

Feinberg Lab at Johns Hopkins
Epigenetics Research

Sinclair Lab at Harvard
Former Epigenetics Focus

Trudiagnostics
Epigenetic Testing

Epimorphy MyDNAge
Epigenetic Testing

FOXO Technologies
Epigenetic Biomarkers

Trume
Epigenetic Testing

Epigenetics

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[MET8] DNA methylation age of human tissues and cell types. Horvath. 2013.
[MET9] The isolation and identification of the anti-black tongue factor. Elvehjem, Madden, Strong, Woolley. 1938.
[MET10] Four genes responsible for a position effect on expression from HML and HMR in Saccharomyces cerevisiae. Rine, Herskowitz. 1987.
[MET11] The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases. Landry et. al. 2000.

Gene Therapy

Introduction

Gene editing has been around for a while, and we now have multiple pathways for directly editing DNA in cells. Since DNA is the primary information storage mechanism of human cells, editing DNA affects the rest of the cell and by extension the tissues, organs, and body. Altering the genetic code is the most fundamental level of control over cell development.

CRISPR

CRISPR is a gene editing mechanism that bacteria use as part of an adaptive immune system to thwart foreign DNA insertion. It can be harnessed to efficiently target and replace DNA in vivo, opening the door to genetic therapy. By directly replacing DNA, it may be possible to control methylation and DNA damage using CRISPR, opening the door to biological immortality.

TALEN

TALEN (Transcription activator-like effector nucleases) are restriction enzymes that create a break in the DNA at a specific sequence. The natural repair mechanism of the cell is used in conjunction with TALEN to introduce new DNA at the break site. The TALEN mechanism was copied from an agriculturally pathogenic bacteria [TAL2].

AAV

Adenoviruses are pathogenic non-enveloped viruses that infect humans. Adeno-associated viruses are nonpathogenic viruses that can be used to infect human cells with engineered genes as a form of gene therapy. [GT14]

Cationic Liposomes

Lentivirus

Gene Therapy

The Next Big Step - Cell Targeting

There seems to be serious concern over the nature of the viruses and other methods used for gene therapy.

Each of the various gene editing techniques has their own pros and cons, but all of them suffer universally from a single problem - how to perform therapy in grown organisms that have diverse gradients of cells present near the target.

Editing the DNA of a fertilized egg leads to body-wide changes, but once an organism is already full grown the difficulty of doing gene therapy increases dramatically. Each cell must be modified. For tissues with constant regeneration such as the liver, this is less daunting because modifying stem cells eventually causes the fibroblasts to change as well. However, for organs that have slow turnover such as the heart or brain then the fibroblasts must be targeted directly. That means exponentially higher dosage of gene editing therapy, on the order of 1000x to 1 million x.

Gene Therapy

Potential Impact - How will this affect us?

Idea Risk: X/S

While gene editing is a mature and relatively safe technology, the ability to target specific cells is a gray area. Depending on the target, it may be child's play or next to impossible to deliver gene editing mechanisms to the right cells.

Yield Potential: A/B

Altering the genome affects the entire cell operation, and has downstream effects which can touch on many other longevity methods. Replacing DNA:
- Replaces epigenetic modifications of the target DNA sequence
- Can alter hormone production
- Can fix DNA mutations
- Can alter telomere length
- Can reverse cellular senescence

Future Possibilities: A

The first prenatal modifications have already been done, but were not well received. However, the future of gene therapy is in the womb. Less cells means easier and more reliable gene therapy.

Gene Therapy

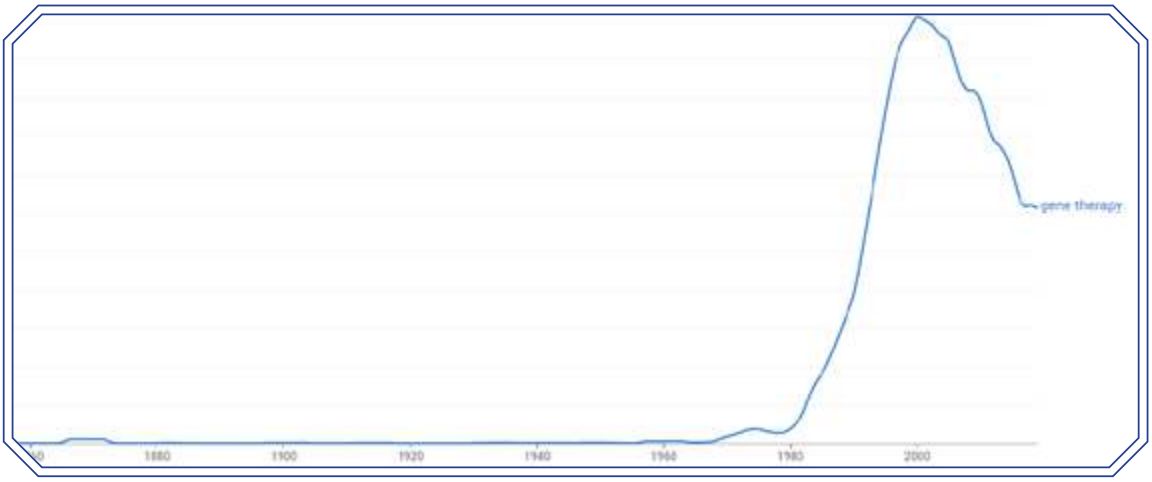
Timeline of Gene Therapy Development

1800

1953 – Discovery of adenoviruses [GT1]
1965 – Discovery of adeno-associated viruses [GT2]
1984 – AAV used to tranduce genes into human genome [GT3]
1993 – RNAi is discovered
1996 – First human clinical trial involving AAV [GT4]
2000 – Short Regularly Spaced Repeats described [GT8]
2001 – self-complementary AAV developed [GT5]
2002 – CRISPR acronym used, cas genes discovered [GT9]
2006 – Adaptive immune response hypothesis [GT10]
2007 – TALEN mechanism observed [GT6]
2007 – Adaptive immune response hypothesis proven [GT11]
2008 – CRISPR shown to target DNA [GT12]
2009 – TALEN mechanism reverse-engineered [GT7]
2013 – CRISPR/Cas9 used for targeted genome editing [GT13]

1900

Word Usage Over Time



{google ngram viewer}

2000

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Genomic Instability
Pillars of Aging: N/A

Gene Therapy

Relevant Organizations: Who is working on this problem?

Wyss Institute
Gene Therapy

Mahajan Lab at Stanford
Gene Therapy Research

Ghivizzani Lab at University of Florida
Athletics Gene Therapy Research

Gene Therapy Center at UNC
Gene Therapy Research

Mueller Lab at UMass
Gene Therapy Research

Gene Therapy Program at UPenn

Adverum
Gene Therapy for Macular Degeneration

Genequine
Gene Therapy for Musculoskeletal Disorders

Repair Biotechnologies
Gene Therapy for atherosclerosis

Gene Therapy

Sources

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[GT9] Identification of genes that are associated with DNA repeats in prokaryotes. Jansen, Embden, Gaastra, Schouls. 2002.
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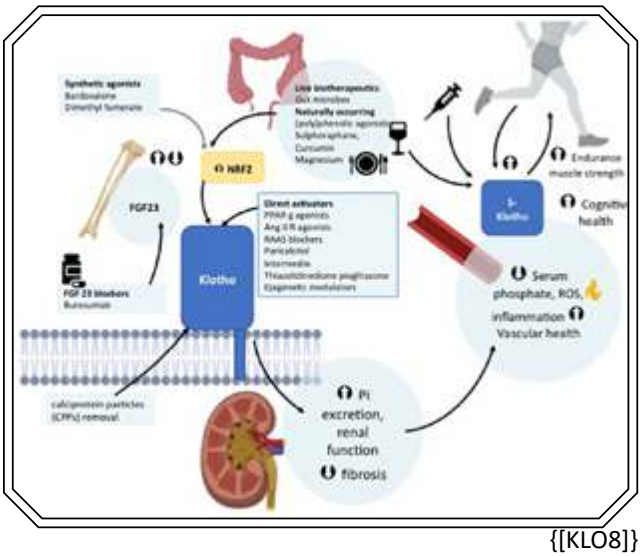
[GT13] Multiplex genome engineering using CRISPR/Cas systems. Cong et. al. 2013.
[GT14] Adeno-associated virus and the development of Adeno-associated virus vectors: A historical perspective. Carter. 2004.
[GT15] The c elegans heterochronic gene lin-4 encodes small rnas with antisense complementarity to lin-14. Ambros et. al. 1993.

Klotho

Introduction

Klotho is a protein that is associated with aging, or the lack thereof. There are two forms – soluble and membrane-bound. Soluble klotho is highly upregulated following exercise. It appears to act on the aging process through multiple pathways. By altering klotho expression, it may be possible to slow aging or even reverse it.

We know what the protein is, we know the gene that encodes it, and we know there are two forms. We know that klotho knockouts in mice create an extreme aging phenotype, and that klotho heterozygous mice exhibit signs of faster than normal aging. It is believed that the kidneys are responsible for producing most of the Klotho in the body, and that there is an intense association with FGF-23 [KLO6]. Skeletal muscle, and by extension exercise, appears to regulate Klotho expression [KLO4].



{[KLO8]}

Klotho

The Next Big Step - Determine the larger protein network

Right now there are many fragments of regulation and signaling data surrounding Klotho. Small pieces of how it behaves, how it interacts with tissues, and how it is regulated. What we lack is a complete picture of the entire network it is involved in.

I believe that Klotho behaves like one of the components of the circadian rhythm network - it is a critical piece of a larger system which regulates a generalized bodily function. For circadian rhythm, it would be sleep. In this case that function is regeneration. We do not have a map of the proteins and components involved like we do with circadian rhythm, and we need to get there.

Once we have that figured out, then we can move on to attempting to influence that mechanism by overclocking or underclocking it, by fixing broken components or tinkering with the underlying design.

Klotho

Potential Impact - How will this affect us?

Idea Risk: M

Investigation into protein interactions is tedious work but has been done many times before.

Yield Potential: C

Klotho, being a naturally occurring protein, has been subject to natural mutation for millennia. If altering klotho levels or altering the klotho protein could create dividends, we should have seen it by now. It is unlikely that simply altering klotho or its related proteins can improve health for normal people, however every system in the human body is subject to malfunction. Since we do not know the klotho super-mechanism, it is likely that the breakdown of that mechanism is responsible for diseases which we currently have no cure for. Figuring out klotho may lead to curing fringe diseases or possibly even common but misunderstood diseases.

Future Possibilities: C

As previously stated, any naturally occurring protein or molecule has seen every permutation and amplitude applied to it in almost every situation. It is highly unlikely that there is great therapeutic potential in klotho.

Klotho

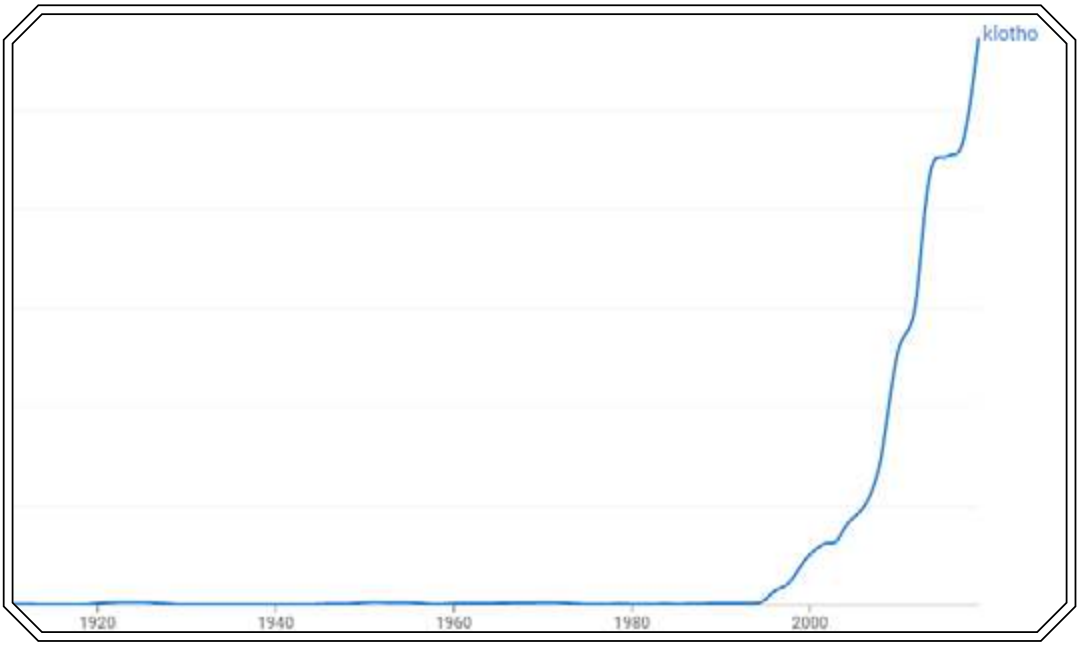
Timeline of Klotho discoveries

1800

1997 – Klotho discovered and associated with aging phenotype [KLO1]
1998 – Mouse Klotho structure [KLO7]
2005 – Soluble Klotho tied to insulin and IGF-1, acts as hormone [KLO2]
2006 – Bound Klotho tied to FGF-23 signaling [KLO3]
2010 – Soluble Klotho production associated with kidneys [KLO6]
2014 – Exercise increases klotho levels [KLO4]

1900

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Programmed Aging
Hallmarks of Aging: Altered Intercellular Communication
Pillars of Aging: N/A

2000

Klotho

Relevant Organizations: Who is working on this problem?

Klotho Therapeutics
Klotho therapy company

Ambrosio Lab at University of Pittsburgh
Klotho research

Ming-Chang Hu Lab at University of Texas
Klotho research

King lab at Creighton University
Klotho research

Dubal Lab at University of California San Francisco
Klotho research

Klotho

Sources

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[KLO2] Suppression of aging in mice by the hormone klotho. Kurosu et. al. 2005.
[KLO3] Klotho converts canonical FGF receptor into a specific receptor for FGF23. Urakawa. 2006.
[KLO4] Skeletal muscle as a regulator of the longevity protein, klotho. Avin et. al. 2014.
[KLO5] The effect of nephrectomy on Klotho, FGF-23 and bone metabolism. Hryszko. 2017.
[KLO6] Klotho deficiency is an early biomarker of renal ischemia–reperfusion injury and its replacement is protective. Moe et. al. 2010.
[KLO7] Structure of the mouse klotho gene and its two transcripts encoding membrane and secreted protein. Nabeshima et. al. 1998.
[KLO8] Klotho, Aging, and the Failing Kidney. Shiels et. al. 2020.

Hormones

Introduction

Hormones are signaling molecules that control sexual maturation, sleep, and other functions in the body. They are the messengers of the chemical control system of the body. Aging alters the production of hormones, resulting in aberrant downstream behavior. Hormones may affect aging by antagonistic pleiotropy – it is possible that human growth hormone is beneficial early in life then becomes detrimental later in life. Control over growth, maintenance, and sexual maturity hormones may allow us to program our bodies to remain in a certain phase of life for an extended period of time or even indefinitely.

Hormone replacement started in the 19th century but really took off in the early part of the 20th century. It's development saw grafting of animal sex glands to humans, injecting humans with animal hormones, injecting humans with synthetic hormones, and altering hormone production in humans. Anatomically, the glands producing hormones in the human body are:

- **Hypothalamus** - While some people don't consider it a gland, the hypothalamus produces multiple hormones that control the pituitary gland. It's also involved in regulating many functions, including sleep-wake cycles, body temperature, and appetite. It can also regulate the function of other endocrine glands.
- **Pituitary** - The pituitary gland is located below the hypothalamus. The hormones it produces affect growth and reproduction. They can also control the function of other endocrine glands.
- **Pineal** - This gland is found in the middle of your brain. It's important for your sleep-wake cycles.
Thyroid - The thyroid gland is located in the front part of your neck. It's very important for metabolism.
- **Parathyroid** - Also located in the front of your neck, the parathyroid gland is important for maintaining control of calcium levels in your bones and blood.
- **Thymus** - Located in the upper torso, the thymus is active until puberty and produces hormones important for the development of a type of white blood cell called a T cell.
- **Adrenal** - One adrenal gland can be found on top of each kidney. These glands produce hormones important for regulating functions such as blood pressure, heart rate, and stress response.
- **Pancreas** - The pancreas is located in your abdomen behind your stomach. Its endocrine function involves controlling blood sugar levels.
- **Gonads** - responsible for the sex hormone testosterone and its derivative, estrogen.

From the perspective of the germ cell, the act of reproduction is equivalent to soma death. Once an organism reproduces, the immortal part of the organism passes on to a new soma. The survival pressure of natural selection on the previous soma tapers off, and it's slow degradation has little consequence to the new (recombinant, in the case of sexual reproduction) gene. Therefore, it makes sense that duration of sexual maturation would be closely tied to lifespan. Sexual maturation is controlled by sexual hormones – altering sexual hormone levels in the body may give us control over lifespan and by extension biological immortality. Sexual maturation is also controlled by growth rate over time, which is controlled by growth hormones.

Several hormonal thresholds exist – andropause, menopause, somatopause, and adrenopause. These hormonal thresholds can be considered 'failstates' that contribute to age-related decline of health for the human body.

Hormones

The Next Big Step - Unknown

Human growth hormone is where most of the attention is right now. Should talk to Greg Fahy to get more info on thymic regeneration via human growth hormone.

Hormones

Potential Impact - How will this affect us?

Idea Risk: M

Hormones in general are well understood. What is not well understood are specific dosages, dosage regimens, and dosage targets for longevity. Parsing out this data will take time and money but is technically possible.

Yield Potential: B

Unknown. Current hormone treatment does appear to have an impact on healthspan, but not much of an impact on lifespan. The value proposition states that healthspan is the thing that really matters, so hormone therapy does have an impact. Unfortunately, that impact is not measured yet. It likely will not be earth shattering, because hormone production and release are downstream of a lot of control mechanisms, and if altered hormone levels could lead to drastic changes in lifespan we would have seen it by now due to natural variation in hormone levels.

Future Possibilities: B

Similar logic to the above paragraph.

Hormones

Timeline of Artificial Organs

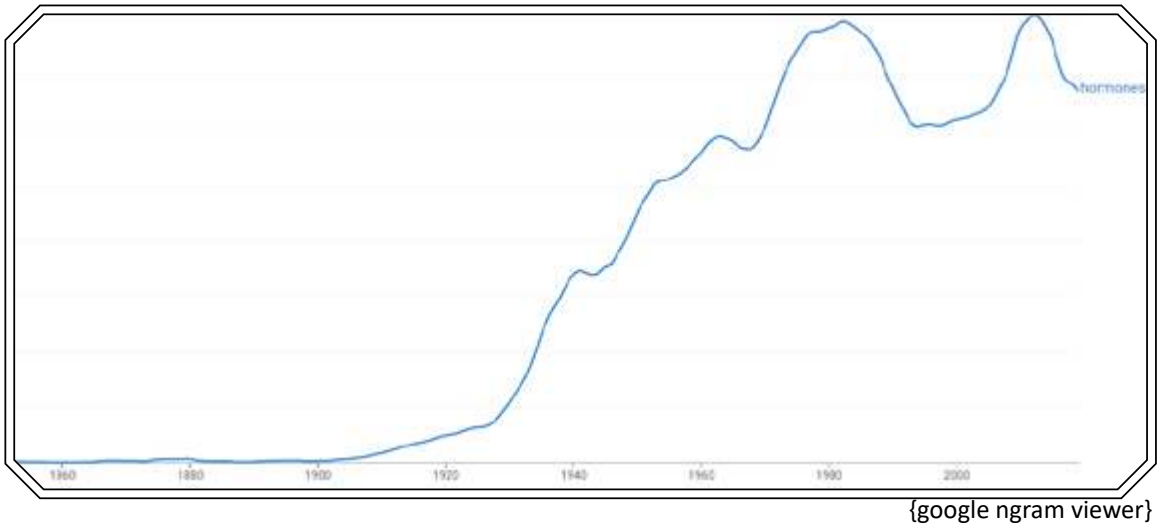
1800

1821 – Menopause coined [MENO1]
1889 – Testosterone likely discovered
1902 – Secretin, first documented hormone, discovered
1914 – Thyroxine isolated
1916 – Aqueous pancreatic extract (containing insulin) discovered
1927 – Thyroxine synthesized
1930 – Estrone (Theelin) discovered [HOR8]
1931 – Estriol (Theelol) discovered [HOR9]
1939 – Estradiol discovered [HOR10]
1956 – Human growth hormone isolated [HOR1]
1958 – Isolation of melatonin
1958 – HGH used as treatment on human [HOR2]
1972 – HGH biochemical structure identified [HOR3]
1978 – Human insulin produced in bacteria
1981 – HGH produced from e coli [HOR4]
1981 – HGH secretion reduced in adults [HOR6]
1990 – HGH attempted as anti-aging therapy [HOR5]

1900

1996 – Ames dwarf mice lacking GH live significantly longer [HOR7]

Word Usage Over Time



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2000

Relevant categorization

Trifecta: Antagonistic Pleiotropy
Hallmarks of Aging: Altered Intercellular Communication
Pillars of Aging: N/A

Hormones

Relevant Organizations: Who is working on this problem?

Greg Fahy

LEAD Lab at University of Wisconsin
Hormone Aging Research

Jacobs Lab at UC Santa Barbara
Hormone Aging Research

Womens Hormones Program at Brigham
Hormone Aging Research

Dixit Lab at Yale
Hormone Aging Research

Andrzej Bartke at Southern Illinois University
Hormone Aging Research

Pellecome
Hormone Replacement Therapy

BioTE Medical
Hormone Replacement Therapy

Hormone Therapy Centers of America
Hormone Therapy Association

Hormone Wizard
Hormone Replacement Therapy

Neurotune
Signaling Rehabilitation Therapy

Keren Therapeutics
Osteocalcin Hormone Modification

Hormones

Sources

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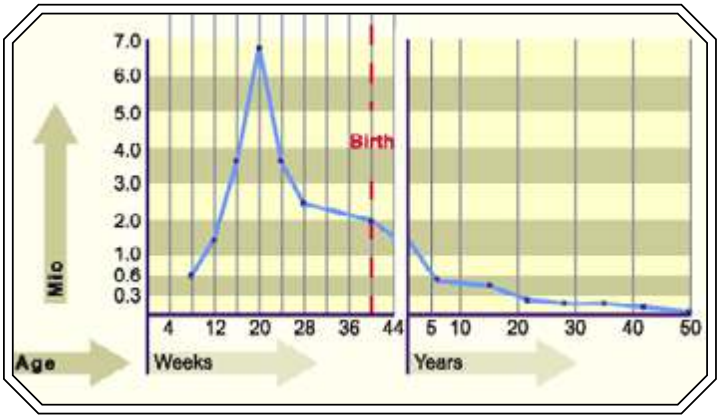
[HOR3] The molecular properties of human growth hormone. Aloj, Edelhoch. 1972.
[HOR4] Purified human growth hormone from e. coli is biologically active. Olson. 1981.
[HOR5] Effects of human growth hormone in men over 60 years old. Rudman et. al. 1990.
[HOR6] Impaired growth hormone secretion in the adult population. Rudman et. al. 1981.
[HOR7] Dwarf mice and the ageing process. Brown-Borg, Borg, Meliska, Bartke. 1996.
[HOR8] The preparation of the crystalline follicular ovarian hormone – Theelin. Veler, Thayer, Doisy. 1930.
[HOR9] Characterization of theelol. Thayer, Levin, Doisy. 1931.
[HOR10] An ovarian hormone. Allen, Doisy. 1923.

Menopause

Introduction

Menopause, and to a lesser extent andropause, are the best evidence for the theory of programmed aging. The prevailing theory for why menopause exists is the “grandmother hypothesis” - that it is useful for a tribe to have older, nonfertile (noncompeting) women involved in childcare or other tasks. Menopause is an off-switch that increases fitness at the species level by shutting down the reproductive system. There are issues with this theory, for instance if it applies to any tribal life then why do so few tribally organized species have menopause?



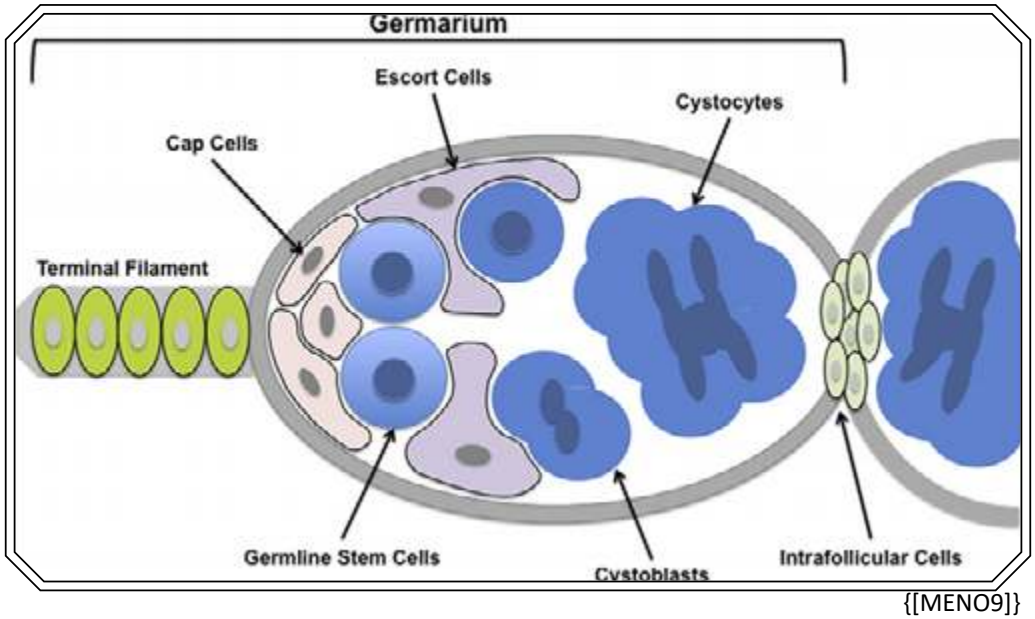
{embryology.ch}

Oocyte Attrition

Prior to birth, the oocyte cell count in human females rises and falls dramatically. Roughly 8 million oocytes are produced, of which ~80% die off prior to birth. The question as to how this happens is still up for debate but the observation of oocyte attrition is widespread enough to accept as being fundamentally true.

Oocyte Stem Cells

The controversial topic of oocyte stem cells was started in 2004 from the discovery that oocytes replenish themselves even in a postnatal ovary [MENO8]. The concept that “a woman is born with all the eggs she’ll ever have” had been an accepted biological truth prior to this. However, as far back as 1921 it was noted that ovaries have the ability to grow new oocytes in postnatal birds after mechanical removal of portions of the ovary [MENO7]. Thus, postnatal oocyte generation must exist to some extent but for some reason was overlooked for nearly a century.



{[MENO9]}

Menopause

The Next Big Step - Clearly define menopause

There are several theories about why menopause exists. The frontrunner appears to be the grandmother hypothesis, which implies that menopause allows for older non-reproducing females to stay part of a tribe and contribute to the fitness of the group. The issue with this hypothesis is that the only mammals which undergo menopause are humans and a small number of toothed whales. If the grandmother hypothesis is to be believed, then many other species would qualify for this kind of benefit.

It appears that, according to some scientists, nonhuman primates do undergo menopause if it is defined slightly differently [MENO4]. The lack of rigorous definition is reducing our ability to understand this phenomena, and is probably the biggest obstacle for the field right now. We need to know how many species are capable of reproductive senescence. Doing so may alter our hypothesis and improve our understanding of the true nature of menopause, leading to breakthroughs by studying species previously dismissed as not being relevant to the field.

The core of the issue is that menopause literally means a pause in menstruation. Many primates do not menstruate, even if they do experience reproductive senescence. The real question is how many species experience a triggered, controlled cessation of reproductive senescence vs. species that simply experience a decline due to lower fitness until reproduction is impossible.

Menopause may be a product of oocyte attrition that simply does not stop. The logarithmic destruction of oocytes in pre- and post-natal humans suggests that the oocytes are the cause of their own demise. We may want to study how oocyte attrition varies in different species - especially between species that lay eggs vs. species with live birth.

Menopause

Potential Impact - How will this affect us?

Idea Risk: S

The investigation of generalized self-imposed reproductive senescence involves mostly a bunch of reading.

Yield Potential: B

Depending on the nature of menopause reversal, it may have an impact for those who are attempting childbirth at a late age or it may impact every single woman. Ideally the latter, as reversing the underlying mechanism of menopause should negate the health decline associated with this phenomena. Weight gain, increased visceral and subcutaneous abdominal adiposity, impaired glucose tolerance, hyperinsulinemia, hypertension, vasomotor symptoms, sleep disturbances, and fatigue are all associated with menopause [MENO4]. At least one company has already made some progress on the commercialization of reversing menopause.

Future Possibilities: B

I can't imagine much fundamental change to society if menopause gets completely solved. Women would simply menstruate longer, and men may retain testosterone levels for longer. That's about it. Not many fundamental, earth-shattering consequences.

Menopause

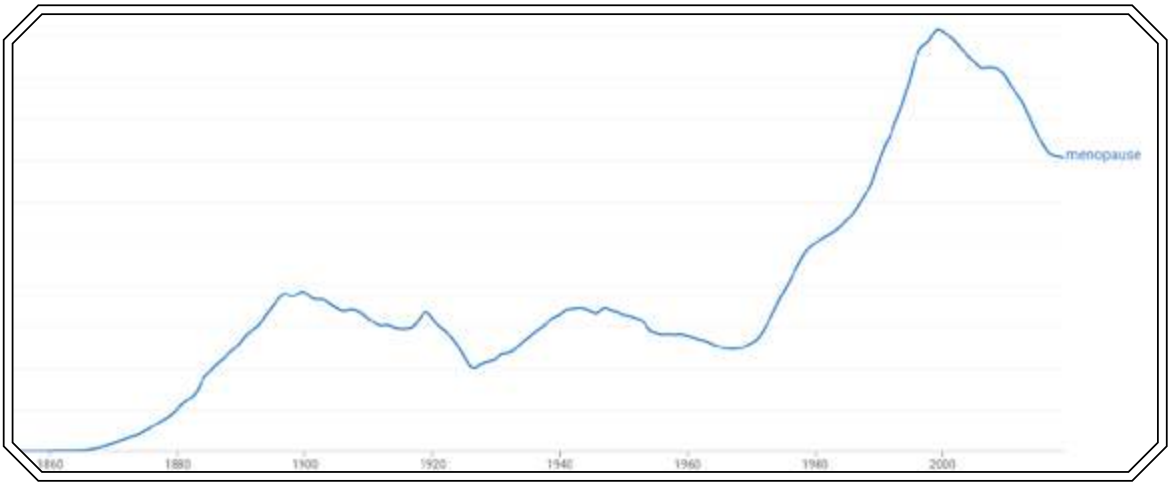
Timeline of Menopause

1800

350BC – Aristotle notes menstruation ceases at age 40 [SOURCE UNAVAILABLE]
1821 – The term “menopause” coined [MENO1]
1920 – Endocrine system mapped out [SOURCE UNAVAILABLE]
1930 – Menopause referred to as hormonal deficiency [SOURCE UNAVAILABLE]
1951 – An Unsolved Problem in Biology [SOURCE UNAVAILABLE]
1984 – Pilot whales observed to undergo menopause [SOURCE UNAVAILABLE]
1990 – Killer whales observed to undergo menopause [SOURCE UNAVAILABLE]
2007 – Bone marrow transplant rescues fertility in mice [MENO2]
2014 – Orangutan reported to undergo menopause [MENO5]
2015 – Inovium founded [SOURCE UNAVAILABLE]

Word Usage Over Time

1900



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Relevant categorization

Trifecta: Programmed Aging
Hallmarks of Aging: Stem Cell Exhaustion
Pillars of Aging: Stem Cells and Regeneration

2000

Menopause

Relevant Organizations: Who is working on this problem?

Inovium Labs
Menopause Reversal Therapy

Genesis Clinic in Athens
Menopause Reversal Therapy

Thurston Lab at University of Pittsburgh
Menopause Research

Menopause Research Group at UMass
Menopause Research

Menopause

Sources

[MENO1] De la menopause ou de l’age critique des femmes. Gardanne. 1821.
[MENO2] Bone Marrow Transplantation Generates Immature Oocytes and Rescues Long-Term Fertility in a Preclinical Mouse Model of Chemotherapy-Induced Premature Ovarian Failure. Lee et. al. 2007.
[MENO3] An Unsolved Problem in Biology. Medawar. 1952.
[MENO4] A qualitative assessment of health behaviors and experiences during menopause - a cross sectional observational study. Redman et. al. 2018.
[MENO5] https://www.bbc.com/news/world-europe-jersey-27913515
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[MENO7] Studies on the physiology of reproduction in the domestic fowl. Pearl and Schoppe. 1921.
[MENO8] Germline stem cells and follicular renewal in the postnatal mammalian ovary. Tilly et. al. 2004.
[MENO9] Ovarian germline stem cells - an unlimited source of oocytes? Hennebold and Hanna. 2014.

Senescence

Introduction

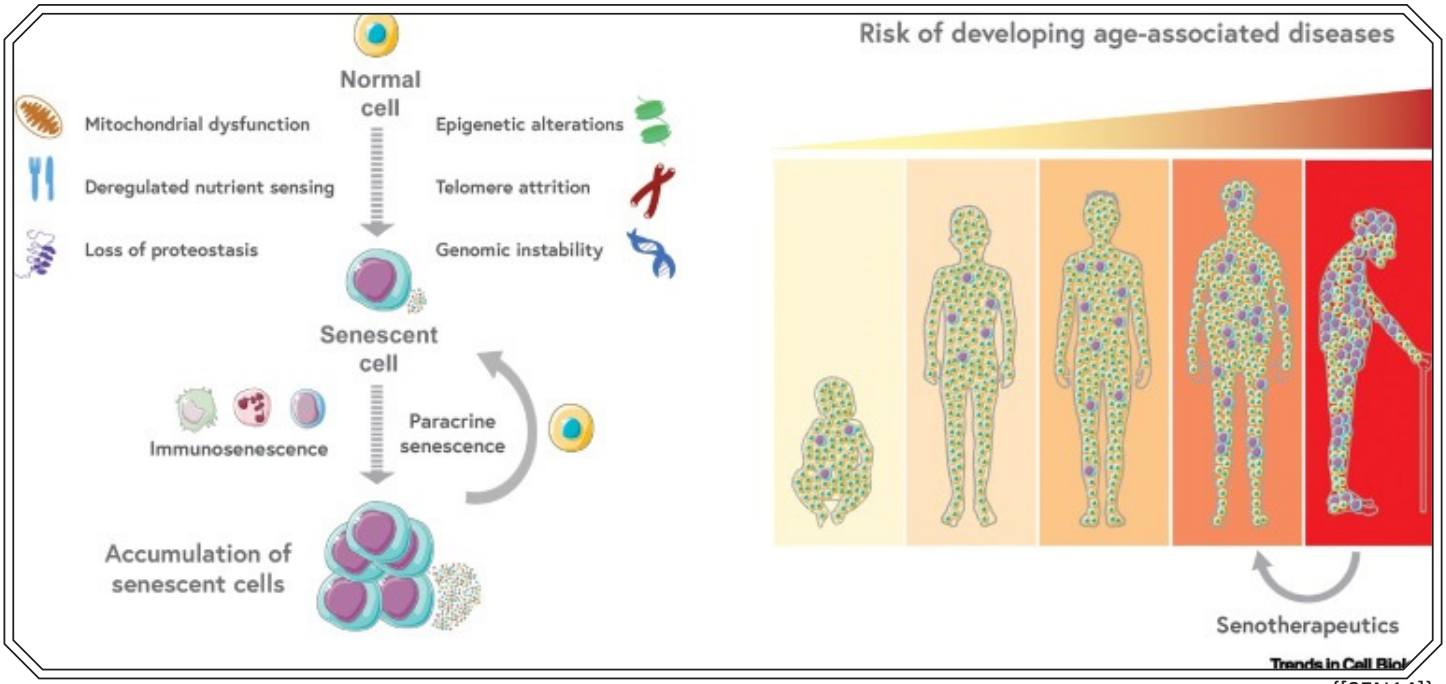
Senescent cells are cells which have ceased to divide but still maintain other functions. The origin of the idea of senescence in biology began in 1891 with Charles Sedgewick Minot [SEN1]. In his paper, he defined senescence as the aging of cells. Fast forward over a hundred years later, and biologists are claiming that senescence is the cause of cellular aging.

A partial redefinition of senescence occurred when Leonard Hayflick discovered that fibroblasts have a limit to cellular division in culture [SEN4]. The Hayflick Limit added a concrete definition to the state of senescence, and is the earliest description of the term that most people are aware of.

The senescent phenotype is diverse, and has no clear definition apart from the inability to divide. However, there are a few dominant traits that tend to align with most senescent cells. Expression of b-galactosidase and secretion of inflammatory proteins are widely considered hallmarks of senescent cells.

The immune system is responsible for removing senescent cells from the body. When the immune system fails, artificial removal becomes the only option. Senolytics is the term for therapies to selectively remove senescent cells from the body. A large industry is beginning to emerge surrounding senolytics.

Eliminating senescent cells is a great tool and a good idea, but some senescent cells are actually part of the normal development process. Uncontrolled removal of senescent cells may damage the body in ways we cannot predict. One difficult task for senolytics has been to differentiate between pathological senescent cells and benign or critical senescent cells.



{[SEN14]}

Senescence

The Next Big Step - Thymus Regeneration

The immune system is largely responsible for clearing senescent cells in a healthy individual. However, the immune system itself experiences senescence - termed immunosenescence. It is likely that once the immune system goes, the rest of the body goes as well.

Regenerating the immune system can be accomplished by regenerating the thymus, one of the key immune/endocrine organs. One strategy is to spike the body with high doses of platelets and human growth hormone.

On the topic of senolytics - one dangerous conclusion from using senolytics is how it is applied to human society as a whole. Systems of organization tend to repeat themselves at different scales. What is true for the human body is often true for the human race. If people are like cells - differentiated, specialized into tasks, passing through reproductive and senescent phases - then what does a solution of senolytics for health maintenance imply? It implies that removal of old people is the key to a healthy nation or species. The old account for the vast majority of health expenditures while providing relatively little value due to retirement. An overabundance of senescent people drags down a tribe. If one looks, one will discover this view has been discovered and acted upon repeatedly throughout history in one form or another. This is one reason I do not see senolytics as being a good solution for aging.

The second reason is that senolytics do not solve the underlying problem. It's akin to burying nuclear waste. Sure, you can get rid of it in the short term, but you aren't solving the issue as to why it gets generated in the first place and the processes responsible will only create more and more of it until even senolytics are no longer a viable solution.

Senescence

Potential Impact - How will this affect us?

Idea Risk: X

Initial trials appear to be having an impact, but the metrics for success were internally defined and may not line up with what most people define as “anti-aging”. Nobody has succeeded at regenerating the immune system so far, so it is unknown whether it is possible to do so.

Yield Potential: A

Removal or regeneration of senescent cells has impacts for almost all age-related diseases. Simply reversing immunosenescence would solve most age pathologies. It is likely that solving immunosenescence would get us most of the way toward curing aging, given how instrumental the immune system is for maintaining health.

Future Possibilities: A

See Above.

Senescence

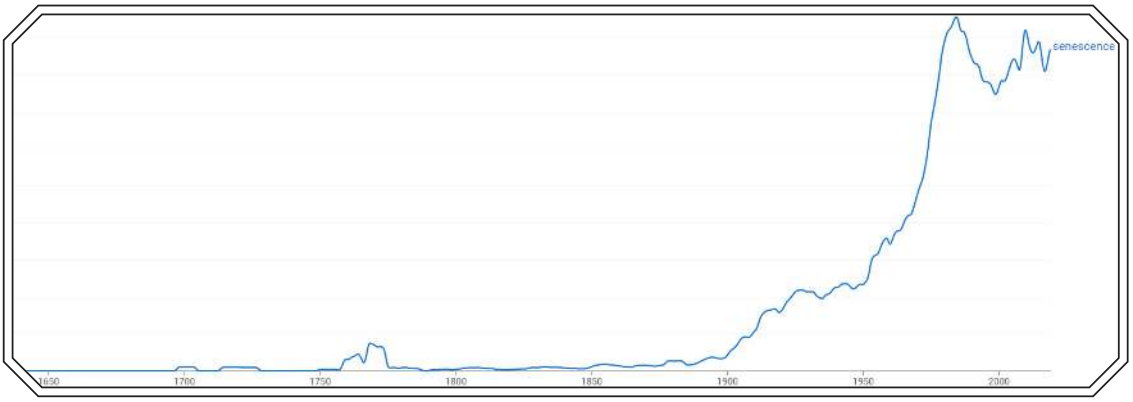
Timeline of Senescence Research

1800

1857 – Quercetin discovered [SOURCE UNAVAILABLE]
1891 – Senescence defined [SEN1]
1894 – Fisetin discovered [SEN11]
1961 – Hayflick limit established [SEN4]
1983 – Glanciclovir used for anti-herpes purposes [SEN6]
1985 – IL-6 (BSF2) discovered [SEN8]
1993 – P16 identified [SEN2]
2004 – Dasatinib discovered as leukemia drug [SEN10]
2008 – Senescence-associated secretory phenotype defined [SEN5]
2011 – Clearance of senescent cells delays aging [SEN3]
2013 – Glanciclovir used to selectively kill senescent cells [SEN7]
2015 – Dasatinib and Quercetin used to selectively kill senescent cells in mice [SEN9]
2016 – Navitoclax used to selectively kill senescent human cells in vitro [SEN13]
2017 – Fisetin used to selectively kill senescent human cells in vitro [SEN12]

1900

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: Cellular Senescence
Pillars of Aging: Stem Cells and Regeneration

2000

Senescence

Relevant Organizations: Who is working on this problem?

Unity Biotechnology
Senolytics company

Deciduous Therapeutics
Senolytics company

Robert and Arlene Kogod Center on Aging
Senescence research

Berger Lab at UPenn
Senescence Research

Campisi Lab at Buck Institute
Senescence Research

Cox Lab at University of Oxford
Senescence Research

Sempowski Lab at Duke
Immune Senescence Research

Zhang Lab at UMass Medical School
Senescence Research

Sedivy at Brown University
Sensecence Research

Bhushan Lab at UCSF
Immunosenescence Research

Senisca
Senescent Cell Regeneration

Senisca
Senescent Cell Regeneration

Cleara
Senescent Cell Clearance

Rubedo Life
Senescent Cell Clearance

Oisin Bio
Senescent Cell Clearance

Siwa Therapeutics
Senescent Cell Clearance

Dorian Therapeutics
Senescent Cell Blocking

Senescence

Sources

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[SEN4] The serial cultivation of human diploid cell strains. Hayflick, Moorhead. 1961.
[SEN5] Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. Coppe et. al. 2008.
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Telomeres

Introduction

In many bacteria, DNA is stored as a circle. In human cells, our DNA is organized into X shaped bundles called chromosomes. The nature of this organization means that unlike bacteria, human DNA has two ends. These endpoints are vulnerable to degradation each time the cell divides.

Our double stranded DNA is not completely symmetrical. The orientation of the phosphate backbone is in opposite directions on either side of the strand. This causes asymmetry when copying DNA due to how the proteins attach new DNA segments - one side will lag behind the other. When a cell duplicates its DNA in preparation for division, a small section of DNA at the ends gets lost.

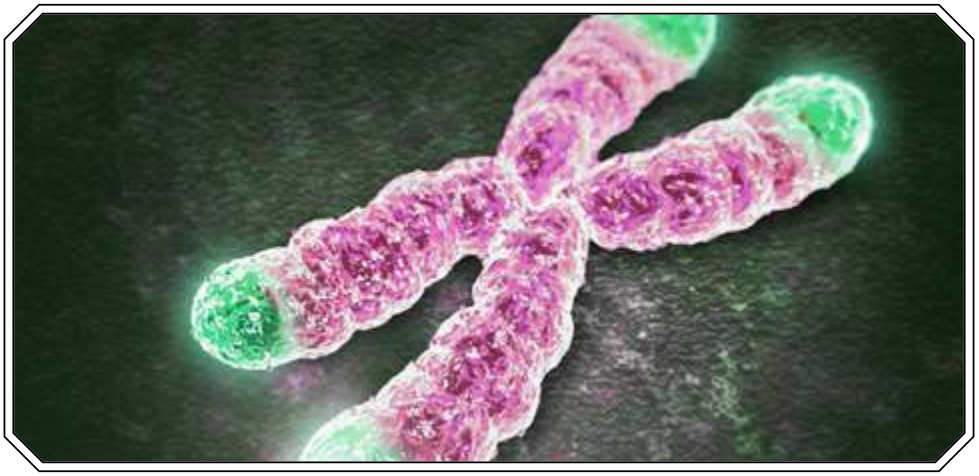
Telomeres are chromosomal endcaps that compensate for this loss of DNA. A large number of TTAGGG repeats makes up the telomere. Losing these repeats doesn't impede the cells normal operation. However, after a certain number of divisions the telomere gets extremely short and triggers a senescent state in the cell, preventing further cellular division. This is known as the Hayflick Limit.

Telomerase is an enzyme that extends the lengths of telomeres, and is present in human stem cells. It adds on TTAGGG repeats to the end of chromosomes after duplication, restoring the full length of the telomere and preventing the senescent state from triggering.

The question then is why does this happen in stem cells and not all cells. It is theorized that telomeres are an anti-cancer mechanism to prevent fibroblasts and other differentiated cells from becoming a threat to the body. For example, in the skin the fibroblasts are exposed to chemical and UV stress which causes mutations which can lead to cancer. The stem cells are deeper under the skin and experience less stress. By limiting cell division of the at-risk cells, the threat of cancer is reduced as these cells have less chance to metastasize.

This point is extremely important and bears repeating - *if you are healthy, telomerase is already active in your pluripotent stem cells*. If one attempts to activate telomerase in the body in an unspecified manner, it is likely that the risk of cancer will significantly increase.

It is possible that aging reduces the stem cells ability to elongate telomeres by reducing telomerase activity. Targeting stem cells for some kind of telomere regeneration could potentially yield benefits for longevity.



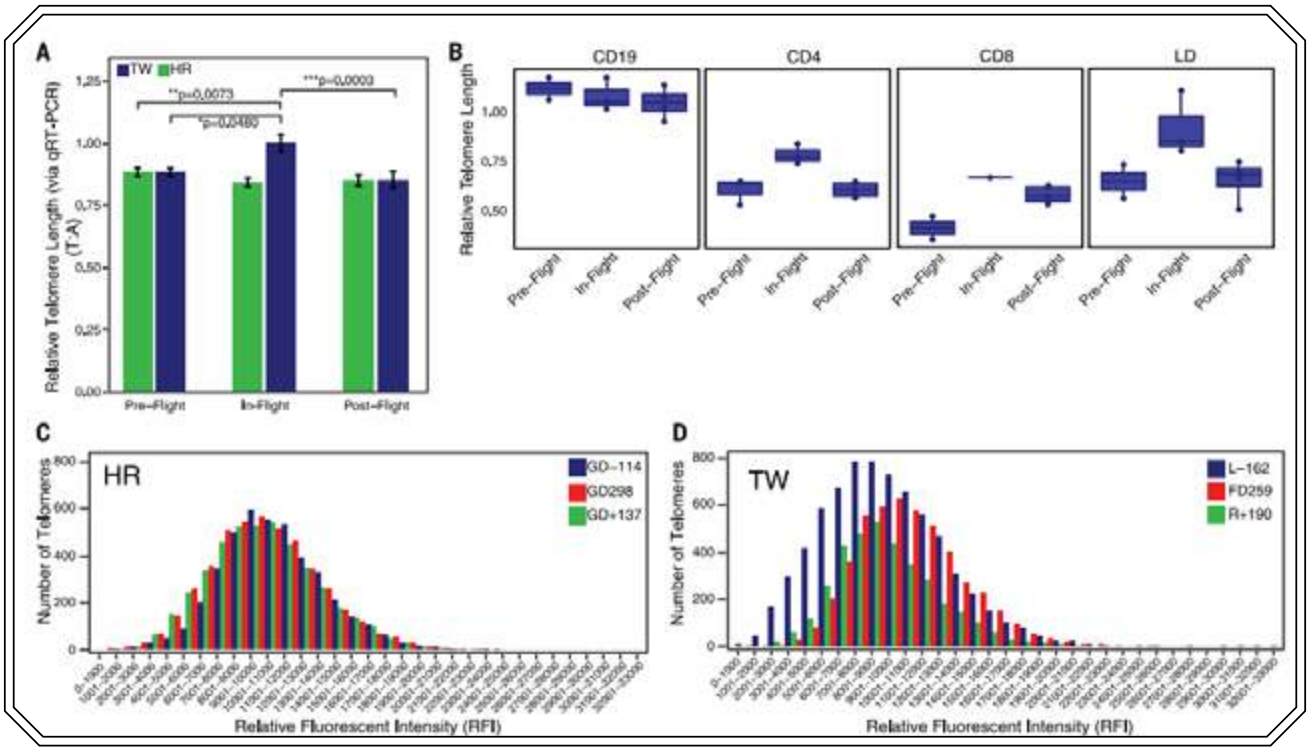
{Stanford}

Telomeres

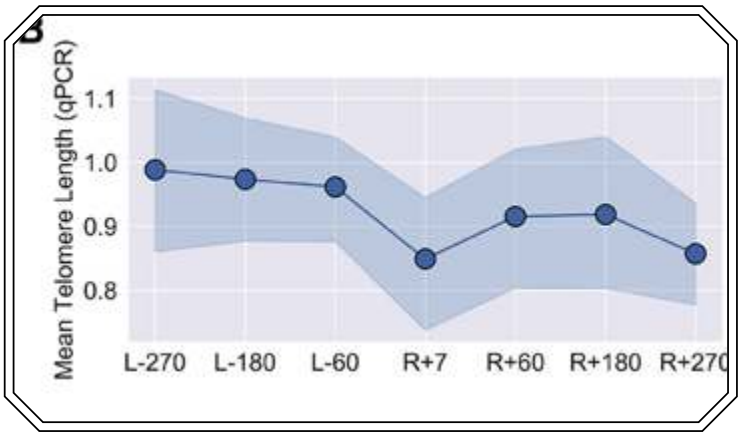
The Next Big Step - Baseline Telomere Flux

Telomere lengths fluctuate massively even in perfectly healthy individuals [TELO5]. Nobody has yet measured this fluctuation on purpose, but there do exist tables of data from which this can be inferenced. Any intervention targeting telomeres cannot give reliable results because there is no way to know whether the outcome is a product of the therapy or natural telomere fluctuation. The first widely public telomere therapy from Bioviva gave results that were within the bounds of normal telomere fluctuation from other experimental data.

We should accurately measure telomere flux over time to get baseline information. Another useful set of data would be to measure how telomere flux shifts with aging.



{NASA twins study data [TELO5]}



{Telomere spaceflight data [TELO11]}

The data above and to the left show how much fluctuation and variability there is in the current telomere length measurement schema.

Telomeres

Potential Impact - How will this affect us?

Idea Risk: S

Measuring telomeres is a standard procedure.

Yield Potential: B

Understanding and controlling telomeres lets us target cancer and senescence better. There is already one company targeting cancer using telomere therapy but they wish to not be associated with the longevity space. Getting accurate and reliable telomere data is the first step toward telomere therapies, which can be used against all types of cancer, likely with less side effects than chemotherapy or radiation.

Future Possibilities: C

It is unlikely that manipulation of the telomere mechanism will lead to radical life extension. At best, it could be used to cure some diseases and incrementally improve some lives.

Telomeres

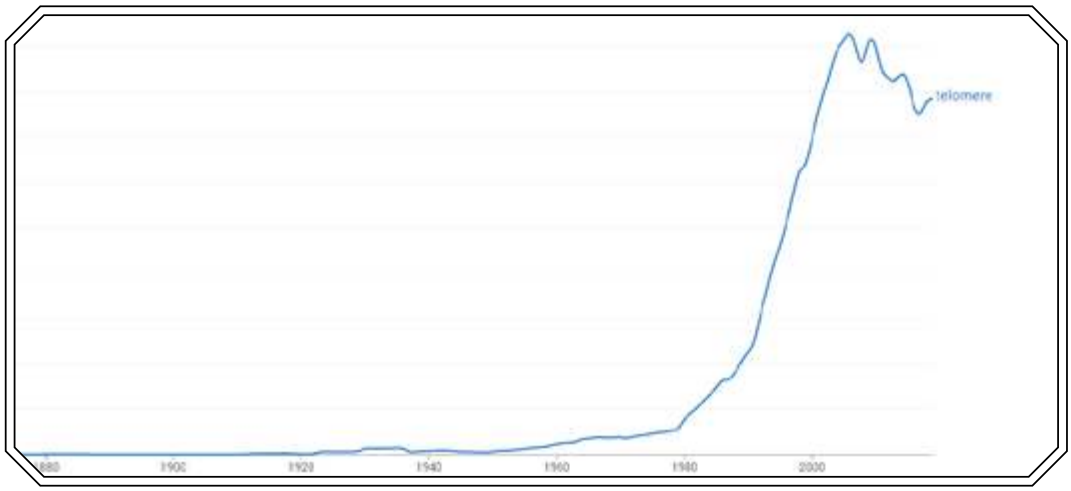
Timeline of Telomere Research

1800

1912 – Chick heart fibroblast cells grown in culture for 34 years, not reproducible[TELO1]
1961 – Senescence of skin fibroblast cells discovered after 40-50 divisions [SEN4]
1978 – Telomeres discovered [TELO2]
1984 – Telomerase discovered [TELO3]
1990 – Telomere measurement, telomeres shorten during aging [TELO4]
1997 – hTRT protein discovered [TELO6]
1998 – hTRT induced in human cells, replicative lifespan increases [TELO7]
2016 – First gene therapy experiment to lengthen telomeres [TELO8]

1900

Word Usage Over Time



{google ngram viewer}

Relevant categorization

Trifecta: Programmed Aging
Hallmarks of Aging: Telomere Attrition
Pillars of Aging: Stem Cells and Regeneration

2000

Telomeres

Relevant Organizations: Who is working on this problem?

Blasco Lab
Telomere Research

Telomere Therapeutics
Telomere therapy company - unlisted

Bioviva
Telomere therapy company - pivoted away from Telomeres

Life Length
Telomere length testing

Sierra Sciences
Libella Gene Therapeutics
Defytime Science
Telomere therapy companies started by Bill Andrews

Telocyte
Telomere therapy for Alzheimers

Geron
Telomerase anticancer therapy company

TAsciences
Supplement sales

Telomere Diagnostics
Telomere length testing

Telomeres

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Cryonics

Introduction

Cryonics is a heated term. In this report we will combine a lot of cryogenics/cryonics into the same category - but we should mention that there are responsible people and irresponsible people in this space.

Cryonics is a method for body preservation born out of the observation that freezing something keeps it from changing. By freezing the human body or - more pragmatically - organs, we can 'pause time' and extend lifespan.

Freezing organs would let us store them for longer. One known problem with freezing living things is that water expands when frozen, due to the formation of ice crystals. Water expansion causes cell rupturing and protein destruction. The University of Wisconsin came up with a cold storage solution in the 1980's which was hailed as a breakthrough, extending organ storage capability. The breakthrough was an extension of storage time from several hours to roughly a day. For robust, reliable organ replacement it is likely we will need storage capability of years or decades. Clearly, our current technology is inadequate by several orders of magnitude.

{University College London}

Cryonics companies - such as Alcor, Cryonics Institute, and CryoRus - have begun freezing human bodies and heads in an attempt to preserve life until technology becomes available for reconstruction. I have no problem with the growing pains these organizations are experiencing due to legal or technical hurdles present in their pathway. However, there are several problems with body preservation which are not discussed openly. First, these companies are not doing any research into the thawing process. Second, they are mirroring ancient Egyptian mentality when it comes to body preservation. The Egyptians discovered a technology - embalmation - which potentially could preserve the body for people of the future to revive them. They used it extensively, operating under the logic that they were definitely going to die anyway so why not at least try to preserve themselves. They used the GDP of an entire nation to build pyramids which actually did do the job - they created a safe space for body storage for thousands of years. Unfortunately, scrambling the brain and pulling it out through the nose makes it difficult to resuscitate a human. Taking the lessons of the past into account, if cryonics companies find a way to passively store humans in extreme low temperature environments, it is more likely these people will be put into museums rather than revived. Which brings up the third point - without passive storage these companies need to be stable for an indefinite amount of time in order to maintain these bodies. Operating costs aside, companies in general are more frail than people and typically do not live even 50 years let alone the hundreds or thousands which may be required to wait for sufficient technological advancement. The Egyptians were able to store bodies for over two millennia and their plans still failed, and the fallout may have been trading away their geopolitical dominance by shunting production into life preservation rather than agriculture, research, military, or civil engineering.

Cryonics

The Next Big Step - Organ Vitrification

Freezing living cells is dangerous due to ice crystal formation. However, it has been known for decades that many insects are capable of surviving subzero temperatures and reviving successfully. This is because they use various forms of antifreeze mixed in with their bodily fluids to prevent the formation of ice crystals.

Vitrification is the official term for freezing water without forming crystals - converting it into a hard amorphous glass state. By mixing specific compounds with blood cells, the water in such cells freeze in place rather than forming ordered molecular structures. This is how frozen blood is stored, and often glycerol is the vitrification agent.

Tissues and cells have been vitrified successfully, but no whole human organ has been vitrified, thawed, and reimplanted into a human. The closest we have come is vitrifying a rabbit kidney - and that rabbit only lived 9 days after reimplantation [CRYO8].

Cryonics

Potential Impact - How will this affect us?

Idea Risk: X

There has never been a successful thawing of a vitrified human organ so far, much less a body.

Yield Potential: A

The current organ donor and transplantation network would benefit greatly from organ vitrification. For the financial impact on the way the system currently works, see the “Organ Replacement” section. It would revolutionize the fields of organ production and organ donation.

Future Possibilities: A

Freezing and resuscitating a human body is the long term goal, although it is questionable how much utility that direct advancement will provide. By the time we get to that point, we may not need it. More likely, the technology discovered along the way will be much more valuable in tangential applications such as perfect food preservation, efficient cooling, and rapid thawing techniques. Imagine a low cost household appliance that can evenly defrost a steak in thirty seconds without accidentally cooking the outside. Imagine an air conditioning system which uses just a fraction of the energy our current technology demands.

Imagine growing and storing any component of your body for immediate surgical implantation whenever you get injured. No more reliance on organ donors, no more waiting lines.

Cryonics

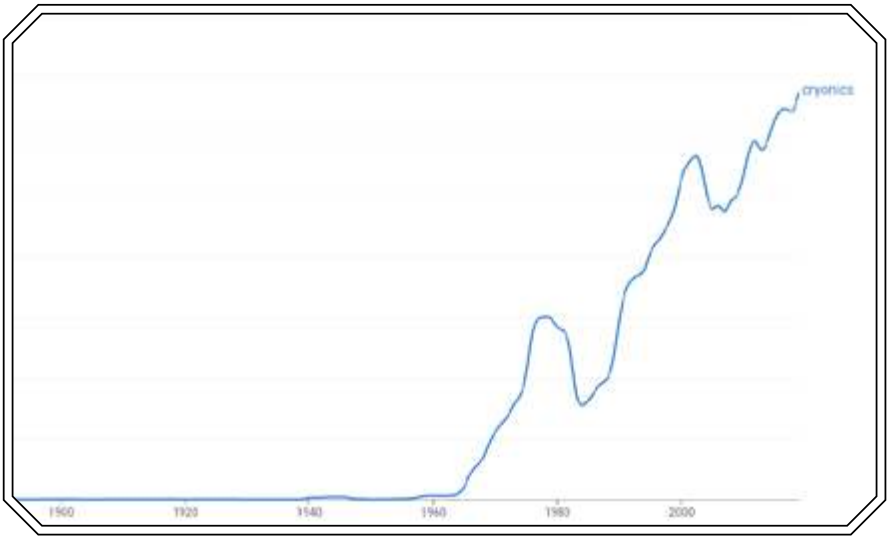
Timeline of Cryonics Development

1800

1720 – Vitrification
1755 – Artificial refrigeration [CRYO7]
1766 – Cryopreservation of cells in snow
1866 – Red blood cells die but nuclei preserved when freezing
1946 – glycerol used to freeze frog cells
1954 – human eye tissue frozen to -79 C and revitalized [CRYO3]
1955 – rats revived from 0C via microwaves with full recovery (no death within 10 days) [CRYO1]
1956 – experiments on insect supercooling and ice crystal nucleation [CRYO2]
1956 – successful conception w/ frozen sperm
1961 – ethylene glycol used to freeze and revive eels, clams observed to freeze
1961 – Embryo chicken hearts frozen to -190C, golden hamsters partially frozen
1967 – Alcor does first human cryopreservation [CRYO4]
1971 – Cryopreserved skin transplantation [ORG9]
1976 – Cryonics institute formed by Robert Ettinger [CRYO5]
1983 – Human pregnancy from cryopreserved embryo [CRYO6]
2003 – Rabbit kidney vitrified [CRYO8]

1900

Word Usage Over Time



{google ngram viewer}

2000

Relevant categorization

Trifecta: Accumulation of Damage
Hallmarks of Aging: N/A
Pillars of Aging: Macromolecular damage

Cryonics

Relevant Organizations: Who is working on this problem?

Alcor
Commercial body preservation

Cryonics Institute
Commercial body preservation

Forever Labs
Stem Cell Cryonic Storage

Greg Fahy
Vitrification Research

Cryonics

Sources

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[CRYO8] Physical and biological aspects of renal vitrification. Phan et. al. 2009.

Biomarkers

Introduction

Biomarkers are one of the most important current topics of discussion in the context of aging research.

Aging studies take a long time to complete and produce data. We want to measure the lifespan effects of various treatments on animals similar to us, but those animals are often long lived and require decades of study before producing useful information. It would be much more efficient to figure out a set of biomarkers related to the aging process that can act as a proxy for lifespan, then use those biomarkers for aging research.

Currently there is no consensus on biomarkers in longevity. Without a standardized set of criteria, experiments can measure whatever metrics they want in order to determine success of a longevity therapy. Various therapies become impossible to compare with one another because of a hodgepodge of clinical, metabolic, or genetic biomarkers measured as goalposts for positive outcomes.

DNA Methylation - One of the more recent developments with a lot of support, DNA methylation clocks appear to be robust predictors of age although the causal relationship is still not clear.

DNA Damage Assays - Identifying and quantifying DNA damage has been used as a biomarker for a while.

Telomere length - While absolute telomere length has fallen out of favor due to massive natural fluctuations and correlation irregularities among different species, the rate of telomere attrition in stem cells is still seen as a biomarker of aging.

NAD/NADH levels - Popularized with the advent of sirtuin and mitochondrial-centric theories of aging, NAD levels have been discovered to change with age.

IGF-1 & HGH - Human Growth Hormone and Insulin Growth Factor-1 levels appear to correlate with age.

Oxidative Stress - While often associated with mitochondrially derived damage, oxidative stress is a general aging biomarker that can occur from ultraviolet damage or chemical stressors.

Senescence associated Beta-galactosidase or P16INK4A - Telltale signs of cellular senescence.

Serum albumin - Decreases with age.

Clinical biomarkers
- Grip strength
- Walking speed
- Body mass index
- Muscle mass

Biomarkers

The Next Big Step - Reverse the Perspective

We may be thinking about this backwards. Why are we searching for biomarkers of aging when we should be searching for biomarkers of non-aging. It's like flight. We are looking for biomarkers common to all nonflying creatures, but the lack of a feature isn't a defining trait.

What we should be looking for is a biomarker of regeneration. We have a diverse spread of organisms to analyze - the germline cells of every living thing on this planet. We analyze those, we find out what biomarkers define regenerative capacity, then we look for the lack of those biomarkers in pathogenic cells.

We may literally need to be "looking for something that doesn't exist", a biomarker that is present in cells with regenerative potential but not present in differentiated or pathogenic cells. Such biomarkers may not even be tied directly to age, as in the case for old but stable germline cells which maintain regenerative potential over time.

Biomarkers

Relevant Organizations: Who is working on this problem?

Edifice Health
Inflammation Biomarkers

Gero
Aging Biomarkers

Insilico Med
Aging Biomarkers

Neurotrack
Brain Aging Biomarkers

Opencures
Aging Biomarkers

Agelabs
Aging Biomarkers

Chronomics
Biomarkers

BioAgeLabs
Aging Biomarkers

TamiRNA
miRNA biomarkers

Biomarkers

Sources

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[BMR4] Relationship between serum albumin level and aging in community-dwelling self-supported elderly population. Moriwaki et. al. 2007.

Longevity Technology Tree Prototype

How are these technologies interconnected?

To answer this question, we have attempted to arrange the technologies into an interconnected tree to figure out how they interact with each other. The following page contains a prototype of a tech tree diagram.

- Core technologies (blue) are basic level research concepts that are required for the progression of the various domains of longevity research.

- General Improvements (yellow) are research breakthroughs that benefit everyone, even people who do not want or care about longevity. These spinoff advances create value for everyone and are important to powering longevity research because they can gain support from those who do not care about the core mission.

- Longevity Tech (purple) are the end goals we are striving for to make healthspan and maximum lifespan improvements possible.

- Nutrition (green) is the most recently added category that will eventually include macro and micronutrients, supplements, drugs, and any other consumable inputs that are relevant to each specific technology.

The plan is to make each of these components clickable, leading to a page with labs, advocacy groups, companies, and notable people for each node.

Longevity Tech Tree v.1

Aaron King | Foresight Institute

Core Technology | Longevity Tech | General Improvement | Nutrition Inputs

Reprogramming

K/P/Na/Ca → Electrodynamics
Yamanaka Factors → Dedifferentiation
Dedifferentiation → Senescence Control
Senolytics → Senescence Control
Senescence Control → Regeneration of Senescent Cells
Telomere Control → Cure for Cancer
Gene Repair Control → Cure for Cancer
Gene Replacement Therapy → Cure for Cancer
Electrodynamics → Gene Expression Control
Epigenetics → Gene Expression Control
Gene Expression Control → Circadian Rhythm Control
Circadian Rhythm Control → Regeneration Cycles
Circadian Rhythm Control → Insomnia Cure

Organic Replacement

Nutrients → NAD
NAD → Molecule Replacement
Molecule Replacement → Hormone Replacement
Molecule Replacement → Cell Replacement
Microbiome Control → Gut Disorder Cures
Stem Cell Therapy → Diabetes Cure
Stem Cell Therapy → Cartilage Regeneration
Platelet Rich Plasma → Menopause Reversal
Cell Replacement → Lab Grown Blood
Hormone Replacement → Klotho → General Regeneration?
Testosterone → Estrogens → Menopause Therapy
Human Growth Hormone → Thymus Regeneration → Immune System Regeneration
Body on a chip → Drug development
3D bioprinting → Organ Scaffolds
Head Transplant → Body Replacement
Tissue Replacement → Organ Replacement → Body Replacement
Extracellular Matrix Reconstruction → Pneumonia Cure
Extracellular Matrix Reconstruction → Skin Renewal
Brain Transplant → Body Replacement
Brain Replacement → Stroke Cure
Brain Replacement → Dementia Cure
Organ Replacement → Organ Transplant Waitlist Solved

Slowing Time

Parabiosis / Blood Dilution
Frozen Blood → Blood Storage → Blood Donations Solved
Blood Storage → Frozen Stem Cells
Surgical Improvements
Organ Storage
Long Distance Space Travel
Frozen Cells → Frozen Tissue → Vitrified Organs → Vitrified Body → Cryonic Revival
Brain Preservation

Synthetic Replacement

Brain Machine Interface → Mind Uploading → Cybernetic Brain
Lifelike Prosthetics
Artificial Muscle → Cybernetic Body
Artificial Organs → Cybernetic Body
Cyborg (synthetic body, human brain)
Android (synthetic body and brain)
Cure Heart Disease
Cure Kidney Failure
ATP to Electricity → Electricity to ATP
Food From Energy

Damage Control

Measure Autophagy in Vivo
Caloric Restriction
mTOR/AMPk
PROTACS
Proteolysis Control
Heat Shock Response Control → Refolding Proteins
Autophagy Control
Recycling Individual Proteins
Recycling Many Proteins
Extracellular Matrix Turnover
Glymphatic System Control
Complete Detritus Removal
Removal of eye floaters
Alzheimers cure
Lipofuscin Degradation → Macular Degeneration Reversal
Sarcopenia Cure
Muscular Dystrophy Cure

Reactive Oxygen Species
Oxidated Lipids
Advanced Glycation Endproduct Removal