The Current State Of The Pursuit Of Biological Immortality

April 2018

FOREWORD

Each year, this report should suck a little bit less.

This report is a result of me not having enough information on what exactly is happening in regards to the quest of biological immortality. I haven't seen a single location or information dump that catalogs all the efforts, so I'm putting this together. If a better report already exists, please point me to it so that I can make my life much easier. So far, I haven't seen anything impressive.

This is a draft. Many parts are unfinished, but the structure of the report seems like it's going in the right direction. I have tried to the best of my ability to include only direct, primary sources (no reviews). I'll need to discuss with localized experts to get better and more accurate information and access to certain ancient materials.

A note on the relevant supplements sections – I just threw in everything that I could find. The efficacy was not evaluated. Most supplements do not do anything but by the next release of this report I should have better and more specific details on supplements and mechanisms of action.

Finally, on the impact of tangible biological immortality: When nuclear weapons were invented, humans gained the ability to destroy the planet and refrained from doing so. Biological immortality seems to be an invention with a similar magnitude of impact. I have faith that, should we prevail and figure this out, we will have the capability to end humanity yet choose not to.

Annuit cœptis

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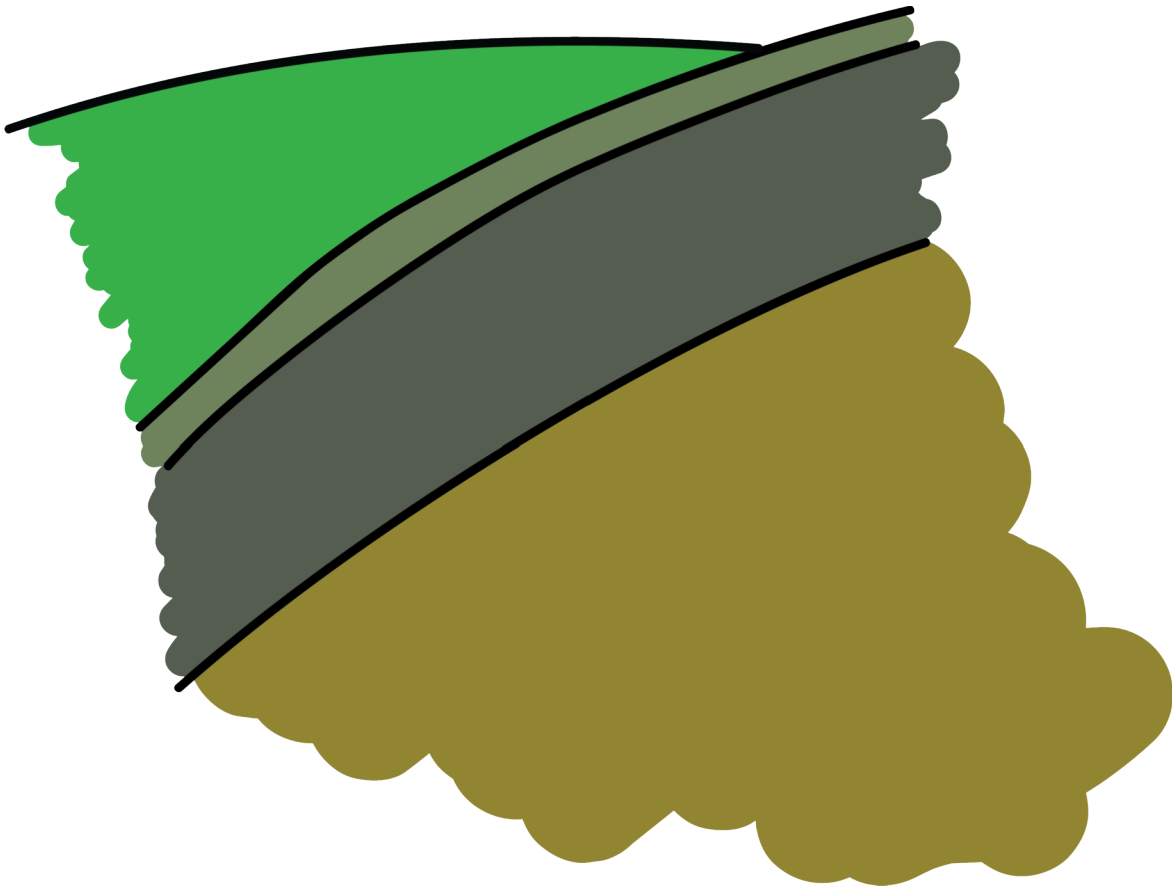
The Wall

Suppose there exists a wall. The wall is infinitely long and made of some kind of unbreakable material.



There are multiple ways for us to attempt to breach the wall. It doesn't matter which way is used, only that the wall is breached. Some attempt to go under, some attempt to go over, some attempt to go around. Some attempt to drill straight through.

The wall is a crude metaphor for our inevitable death.

There might be multiple methods to achieve biological immortality. This report attempts to summarize every method ever conceived by man and the current progress along each route, as well as what is necessary for each method to succeed. Having multiple methods implies robustness, robustness implies security. The truth is that beyond our own egos we shouldn't care *how* the wall is breached, only that it is breached and breached in as many ways as humanly possible.

The Goal

Biological immortality implies immortality of the soma. The gene is already immortal. At least one cell has remained immortal within your genetic lineage stretching back to the dawn of life itself. Our objective then is to attain immortality for the rest of the body – or at the very least the brain, which houses self-awareness.

One could argue – justifiably – that every single medical advance is in pursuit of longevity. However, there is a clear distinction between patching a kidney or mending a broken bone and attempting to completely replace the kidney or bone such that it returns to mint-condition. This report attempts to distinguish between methods that chase biological immortality and normal medical advancements.

The current visible pathways to immortality are – biological replacement, synthetic replacement, repair, reprogramming, prevention of damage, and stopping time.

Biological Replacement

The simplest solution is often the best – replace failing components of the human body with exact duplicates, and the problem of death goes away. However, biological replacement requires that we build every component of the human body and figure out how to replace it.

There are 78 organs, 206 bones, 4 tissue types, 50 hormones, 200 types of cells in the human body.

By mass, bone makes up around 15% of the body and muscle accounts for 30-40%, which means if we figure out how to replace bone and muscle we can solve about half of the body mass.

Full body replacement – Head Transplant

A brain transplant has the ability to completely renew every part of the body that is not the brain by transplanting an old brain/head onto a young body. This is a quick and easy method of regenerating the entire body, and could potentially lead to immortality if the brain somehow regenerates from the presence of a new body via some kind of parabiotic effect. Much more likely what will need to happen is for some kind of brain regeneration procedure alongside a full body replacement. This procedure is classified as evil until bioprinting or some other method is capable of creating an entire body from scratch. Full body replacements require a stream of habitual human sacrifice, which is unsustainable and inevitably leads to slavery or war.

History:

1908 – Dog head graft, dead within hours [SOURCE UNAVAILABLE]
1954 – Dog head/legs graft, dead after 29 days [HT2][SOURCE UNAVAILABLE]
1965 – Dog brain grafting, dead within 2 days [HT4]
1970 – Monkey head transplant, dead within 3 days [SOURCE UNAVAILABLE]
2000 – Polyethylene glycol used to fuse nerve membranes [HT6]
2004 – Injured spinal cord observed to form new circuits in rats [HT5]

Challenges:

Blood vessel reconstruction – solved in 1902 [SOURCE UNAVAILABLE]
Immune response – partially solved in 1958 [HT3]
Spinal cord fusion – unsolved

Other challenges of head transplantation stem from damage inflicted during the operation, which could conceivably be eliminated with better cryogenic techniques. If you are going to go through the trouble of transplanting a head, you might as well use cryonics to assist in the procedure.

Development Pathway:

It appears the current problem revolves around spinal cord fusion. Beyond that, evidence is conflicting. Parabiosis experiments on mice indicate that rejuvenation of the brain is possible if it is connected to young organs, but to what extent is unknown. It is likely that a head transplant only delays the inevitable rather than leading to complete rejuvenation. If this is the case, further development on brain regeneration is needed once head transplants are successful.

Relevant Goals:

The goal of head transplantation is to transplant the head of an old human to a compatible young human body.

Relevant Organizations:

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Rockefeller Institute

Sources:

[HT1] *The History of Head Transplantation: A Review.* Lamba, Holsgrove, Broekman. 2016.
[HT2] *Experimental Transplantation of Vital Organs*. Demikhov. 1963. Unavailable online.
[HT3] *Effect of 6-Mercaptopurine on Antibody Production*. Schwartz, Stack, Dameshek. 1958.
[HT4] *Brain transplantation: prolonged survival of brain after carotid-jugular interposition*. White, Albin, Locke, Davidson. 1965.
[HT5] *The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats*. Bareyre. 2004.
[HT6] *Immediate recovery from spinal cord injury through molecular repair of nerve membranes with polyethylene glycol*. Borgens, Shi. 2000.

Replace Tissue/Organ

Organ and tissue replacement encounters a barrier to biological immortality when thinking about brain regeneration. The brain is the organ we are attempting to retain continuity of, therefore replacing it outright is not an option. One potential solution is to replace parts of brain tissue "ship of Theseus" style, retaining psychological continuity.

Progress:

1597 – Skin autograft [ORG1]
1871 – Skin graft [ORG2]
1902 – Blood vessel suturing [SOURCE UNAVAILABLE]
1905 – Xenotransplantation
1937 – Blood bank [ORG3]
1949 – Tissue bank [SOURCE UNAVAILABLE]
1950 – Kidney transplant [ORG4]
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]
1998 – Hand transplant [ORG10]
1999 – Bioengineered bladder replacement [ORG11]
2005 – Ovarian transplant [ORG12]
2005 – Bioengineered trachea [ORG13]
2008 – First baby born from transplanted ovary
2010 – Full face transplant [ORG14]

Development pathway:

- A list of all tissues/organs in the human body
- The ability to biologically create each tissue/organ
- Procedures for how to replace each tissue/organ

We have completed a list of all tissues/organs in the human body.

We can biologically create each tissue/organ via the evil pathway of using another human to do so. To get around the evil aspect, we wait until people die before harvesting their organs. However, this does not allow access to organs when they are needed.

Bioprinting, xenotransplantation, and scaffold bioengineering present potential non-evil pathways toward organs on demand. Use of scaffolds limits the types of organs that can be created, and bioprinting is blocked at the vascularization problem. Xenotransplantation

List of tissues and organs:

Tissues:
Nervous – nerves, brain, spinal cord
Connective – bone, tendon, fat
Epithelial – squamous, columnar, cuboidal
Muscular – skeletal, smooth, cardiac

Organs:
Integumentary System – skin, nail, hair
Musculoskeletal System – bones, muscles, cartilage, tendons, ligaments, joints
Cardiovascular System – Heart, blood vessels, spleen
Respiratory System – trachea, lungs, mouth/nasal cavity
Urinary System – Kidneys, ureters, bladder, urethra
Nervous System – Brain, spinal cord, nerves
Gastrointestinal System – esophagus, stomach, small intestine, large intestine, liver, appendix, salivary glands
Reproductive System – scrotum, epididymis, prostate, vas deferens, penis, uterus, breasts
Endocrine System – pineal, pituitary, pancreas, ovaries, testes, thyroid, parathyroid, adrenal

This list is incomplete. A full list of every component of the human body with individual progress reports is the goal here, but I skipped anatomy in undergrad so this is what I'm starting with. There are apparently 78 organs in the human body, but when it comes to bone and muscles the definitions get obtuse. 206 bones, 800+ muscles, but these can be counted as tissues not organs.

Challenges:

Immune rejection – partially solved with immunosuppressents. [HT3]

Scaffold materials – Availability of materials that could be put into a human body safely used to be an issue. However, this has been largely overcome thanks to materials engineering and development.

Vascularization – "When the thickness of the engineered tissue exceeds 150–200μm, it will surpass the oxygen diffusion limitation. The cell seeding and penetration is not effective to the pre-formed scaffold. Tissue formation or maturation is not uniform throughout the scaffold on the time scale of months. Although scaffold design has been significantly improved for effective cell seeding and migration, the approaches are still far from optimal. Multiple cell types are usually required to fabricate organs with complex structure. However, the precise placement of cells and growth factors in 3D is still far from being resolved. Vascular or microvascular system is crucial for thick and complex tissue engineering, which must be fabricated simultaneously with scaffold construction. However, the traditional approach is not able to construct the vascular system with pre-designed 3D patterns."

Cell types – certain cell types are not capable of being grown or expanded in culture, which means the tissues and organs that rely on those cell types cannot be fabricated.

Relevant Organizations:

Organovo
Wake Forest Regenerative Medicine Institute
Organogenesis
Allevi
Ott lab for organ engineering and regeneration
Organ preservation alliance
New organ alliance
21cm medicine
Cryoprize
Singapore center for 3D bioprinting
Cellink
Biorg
3D bioprinting solutions

End Goal:

The goal is to be capable of replacing any organ or tissue on demand.

Sources:

[ORG1] *De curtorum chirurgia per insitionem*. Taliacotii. 1597.
[ORG2] *Etude sur L'urethrotomie interne*. Reverdin. 1871.
[ORG3] *The therapy of the cook county hospital*. Fantus. 1938.
[ORG4] *Homotransplantation of the kidney in the human*. Lawler et. al. 1950.
[ORG5] *Lung homotransplantation in man*. Hardy et. al. 1963.
[ORG6] *Heart transplantation in man*. Hardy et. al. 1964.
[ORG7] *Orthotopic transplantation of the human liver*. Starzl et. al. 1968.
[ORG8] *A human cardiac transplant – an interim report of a successful operation performed at groote schuur hospital cape town*. Barnard. 1967.
[ORG9] *Clinical experience with viable frozen human skin and a frozen skin bank*. Bondoc, Burke. 1971.
[ORG10] *First human hand transplantation*. Dubernard et. al. 2000.
[ORG11] *De novo reconstitution of a functional mammalian urinary bladder by tissue engineering*. Oberpenning, Meng, Yoo, Atala. 1999.
[ORG12] *Ovarian transplant: a new frontier*. Mhatre, Mhatre, Magotra. 2005.
[ORG13] *Regenerative medicine of the trachea – the first human case*. Omori et. al. 2005.
[ORG14] *Full face transplant*. Barret et. al. 2011.

Replace Cells – Stem Cells

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.

History:

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]

Development:

To attain complete biological replacement, we need the following

- A list of all stem cells in the human body
- The ability to create each type of stem cell in vitro
- How to expand cultures of all stem cells in vitro
- Procedures for injecting each type of stem cell for each necessary condition

Relevant Organizations:

Better humans
US Food and Drug Administration
Stem Cell Institute
Regenexx
Nygard Biotechnology
Ichor Therapeutics
Forever Labs
David Steenblock
Centagen
Ascendance
AgeX Therapeutics
Rando Lab at Stanford
Harvard Stem Cell Institute
Columbia Laboratory for Stem Cells and Tissue Engineering

Relevant Supplements:

Vitamin D3
Curcumin
Quercetin
Glucosamine
Chondroitin
Vitamin C
Resveratrol
Blueberry
Green Tea
Carnosine

Relevant Goal:

The end goal for stem cells is to be capable of inducing complete regeneration of any cell or tissue in the human body.

Sources:

[STEM1] *Naturliche Schopfungsgelchichte*. Haeckel. 1868. {1879}
[STEM2] *Embryonic stem cell lines derived from human blastocysts*. Thompson et. al. 1998.
[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.
[STEM8] *Haematopoietic stem cells in human cord blood*. Prindull, Prindull, Meulen. 1978.
[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*

Replace Cells – Microbiome

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. It has recently been reported that human breastmilk contains oligosaccharides that are undigestible 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 prevailing theory is that it helps restore the microbiome in the event of rapid discharge [MB3].

Two methods of controlling the microbiome are direct manipulation of bacterial/fungal populations through diet or antibiotics 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 has the largest effect on microbiome population shifts. Shifts in microbiome populations are associated with aging, although direction of causality is not clear. Unless the digestive tract is replaced by a synthetic substitute, it is likely that control of the microbiome is necessary for biological immortality.

History:

1671 – Discovery of bacteria [MB11]
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 (up to 10 million now?)
2012 – uBiome founded

Development pathway:

1) Develop a list of every microbe that could potentially be in the human gut
2) Map out the microbial metabolic pathways
3) Control the population of each microbe
4) Determine what metabolic deficiencies affect an individual and alter microbiome to compensate

Challenges:

List all species in human body – partially solved
List all genes of microbes in human body – partially solved

Relevant Goals:

The goal of microbiome research is to know the optimal composition for a given condition and be

capable of controlling the composition of the microbiome.

Relevant Organizations:

Human Microbiome Project
uBiome
Zymo
MapMyGut
American Gut Project
International Human Microbiome Consortium
Metagenomics of the Human Intestinal Tract
Vedanta Biosciences
Synthetic Biologics
Seres Therapeutics
Rebiotix
Osel
Optibiotix
Microbiome Therapeutics
Metabiomics Corp
Enterome Biosciences
AO Biome
Metabogen
Evelo Biosciences
ARTPred
MaaT pharma
Blue Turtle Bio
Axial Biotherapeutics
Whole Biome
4D pharma
Symbiotix biotherapeutics
Phi Therapeutics
Synlogic
Biospherex
Finch Therapeutics group
OpenBiome
The Microbiome Center

Relevant Supplements:

Iron
Magnesium
L-glutamine
Vitamin D
Prebiotics (nebulous term) – trans-galactooligosaccharide [MB6], inulin [MB6], resistant starch [MB7],

pectin [MB8], beta-glucans [MB9], xylooligosaccharides, fructooligosaccharide, isomalto-oligosaccharide, etc.
Probiotics (nebulous term) – any food that is capable of seeding the human gut with live microbes
Rapamycin, Metformin, other antibiotics

Sources:

[MB1] *Human milk oligosaccharide consumption by intestinal microbiota. Marcobal, Sonnenburg. 2012*.
[MB2] *Distribution of immunoglobulin producing cells is different in normal human appendix and colon mucosa*. Bjerke, Brandtzaeg, Rognum. 1986.
[MB3] *The appendix may protect against Clostridium difficile recurrence*. Im, Modayil, et. al. 2011.
[MB4] *History of Medicine: Origin of term microbiome and why it matters*. Prescott. 2017.
[MB5] https://hmpdacc.org/hmp/overview/
[MB6] *Prebiotics: The concept revisited*. Roberfroid. 2007.
[MB7] *The potential of resistant starch as prebiotic*. Zaman, Sarbini. 2015.
[MB8] *Purification characterization and prebiotic properties of pectic oligosaccharides from orange peel wastes*. Gomez et. al. 2014.
[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.

Replace Cells – Blood

Blood transfusions are an easy way of replacing a large component of the human body, and have been carried out successfully since 1818, unfortunately there exists no direct evidence for this online anywhere [BL1]. Assuming it wasn't a made up story that's been amplified through the ages, it would mean blood was the earliest component of the human body reimplanted into a human. It is definitely 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 based on experiments involving parabiosis [BL4]. Parabiosis between mice leads to rejuvenation of an old mouse via attaching the circulatory system of a young mouse. The concept is that this will carry over to humans, and young blood will rejuvenate the old body. This method of rejuvenation can be classified as evil due to the requirement of habitual sacrifice of another human's biological material. One could easily imagine a scenario where humans are forced to give up their blood for the sake of old, powerful people who don't want to die. However, 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].

Current evidence leans toward blood parabiosis as being an unlikely method of attaining biological immortality.

History:

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]
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]
1990: Recombinant hemoglobin from e.coli [BL16]

2011: Lab grown artificial blood transfusion [BL5]
2016: Old blood inhibits tissues [BL20]

Development:

Novel idea – longitudinal self-parabiosis using cryonically stored blood

Challenges:

Blood compatibility – solved with discovery of blood types in 1900 [BL11]
Blood coagulation – solved with anticoagulants in 1914 [BL13]
Blood storage – solved with cryogenics in 1964 [BL3]
Not enough blood – still unsolved, potential solutions are synthetic blood or lab grown blood

Relevant Supplements:

Vitamin K – blood thinner
Iron
Folic Acid
Vitamin B, C, E
Brewers Yeast
Niacin

Relevant Organizations:

Young Blood Institute
Alkahest
Ambrosia
Naval Blood Research Laboratory

Sources:

[BL1] https://bloodcenter.stanford.edu/a-brief-history-of-blood-transfusion-through-the-years/
[BL2] http://special.lib.gla.ac.uk/exhibns/month/june2007.html
[BL3] *Frozen Blood*. Huggins. 1964.
[BL4] *Parabiosis for the study of age-related chronic disease*. Eggel, Wyss-Coray. 2014.
[BL5] *Proof of principle for transfusion of in vitro-generated red blood cells*. Giarratana et. al. 2011.
[BL6] https://www.redcrossblood.org/learn-about-blood/blood-transfusions/history-blood-transfusions
[BL7] *Haemorrhagic diathesis: Successful transfusion of blood*. Lane. 1840.
[BL8] *Der Chemismus in der tierescher Organization*. Hunefeld. 1840.
[BL9] *La Graffe Animale*. Bert. 1863.
[BL10] *Early history of blood substitutes: transfusion of milk*. Oberman. 1969.
[BL11] *On agglutination of normal human blood*. Landsteiner. {1900}.

[BL12] *Ueber Parabiose kunstlich vereinigter Warmbluter.* Sauerbruch, Heyde. 1908. Unavailable Online.
[BL13] *The introduction of citrate as an anticoagulant for transfusion and of glucose as a red cell preservative*. Mollison. 2000.
[BL14] https://bloodcenter.stanford.edu/a-brief-history-of-blood-transfusion-through-the-years/
[BL15] *An agglutinable factor in human blood recognized by immune sera for rhesus blood*. Landsteiner, Wiener. 1940.
[BL16] *Expression of fully functional tetrameric human hemoglobin in escherichia coli*. Hoffman et. al. 1990.
[BL17] *Plasma removal – plasmaphaeresis*. 1915.
[BL18] *The historical development of automated hemapheresis*. Millward, Hoeltge. 1982.
[BL19] *Mortality in syngeneic rat parabionts of different chronological age*. Ludwig, Elashoff. 1972.
[BL20] *A single heterochronic blood exchange reveals rapid inhibition by old blood*. Rebo et. al. 2016.

Replace Genes – Adenoviruses

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. [AAV1]

History:

1953 – Discovery of adenoviruses [AAV6]
1965 – Discovery of adeno-associated viruses [AAV2]
1984 – AAV used to tranduce genes into human genome [AAV3]
1996 – First human clinical trial involving AAV [AAV4]
2001 – self-complementary AAV developed [AAV5]

Development:

Challenges:

Adenoviruses are pathogenic – solved with AAV [AAV2]

Second strand synthesis as rate limiting step – solved with scAAV [AAV5]

Relevant Organizations:

Wyss Institute

Sources:

[AAV1] *Adeno-associated virus and the development of Adeno-associated virus vectors: A historical perspective*. Carter. 2004.
[AAV2] *Adenovirus-associated defective virus particles*. Atchison, Casto, Hammon. 1965.
[AAV3] *Use of adeno-associated virus as a mammalian DNA cloning vector Transduction of neomycin resistance into mammalian tissue culture cells*. Hermonat, Muzyczka. 1984.
[AAV4] *A phase I study of an Adeno-associated virus-CFTR gene vector in adult CF patients with mild lung disease*. Flotte et. al. 1996.
[AAV5] *Self-complementary recombinant adeno-associated virus vectors promote efficient transduction independently of DNA synthesis*. McCarty, Monahan, Samulski. 2001.
[AAV6] *Isolation of a cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture*. Rowe, Huebner, Gilmore, Parrott, Ward. 1953.

Replace Genes – 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.

History:

2007 – TALEN mechanism observed [TAL1]
2009 – TALEN mechanism reverse-engineered [TAL2]

Development:

Challenges:

Relevant Organizations:

Sources:

[TAL1] *A bacterial effector acts as a plant transcription factor and induces a cell size regulator.* Kay, Hahn, Marois, Hause, Bonas. 2007.
[TAL2] *Breaking the code of DNA binding specificity of TAL-type III effectors.* Boch et. al. 2009.

Replace Genes – 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.

History:

2000 – Short Regularly Spaced Repeats described [CRS1]
2002 – CRISPR acronym used, cas genes discovered [CRS2]
2006 – Adaptive immune response hypothesis [CRS3]
2007 – Apative immune response hypothesis proven [CRS4]
2008 – CRISPR shown to target DNA [CRS5]
2013 – CRISPR/Cas9 used for targeted genome editing [CRS6]

Development:

Challenges:

Sources:

[CRS1] *Biological significance of a family of regularly spaced repeats in the genomes of archaea bacteria and mitochondria*. Mojica, Diez-Villasenor, Soria, Juez. 2000.
[CRS2] *Identification of genes that are associated with DNA repeats in prokaryotes*. Jansen, Embden, Gaastra, Schouls. 2002.
[CRS3] *A putative RNA-intereference-based immune system in prokaryotes - computational analysis of the predicted enzymatic machinery, functional analogies with eukaryotic RNAi and hypothetical mechanisms of action*. Makarova, Grishin, Shabalina, Wolf, Koonin. 2006.
[CRS4] *CRISPR provides aquired resistance against viruses in prokaryotes.* Barrangou et. al. 2007.
[CRS5] *CRISPR interference limits horizontal gene transfer in staphylococci by targeting DNA*. Marraffini, Sontheimer. 2008.
[CRS6] *Multiplex genome engineering using CRISPR/Cas systems*. Cong et. al. 2013.

Replace Molecules – Hormones

Hormones are signaling molecules that control sexual maturation, sleep, and other functions in the body. Aging affects hormones by causing a degradation in the consistency and production of hormones, resulting in aberrant downstream behavior. Hormones potentially affect aging by antagonistic pleiotropy – it is possible that the underlying mechanism of things like human growth hormone are beneficial early in life then become 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 indefinitely, which is a possible pathway to biological immortality. Other hormones are medically important but do not appear to be a viable pathway to life extension.

Hormone replacement started in the 19th century but really took off in the early part of the 20th century. It includes grafting animal sex glands to humans, injecting humans with animal hormones, injecting humans with synthetic hormones, and altering hormone production in humans. Hormonal production follows an arc, and as an organism ages its sex hormone production becomes disregulated.

From the perspective of the gene, 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.

List of hormones found in the human body:

<u>Amino acid derived</u>
Epinephrine
Melatonin
Triiodothyronine
Thyroxine

<u>Eicosanoid</u>
Prostaglandins
Leukotrienes
Prostacyclin
Therocis

Peptides
Amylin
Anti-Mullerian Hormone
Adiponectin
corticotropin
angiotensin
Angiotensinogen
vasopressin
atriopeptin
Brain natriuretic peptide
Calcitonin
Cholecystokinin
Corticotropin-releasing hormone
Cortistatin
Enkephalin
Endothelin
Erythropoietin
Follicle-stimulating hormone
Galanin
Gastric inhibitory polypeptide
Gastrin
Ghrelin
Glucagon
Glucagon-like peptide-1
Gonadotropin-releasing hormone
Growth hormone-releasing hormone
Hepcidin
Human chorionic gonadotropin
Human placental lactogen
Growth hormone
Inhibin
Insulin
Insulin-like growth factor (IGF)
Leptin
Lipotropin
Luteinizing hormone
Melanocyte stimulating hormone
Motilin
Orexin
Osteocalcin
Oxytocin
Pancreatic polypeptide
Parathyroid hormone

Pituitary adenylate cyclase-activating peptide
Prolactin
Prolactin releasing hormone
Relaxin
Renin
Secretin
Somatostatin
Thrombopoietin
Thyroid-stimulating hormone
Thyrotropin-releasing hormone
Vasoactive intestinal peptide
Guanylin
Uroguanylin

Steroids
Testosterone
Dehydroepiandrosterone
Androstenedione
Dihydrotestosterone
Aldosterone
Estradiol
Estrone
Estriol
Cortisol
Progesterone
Calcitriol
Calcidiol

History:

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

Relevant Supplements:

17-beta estradiol
estradiol acetate
estradiol hemihydrate
micronized progesterone USP
somatotropin
Iodine
Selenium
Zinc
DHEA
Turmeric
Thyroxine
HGH
BGH
Epinephrine
Insulin
Melatonin

Sources:

[HOR1] *Preparation and properties of growth hormone from human and monkey pituitary glands.* Li, Papkoff. 1956.
[HOR2] *Treatment of a pituitary dwarf with human growth hormone*. Raben. 1958.
[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.

Synthetic Replacement

Prosthetics have been around for thousands of years, although mostly in a crude form that gave the most basic functionality. Cybernetics – a field devoted to human control of machinery – is a logical extension of prosthetics. Combined with mind uploading, artificial replacement is a viable pathway to tangible immortality. The advantages of artificial limbs and organs is ease of replacement as compared to organic material. However, artificial body parts tend to wear out faster and do not contain the kind of redundancies that organic body parts do. If an artificial body part breaks, the results could be immediately catastrophic as compared to a slow decline that allows for transport to a hospital in reasonable time. Another barrier is the level of complexity – artificial organs must be manufactured and to create technology with the kind of complexity of an organ is very expensive compared to growing it naturally.

What we need to know:

- A list of every component of the human body
  - At least 640 muscles, up to 840 depending on classification system
  - 206 bones
  - 78 organs (some likely unnecessary for synthetic body)
  - 4 types of tissues
- How to build every component of the human body
  - Manufacturing process
  - Material composition
  - Expense
- Procedures for how to replace every component of the human body

OR

- A list of every component needed for a functional immortal body
- How to build every component in that list
- Procedures for how to replace the human body with the functional immortal body

Currently the second option is not being worked on by anyone. Nobody knows how to create a completely new body, and nobody is working on it. Therefore, the focus of this report will be on current and past efforts to mimic the human body.

Replace Body – Brain in a Vat

One of the older concepts for artificial replacement is to do away with the entire body except the brain, keeping it alive in a vat of nutrients and having it be synthetically connected to a robotic body. The logic is that the artificial body is easier to maintain and replace than a biological one, making the brain the sole 'failure point' for death. This method leads to biological immortality if the brain can be made immortal (a much easier task than immortalizing both the brain and the body) or if by virtue of having an artificial body the brain can be made immortal (by having direct control over all inputs to the brain, maybe it becomes easier to stop it from aging).

History:

1812 – Concept of resuscitating severed heads [HED1]
1836 – Rabbit and dog isolated brain experiments [HED2]
1887 – First recorded attempt to revive the heads of executed criminals [HED5]
1928 – Autojector used on dog head [HED3]
1993 – Guinea-pig brain isolated in a fluidic profusion system in vitro, survived for few days [HED4]

Development:

Challenges:

Relevant Organizations:

none

Sources:

[HED1] *Experiences sur le principe de la vie*. Gallois. 1812.
[HED2] *On tying the carotid and vertebral arteries and the pneumo-gastric phrenic and sympathetic nerves*. Cooper. 1836.
[HED3] *Off with your heads: Isolated organs in early soviet science and fiction*. Krementsov. 2009.
[HED4] *The isolated and perfused brain of the guinea-pig in vitro*. Muhlethaler, Curtis, Walton, Llinas. 1993.
[HED5] *Les Tractions Rythmees de la Langue*. Laborde. 1894.

Replace Body — Prosthetic Limbs

Prosthetics are the earliest form of synthetic body replacement. They started as an aesthetic tool but gradually gained functionality as technological ability progressed. Prosthetics are the most accessible synthetic replacement for body parts and are close to being sufficiently advanced enough to replace human motor function.

History:

950BC – Egyptian prosthetic toe [SOURCE UNAVAILABLE]
300BC – Roman prosthetic leg [SOURCE UNAVAILABLE]
210BC – Roman iron hand [SOURCE UNAVAILABLE]
1508 – Iron hands w/ manipulation ability [SOURCE UNAVAILABLE]
1536 – Leg prosthetics with knee lock control [SOURCE UNAVAILABLE]
1696 – nonlocking below knee prosthetic [SOURCE UNAVAILABLE]
1800 – Anglesey leg [SOURCE UNAVAILABLE]
1858 – Doctor Bly's anatomical leg [SOURCE UNAVAILABLE]
1901 – Ear trumpet [SOURCE UNAVAILABLE]
1912 – First aluminum prosthetic [SOURCE UNAVAILABLE]
1915 – Powered prosthetic [SOURCE UNAVAILABLE]
1948 – Myoelectric prosthetic [SOURCE UNAVAILABLE]
1948 – CO2 powered limbs [SOURCE UNAVAILABLE]
1961 – Industrial automated arm UNIMATE [PRO3]
1972 – First anthropomorphic robot WABOT-1 [PRO1]
1997 – Microprocessor prosthetic control [SOURCE UNAVAILABLE]
2010 – Bebionic hand [PRO2]
2014 – Implanted EMG control of leg prosthetic [PRO5]

Development:

Challenges:

Relevant Goal:

Create a prosthetic for all limbs and sensory organs that can mimic complete human functionality.

Relevant Organizations:

Blatchford
Fillauer
Ossur
Ottobock
Ohio willow wood
Freedom Innovations

Amputee coalition
Touch Bionics
Limbless association
HDT Global
Syntouch
Shadow Robot Company
Endolite
Boston Dynamics
TOSY Robotics
Aldebaran robotics
Fujitsu
Robotcub Consortium
Honda
Sony
NASA

Sources:

[PRO1] *Information-power machine with senses and limbs (Wabot 1)*. Kato, Ohteru, Kobayashi, Shirai, Uchiyama. 1973.
[PRO2] *Bebionic prosthetic design*. Medynski. 2011.
[PRO3] *Programmed article transfer*. Devol. 1961.
[PRO5] *Fully implantable multichannel EMG measurement system – first results*. Lewis, Russold, Hahn, Aszmann.

Replace Organs – Artificial Heart

The heart and brain are two vital organs which have the slowest rates of regeneration and cellular turnover. The heart regenerates around 1% of its mass per year. Compare that to skin, which completely regenerates every few weeks. Thus, much of the effort for repair or replacement is centered around the heart and brain.

History:

1937 – First artificial heart transplanted to dog [SOURCE UNAVAILABLE]
1952 – First artificial heart machine used on human [SOURCE UNAVAILABLE]
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 [HAR1]
1993 – SynCardia heart [SOURCE UNAVAILABLE]
1996 – Phoenix-7 heart [SOURCE UNAVAILABLE]
2001 – Abiomed AbioCor heart [SOURCE UNAVAILABLE]
2005 – Magscrew heart [SOURCE UNAVAILABLE]
2008 – Impella heart pump [SOURCE UNAVAILABLE]
2017 – Soft artificial heart [HAR2]

Challenges:

100% Duty cycle
Duration of use

Relevant Goal:

Create an artificial heart that completely mimics human functionality.

Relevant Organizations:

Syncardia
Abiomed
Carmat
Cleveland Heart
Bivacor

Sources:

[HAR1] *Orthotopic cardiac prosthesis for two-staged cardiac replacement*. Cooley. 1969.
[HAR2] *A soft total artificial heart – first concept evaluation on a hybrid mock circulation*. Cohrs et. al. 2017.

Replace Organs – Artificial Lung

Artificial lungs have developed from external steel behemoths to small internal contraptions in the span of a hundred years.

History:

1832 – Negative pressure ventilator [SOURCE UNAVAILABLE]
1929 – Iron Lung [LUNG2]
1953 – Extracorporeal membrane oxygenation [SOURCE UNAVAILABLE]
1992 – Intravascular Oxygenator [LUNG4]
2000 – Pumpless extracorporeal lung assist [LUNG5]
2017 – Wearable artificial lung [LUNG6]

Challenges:

Development:

Relevant Goal:

Create an artificial lung that completely mimics human lung functions.

Sources:

[LUNG2] *An apparatus for the prolonged administration of artificial respiration*. Drinker, Shaw. 1929.
[LUNG4] *Intravascular Oxygenator A new alternative method for augmenting blood gas transfer in patients with acute respiratory failure*. Mortensen. 1992.
[LUNG5] *Pumpless extracorporeal lung assist and adult respiratory distress syndrome*. Reng et. al. 2000.
[LUNG6] *In vitro and in vivo evaluation of a novel integrated wearable artificial lung*. Madhani et. al. 2017.

Replace Organs – Artificial Pancreas

The first artificial pancreas was approved by the FDA in 2016 and can be classified as an external organ. The device delivers insulin using algorithms to predict future behavior and prevent insulin shock.

History:

1963 – Controlled glucose monitoring [PAN1]
1974 – Biostator commercial device [PAN2]
1982 – Wearable pancreas [PAN3]
2016 – Minimed 670 approved by FDA [SOURCE UNAVAILABLE]

Challenges:

Insulin shock – solved with algorithm
Septum infection

Relevant Organizations:

Medtronic

Sources:

[PAN1] *Automation control of blood sugar a servomechanism for glucose monitoring and control. Kadish*. 1963.
[PAN2] *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.
[PAN3] *Wearable artificial endocrine pancreas with needle-type glucose sensor*. Shichiri et. al. 1982.

Replace Joints – Knee

The knee joint is comprised of the patella, quadriceps tendon, patellar tendon, lateral condyle, medial condyle, articular cartilage, lateral collateral ligament, anterior cruciate ligament, posterior cruciate ligament, meniscus, and medial collateral ligament. Knee cartilage wears out over time. Currently an operation is available to replace the knee with artificial materials.

History:

1880 – Joint replacement by ivory [SOURCE UNAVAILABLE]
1891 – Knee replacement [KNE1]
1908 – Biological knee joint replacement [ANK1][SOURCE UNAVAILABLE]
1952 – Tibia surface replacement [KNE2]
1960 – Duocondylar knee [SOURCE UNAVAILABLE]
1970 – Duopatellar knee [SOURCE UNAVAILABLE]
1973 – Total condylar knee [SOURCE UNAVAILABLE]
1977 – Low contact stress knee [SOURCE UNAVAILABLE]
1978 – IBPS knee [SOURCE UNAVAILABLE]
1980 – Porous-coated anatomical knee [SOURCE UNAVAILABLE]
1988 – IBPS-II knee [SOURCE UNAVAILABLE]
1992 – Medially biased kinematics knee [SOURCE UNAVAILABLE]
1994 – Optetrak Posterior-stabilized knee [SOURCE UNAVAILABLE]
1997 – Two area radii contact knee [SOURCE UNAVAILABLE]

Challenges:

Immune rejection

Relevant Organizations:

Johns Hopkins Medicine
Zimmer
Stryker
DePuy
Smith & Nephew
Conformis

Sources:

[KNE1] *The Classic – report on the positive results obtained by the modern surgical experiment regarding the suture and replacement of defects of superior tissue, as well as the Utilization of Re-absorbable and Living Tamponade in Surgery*. Themistocles Gluck. 1891. {2011}
[KNE2] *The Classic – Tibial plateau prosthesis*. McKeever. 1960. {2005}

Replace Joints – Jaw

Jaw replacement is difficult for me to understand. What I've gathered is that various materials have been used over the years, and it appears the jaw was the first implant to use tantalum. There was also a controversy surrounding silastic, with it being used, then banned, then apparently brought back many years later? Except the references I found for silastic being re-approved involve breast implants, not jaw implants.

History:

1947 – Tantalum used in jaw replacement [JAW1] [SOURCE UNAVAILABLE]
1952 – Vitallium used for jaw replacement [JAW4]
1957 – Stainless steel plate used in jaw replacement [JAW2]
1967 – Silastic used in human [JAW3]
1980 – Silastic used for jaw replacement [SOURCE UNAVAILABLE]
1988 – Silastic found to be dangerous [JAW5]

Challenges:

Immune rejection

Development:

Relevant Organizations:

Xilloc

Sources:

[JAW1] *Tantalum as a replacement for bone in oral surgery*. Rieger. 1950.
[JAW2] *A new surgical procedure for the creation of a false temporomandibular joint in cases of ankylosis by means of non-electrolytic metal*. Smith, Robinson. 1957.
[JAW3] http://www.acpoc.org/index.php/membership/newsletters-journals/icib--jacpoc-volumes-1961-1989/volume-10/number-6/a-silicone-rubber-implant-to-supplement-the-keller-toe-arthroplasty
[JAW4] *Vitallium Jaw Replacement*. Genest. 1956.
[JAW5] *Silicone-induced foreign-body reaction after temporomandibular joint arthroplasty - case report.* Acton, Hoffman, McKenna, Moloney. 1969.

Replace Joints – Hip

History:

1891 – Artificial hip replacement [SOURCE UNAVAILABLE]
1925 – Pyrex hip [HIP1]
1938 – Steel hip [HIP5]
1953 – Chrome-cobalt hip [HIP2]
1959 – PTFE hip [HIP6]
1961 – Low Friction Arthroplasty [HIP4]
1962 – High molecular weight polyethylene hip [HIP6]
1970 – Ceramic hip [HIP7]

Challenges:

Septic complications
Immune rejection
Polyethylene debris
Metallosis

Development:

Relevant organizations:

Orthopaedic Research Institute
Stryker
Zimmer
DePuy
Smith & Nephew

Sources:

[HIP1] *The Classic – Evolution of mould arthroplasty of the hip joint*. Smith-Petersen. 1948. {2006}
[HIP2] *Replacement of arthritic hips by the McKee-Farrar prosthesis*. McKee, Watson-Farrar. 1966.
[HIP4] *Arthroplasty of the hip a new operation*. Charnley. 1961.
[HIP5] *The surgery of the osteo-arthritic hip*. Wiles. 1958.
[HIP6] *Total hip replacement*. Charnley. 1974.
[HIP7] *Arthroplastie totale de la hanche par prothese en alumine frittee – Etude experimentale et premieres applications cliniques*. Boutin. 1972. {2014}

Replace Bones – Femur

Femur replacement is a standard orthopedic procedure that dates back to the 1950's. Original papers and sources are lacking online, and no review on the history of femoral replacement has been done.

History:

Have not found a historical review or summary

Challenges:

Infection due to long operation time – partially ameliorated by silver coating
Blood Loss – solved

Relevant organizations:

Zimmer Biomet

Sources:

Replace Joints – Shoulder

Shoulder bones:

Humerus
Scapula
Acromion
Clavicle

History:

1893 – First documented artificial shoulder joint [SHO1][SOURCE UNAVAILABLE]
1955 – Vitallium shoulder joint [SHO2]
1974 – Reverse artificial shoulder joint [SHO3]
1985 – Grammont artificial shoulder joint [SOURCE UNAVAILABLE]

Sources:

[SHO1] *Artificial shoulder joint by Pean (1893)*. Lugli. 1978.
[SHO2] *The classic – Articular replacement for the humeral head*. Neer. 1955. {2011}
[SHO3] *A total shoulder endo-prosthesis*. Reeves, Jobbins, Dowson, Wright. 1974.

Replace Joints – Ankle

Ankle bones:

calcaneus
talus
navicular
medial cuneiform
intermediate cuneiform
lateral cuneiform
cuboid

History:

1911 – First biological ankle joint replacement [ANK1]
1970 – Total ankle replacement [SOURCE UNAVAILABLE]
1976 – New Jersey Cylindrical Design [SOURCE UNAVAILABLE]
1976 – Irvine ankle arthroplasty [ANK3]
1980 – TNK ceramic ankle [ANK4]
1981 – Scandanavian total ankle replacement [SOURCE UNAVAILABLE]
1984 – Agility ankle [SOURCE UNAVAILABLE]

Sources:

[ANK1] *Implantation of joints*. Eloesser. 1913.
[ANK3] *Irvine ankle arthroplasty*. Waugh, Evanski, McMaster. 1976.
[ANK4] *TNK ankle – the ceramic 2-component total ankle prosthesis*. Kosugi et. al. 2014.

Replace Tissues – Skeletal Muscle

Synthetic muscles are attempts at replacing human muscle when it fails to perform. I think a good synthetic muscle has these features – a built in power supply, single wire control, real-time variable control, similar speed as a human muscle, and flexibility.

History:

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]

Challenges:

Development:

The McKibben muscle can be improved by increasing the number of pneumatic bottlenecks it has. Most of the contraction is done on the very ends of the tubing, where the rubber goes horizontal. By adding bottlenecks to the main line, it should be possible to increase the contraction length.

Currently no artificial muscle uses the mechanism present in an organic muscle, which is to pull threads past each other via a ratchet mechanism. A half-baked outline of a synthetic muscle concept is included in the attached document "Novel concepts for biological immortality".

Sources:

[MUS1] *Ueber die durch electricitut bewirkten formund volumenanderungen von dielectrischen korpern*. Rontgen. 1880.
[MUS2] *Piezoelectric effect in polarized poly (vinylidene fluoride)*. Fukada, Takashita. 1969.
[MUS3] *An electrochemical investigation of solid cadmium-gold alloys*. Olander. 1932.
[MUS4] *Artificial muscles from fishing line and sewing thread*. Haines et. al. 2014.
[MUS5] *Birefringence and ultrastructure of muscle*. Fischer. 1947.
[MUS6] *Hydraulically amplified self-healing electrostatic actuators with muscle-like performance*. Acome et. al. 2018.

Replace Cells – Nanobots

Nanobots are extremely small robots that perform specific functions. The concept is to inject them into the human body to complement or replace the functions of natural cells. When people think of nanobots they typically think of small robots repairing damage in the body but they could theoretically add abilities that are not currently available to humans. One example is neural dust (derived from Smart Dust [NANO12]), a project that aims to allow easy communication between the brain and external computing devices.

Nanorobotics and by extension nanomedicine can theoretically lead to biological immortality via nanoscale replacement of cells – replacing either the core functions of cells or replacing and augmenting repair mechanisms.

History:

1959 – "There's Plenty Of Room At The Bottom" lecture [NANO1]
1972 – Scanning Tunneling Microscopy [NANO2]
1986 – Atomic Force Microscopy [NANO3]
1986 – "Engines of Creation" published [NANO4]
1989 – Swarm Intelligence coined [SOURCE UNAVAILABLE]
1999 – "Nanomedicine" first technical book on nanorobotics published [NANO6]
1999 – Feature Oriented Scanning [NANO10]
1999 – Molecular rotor [NANO8]
2003 – Mechanosynthesis demonstrated [NANO9]
2018 – Nanobot used to target cancer in vivo [NANO11]

Developmental Pathways:

1) Understand every molecular mechanism in the human body
2) Replicate each mechanism using nanorobotics
3) Replace every mechanism in the human body with engineered replaceable nanoparts

1) Understand every repair mechanism in the human body
2) Build nanobots to emulate those repair mechanisms
3) Deliver nanobots to humans to replace those repair mechanisms

1) Design new repair mechanisms endemic to nanorobotic technology
2) Build nanobots with these repair mechanisms
3) Deliver nanobots to humans to repair the body

Current Challenges:

Test material availability – it is difficult to create a lot of material for test environments for nanorobots.

Design – it is difficult to design nanorobotics for nanomedicine because it requires expertise in biology, mechanical engineering, chemistry, and nanotechnology. Questions like "if a person falls asleep next to a magnet, will they get a blood clot?" remain unanswered for circulating nanobots.

Relevant Goals:

Replicate all human cellular machinery in artificial nanobot format.

Relevant Organizations:

Institute for Molecular Manufacturing
Nanofactory Collaboration
Laboratory for Multiscale Regenerative Technologies
IBM Nanotechnology Research Division

Sources:

[NANO1] *There's plenty of room at the bottom*. Feynman. 1960.
[NANO2] *The topografiner – An instrument for measuring surface microtopography.* Young, Ward, Scire. 1972.
[NANO3] *Atomic Force Microscope*. Binnig, Quate, Gerber. 1986.
[NANO4] http://e-drexler.com/d/06/00/EOC/EOC_Table_of_Contents.html
[NANO6] http://www.nanomedicine.com/NMI.htm
[NANO8] *Unidirectional rotary motion in a molecular system*. Kelly, De Silva, Silva. 1999.
[NANO9] *Mechanical vertical manipulation of selected single atoms by soft nanoindentation using near contact atomic force microscopy*. Oyabu et. al. 2003.
[NANO10] *Method for measuring surface relief by means of scanning probe type microscope*. Lapshin. 1999.
[NANO11] *A DNA nanorobot functions as a cancer therapeutic in response to a molecular trigger in vivo*. Li et. al. 2018.
[NANO12] *Smart dust – communicating with a cubic-millimeter computer.* Warneke, Last, Liebowitz, Pister. 2001.
[NANO13] *Brain-machine interfaces as the new frontier in extreme miniaturization.* Rabaey. 2011.

Replace Genes – Synthetic Genomics

Synthetic genomics is the pursuit of completely artificial genes. Currently, they are still based off of the GCAT code that is used in DNA but theoretically may include novel nucleotides in the future. By having the ability to build artificial genomes, it may be possible to engineer DNA that performs better than the current system – especially in regard to epigenetics and regulation. Artificial DNA may allow biological immortality by being easier to repair and maintain, reducing the effort required for maintenance.

It may be possible to create a 'purified' genome (including epigenetic patterns) outside the cell then deliver it into the body to replace the aging, degraded genome.

History:

1910 – Synthetic Biology terminology used [SOURCE UNAVAILABLE]
2000 – Synthetic biological circuit [SOURCE UNAVAILABLE]
2010 – Synthetic genome transplanted into bacteria [SG3]

Sources:

[SG3] *Creation of a bacterial cell controlled by a chemically synthesized genome*. Venter et. al. 2010.

Repair Damage

Damage repair is a straightforward method of attempting biological immortality. When the body gets damaged, repair it. For repair to constitute a pathway to immortality it must repair the system such that it becomes impossible to tell that damage took place at all. Most methods of medical repair are not capable of complete repair.

Repair Body – Hormesis

Hormesis is defined as two mechanisms.

1) The triggering of natural repair mechanisms via induced stress. Eating polyphenols triggers an immune response that is beneficial (so the theory goes).

2) Direct positive response to low levels of stress vs. negative response to high levels of stress. Mildly heating the body kills certain bacteria while normal body cells remain unaffected. Extreme heating of the body kills everything.

Philosophically the first mechanism presents a problem to those who wish for stability, in the sense that the core mechanism relies on instability. To clarify – hormesis theoretically should only work if the body isn't used to the stressor. Once the body gets used to the stressor, the compensatory reaction changes and likely becomes less effective.

Consider a house that is located in Florida, in a hurricane zone. The house has got some wear and tear, and a few shingles are missing. In order to repair the house, the homeowner lies about an incoming hurricane (this is the hormetic stressor), causing a repairman to come to the house and fix it. The hurricane never comes, but now the house is in better condition. However, the next time the homeowner lies about a hurricane, the repairman figures that nothing is actually wrong and doesn't bother to repair the house as well as he did the first time. Now the homeowner needs to find something else – maybe a rogue tornado, or a tsunami threat – to lie about in order to achieve the same effect.

Similarly, exposing the body to low doses of stressors such as polyphenols, radiation, or xenohormetics may require that the body is ill-adapted to the stressor to begin with, and that subsequent exposure creates less of a beneficial effect.

History:

1888 – Yeast stimulated to grow via small doses of poisons [SOURCE UNAVAILABLE]
1943 – Hormesis coined [HES1][SOURCE UNAVAILABLE]

Novel Concepts:

So on the one hand, we are looking for an infinitely evolving stressor that doesn't necessarily kill people but that will reliably cause some kind of hormetic reaction. And on the other hand, we have the flu virus – an infinitely evolving, uncurable disease which doesn't necessarily kill people who have functioning immune systems. There may be something there.

Relevant Supplements:

Docosahexaenoic Acid
Extra Virgin Olive Oil
Curcumin
Alcohol
Flavonols
Sulforaphane
Capsaicin
Allicin
Resveratrol
Isothiocyanate

Sources:

[HES1] *Effects of extracts of western redcedar heartwood on certain wood-decaying fungi in culture*. Southam. 1943. UNAVAILABLE ONLINE.

Repair Tissue – Skin

Skin repair is a target of the cosmetics industry. Despite the conspiratorial outlook that makeup companies want us to have bad skin so they sell more product, organizations like Loreal are attempting to solve the underlying mechanisms for skin regeneration. They are just currently bad at it.

History:

Challenges:

Scar tissue formation – solved upon discovery that hair follicles prevent scar tissue formation during skin regrowth. [SKIN1]

Relevant Organizations:

Relevant Goals:

Repair the skin to the condition of a teenager.

Sources:

[SKIN1] *Regeneration of fat cells from myofibroblasts during wound healing*. Plikus et. al. 2017.

Repair Cells – Nanobots

See “Replace Cells – Nanobots”

Repair Cells – Proteolysis

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.

It is thought that part of why hormesis works is that it increases the rate of proteolysis beyond the bare minimum, repairing proteins before they lose full functionality thereby keeping cells in better condition.

History:

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]

Challenges:

Cannot measure proteolytic rates in vivo

Relevant Goals:

Maximize proteolytic rate within given biological boundary conditions. Be capable of fixing all components of the proteolytic system.

Relevant Organizations:

Proteostasis Therapeutics

Relevant Supplements:

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.

Repair Cells – Autophagy

Like proteolysis, autophagy is a natural repair mechanism but instead of only breaking down proteins it involves the wholesale breakdown of entire cell structures. 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. It's also a buzzword for supplement effects, effective because it is commonly understood and because it is difficult to measure. By attaining better control over autophagy it may be possible to improve the repair of our cells to the point of reaching biological immortality.

Autophagy and proteolysis share many historical moments given their intimate connection.

History:

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]

Challenges:

Cannot measure autophagy in vivo, therefore cannot determine efficacy of any attempt at controlling autophagy in vivo.

Development:

Relevant Organizations:

Nordic Autophagy Society

German Autophagy Association
Transautophagy (COST)
Danish Cancer Society – Center for Autophagy, Recycling, and Disease

Relevant Goals:

Attain selective control of rate of autophagy and autophagy targets within each cell in the body.

Relevant Supplements:

Oleander leaf
Isoflavonoid glabridin
Icariin
Solanum nigrum
Ipomoea batatas
Indukantha Ghritha
Saussurea lappa
Astragalus corniculatus
Coffee
lysine
Green Tea
Lithium
Resveratrol
Vitamin D
Rapamycin [AUTO7]
Nigericin [AUTO7]
Wiskostatin [AUTO7]
Fluspiriline [AUTO7]
Niguldipine [AUTO7]
Trifluoperazine [AUTO7]
Nicardipine [AUTO7]
Penitrem A [AUTO7]

Sources:

[AUTO1] *The dynamic state of body constituents*. Schoenheimer. 1942.
[AUTO2] *Independent genetic control of the catalytic activity and the rate of degradation of catalase in mice*. Ganschow, Schimke. 1968.
[AUTO3] *Cytoplasmic components in hepatic cell lysosomes*. Ashford, Porter. 1962.
[AUTO4] *Studies on cellular autophagocytosis: The formation of autophagic vacuoles in the liver after glucagon administration*. Arstila, Trump. 1968.
[AUTO5] *3-Methyladenine: specific inhibitor of autophagic/lysosomal protein degradation in isolated rat hepatocytes*. Seglen, Gordon. 1982.
[AUTO6] *Amino acid inhibition of the autophagic lysosomal pathway of protein degradation in*

isolated rat hepatocytes. Seglen, Gordon, Poli. 1980.
[AUTO7] *Small molecule regulators of autophagy identified by an image-based high-throughput screen*. Zhang et. al. 2007.
[AUTO8] *Isolation and characterization of autophagy-defective mutants of saccharomyces cerevisiae*. Tsukada, Ohsumi. 1993.
[AUTO9] *Selective mitochondrial autophagy or Mitophagy as a targeted defense against oxidative stress mitochondrial dysfunction and aging*. Lemasters. 2005.
[AUTO10] *Tor a phosphatidylinositol kinase homologue controls autophagy in yeast*. Noda, Ohsumi. 1998.
[AUTO11] *Autophagy regulates lipid metabolism*. Singh et. al. 2009.
[AUTO12] *Mature ribosomes are selectively degraded upon starvation by an autophagy pathway requiring the UBp3p-Bre5p ubiquitin protease*. Kraft, Deplazes, Sohrmann, Peter. 2008.
[AUTO13] *Isolation and characterization of yeast mutants in the cytoplasm to vacuole protein targeting pathway*. Harding, Morano, Scott, Klionsky. 1995.
[AUTO14] *Ciba Foundation Symposium – Lysosomes chapter 1*. Duve. 1963.

Repair Genes – DNA Repair

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, HSF-1,

History:

1904 – Werner's syndrome defined [DNA7] [SOURCE UNAVAILABLE]
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]

Challenges:

Political turmoil prevented early progress

Development:

It appears we have identified all the various DNA repair mechanisms, but have not yet attained control over any of them. We can artificially inhibit DNA repair through various methods, but cannot induce it or increase the rate.

Relevant Organizations:

(too many to list?)

Relevant Supplements:

Vitamin C, E, B6, B12
Folate
Phosphorous
Zinc
Carotenoids
Nicotinamide
Magnesium

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.

Prevent Damage Accumulation

If you don't break the car, you don't have to fix it. Preventing damage means you don't have to fix it later.

Prevent Body Damage – Caloric Restriction

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.

History:

??? BC – origin of meal times [SOURCE UNAVAILABLE]
??? BC – Identification of obesity as a disorder [SOURCE UNAVAILABLE]
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]

Development:

Caloric restriction increases lifespan
Caloric restriction in early life increases lifespan more

Relevant Organizations:

Caloric Restriction Society

Sources:

[CAL1] *The effect of retardation of growth upon the breeding period and duration of life of rats*. Osborne, Mendel. 1917.
[CAL2] *New aspects of the dietary effect of life prolongation in rodents – what is the role of obesity in aging?* Stuchlikova, Juricova-Horakova, Deyl. 1975.
[CAL3] *An essay on health and long life.* Cheyne. 1724.
[CAL4] *A receptor in pituitary and hypothalamus that functions in growth hormone release.* Howard et. al. 1996.

Prevent Body Damage – Assorted Toxins and Mutagens

History:

??? BC – Olive oil used as sunscreen
200 BC – Greeks describe lead poisoning
210 BC – Chinese emperor dies from mercury poisoning in pursuit of immortality
1801 – UV radiation discovered
1900 – Gamma radiation discovered
1967 – Selenium counteracts mercury poisoning [ROS6]
2008 – Selenium-mercury interaction inverted, mercury is toxic because it removes selenium

Banana radiation
Benzoapyrene – polyaromatic hydrocarbons
Dioxins
Vinyl Chloride
Methanol
Arsenic

This section is probably going to be eliminated

Sources:

[ROS6] The protective effect of small amounts of selenite in sublimate intoxication. Parizek, Ostadalova. 1966.

Prevent Cell Damage – Advanced Glycation Endproducts

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. Unlike other toxins – such as mercury – AGE's have a receptor associated with them which implies that to some extent they are part of the metabolic system. AGE's are also often very aesthetically attractive – the browning on bread and meat is attributed to advanced glycation endproducts.

History:

1912 – Maillard reaction postulated [SOURCE UNAVAILABLE]
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 – Browning 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]

Development:

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 an 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, 22 amino acids (depending on who you ask), and 5 nucleotides. That's a total of 57 potential matching partners for the various sugars. I can't find a good list of sugars, but I did find a list of 20 monosaccharides for mass spectrometry. Just for the monosaccharides, that gives 1140 potential adducts, not including various permuations and cleavages of each. Add to this the possibility of involving multiple amino acids, or other lipid types such as phospholipids, and the list balloons out logarithmically.

The current 'star' of AGE's is CML – carboxymethyl(lysine), which is derived from an oxidatively cleaved Fructose-Lysine adduct. Three different strains of thought combine in this sentence – oxidative degradation, excess fructose toxicity, and excess lysine toxicity.

Relevant Supplements:

Vitamin C
Benfotiamine
Pyridoxamine
Alpha-lipoic acid
Taurine
Pimagedine
Aspirin
Carnosine
Metformin
Pioglitazone
Pentoxifylline

Sources:

[AGE2] *Dehydrated foods – chemistry of browning reactions in model systems*. Hodge. 1953.
[AGE3] *Scavenger receptor of human monocytic leukemia cell line THP-1 and murine macrophages for nonenzymatically glycosylated proteins*. Takata et. al. 1989.
[AGE4] *Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins*. Neeper et. al. 1992.
[AGE5] *Structure of carbohydrate of hemoglobin AIc*. Koenig, Blobstein, Cerami. 1976.
[AGE6] *Nonenzymatic browning in vivo – possible process for aging of long-lived proteins.* Monnier, Cerami. 1981.
[AGE7] *Oxidation of glycated proteins – age-dependent accumulation of N-carboxymethyl lysine in lens proteins*. Dunn, Patrick, Thorpe, Baynes. 1989.
[AGE8] *Orally absorbed reactive glycation endproducts (glycotoxins) - an environmental risk factor in diabetic nephropathy.* Koschinsky et. al. 1997.

Prevent Cell Damage – Heat Shock Proteins

The heat shock response is a protein based response to thermal damage. Heat causes motion, which leads to unfolding of proteins and breaking of weak atomic bonds in vital cell structures. To prevent heat damage, specific proteins activate during heat stress and attach to other proteins, stabilizing cell structures and preventing unfolding.

History:

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]

Development:

We have a list of the relevant proteins and processes involved in the heat shock response. We cannot artificially trigger the response yet.

Relevant Supplements:

Sulforaphane
Extra Virgin Olive Oil
Zinc
Circumin
Resveratrol
Blueberry
Colostrum
Lion's Mane
Graviola
Lavender oil
Celastrol
Artemesia extracts

Relevant Organizations:

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.

Prevent Cell Damage – Reactive Oxygen Species

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. The “Afterburner” theory of aging.

History:

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]

Development:

Reactive oxygen species identified
Various methods of counteracting ROS developed

Relevant Organizations:

Relevant Supplements:

Selenium
Glutathione precursors
Antioxidants
Polyphenols
Quercetin
Coenzyme Q10
Saffron

Sources:

[ROS1] *La Pression Barometrique*. Bert. 1878.
[ROS2] *An instance of trivalent carbon – triphenyl-methyl*. Gomberg. 1900.
[ROS3] *Aging – A theory based on free radical and radiation chemistry*. Harman. 1956.
[ROS4] *Selenium as an integral part of factor 3 against dietary necrotic liver degeneration.* Schwarz, Foltz. 1957.
[ROS5] *Enzymatic synthesis of deoxyribonucleotides – Isolation and characterization of thioredoxin, the hydrogen donor from escherichia coli B*. Laurent, Moore, Reichard. 1964.
[ROS6] *The protective effect of small amounts of selenite in sublimate intoxication*. Parizek, Ostadalova. 1966.
[ROS7] *Superoxide Dismutase an enzymatic function for erythrocuprein*. McCord, Fridovich. 1969.
[ROS8] *Glutathione peroxidase – a selenoenzyme*. Flohe, Gunzler, Schock. 1973.
[ROS9] *Clostridial glycine reductase complex – purification and characterization of the selenoprotein component*. Cone, Martin del Rio, Stadtman. 1977.
[ROS10] *Effects of a low selenium status on the distribution and retention of selenium in the rat*. Behne, Hofer-Bosse. 1984.
[ROS11] *Dietary and tissue selenium in relation to methylmercury toxicity*. Ralston, Ralston, Blackwell III, Raymond. 2008.
[ROS12] *Deletion of the mitochondrial superoxide dismutase sod-2 extends lifespan in caenorhabditis elegans*. Raamsdonk, Hekimi. 2009.
[ROS13] *Does the oxidative stress theory of aging explain longevity differences in birds?* Montgomery, Hulbert, Buttemer. 2012.

Remove Damage After Accumulation

It is my opinion that simply removing damage will not lead to biological immortality, but there are those who disagree and there is some evidence to support the idea that damage removal could lead to immortality. The hydra, a small multicellular organism famous for not aging, relies on systematically shedding damaged components as its mechanism of youth. Removal of damage after accumulation relies on the assumption that the body can regenerate completely if only accumulated damage was not getting in the way. Sometimes this is the case, other times it is not. This report will focus on damage removal that leads to complete repair.

Remove Cell Damage – Senolytics

Senolytics is the process of selectively removing senescent cells from the body.

This process cannot lead to biological immortality, because it doesn't target the underlying mechanisms of aging. However, it can delay the aging process.

History:

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]

Relevant Organizations:

Unity Biotechnology
Robert and Arlene Kogod Center on Aging
Mayo Clinic

Development:

Various senolytics have been discovered and tested in vitro on human cells or in vivo on mice. No confirmation that senolytics extend lifespan in humans yet.

Sources:

[SEN1] *Senescence and Rejuvenation*. Minot. 1891.
[SEN2] *Subunit rearrangement of the cyclin-dependent kinases is asssociated with cellular transformation*. Xiong, Zhang, Beach. 1993.
[SEN3] *Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders*. Baker et. al. 2011.
[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.
[SEN6] *9-2-hydroxy-1-hydroxymethylethoxymethylguanine – a selective inhibitor of herpes group virus replication*. Field et. al. 1983.
[SEN7] *Mitochondrial DNA damage induces apoptosis in senescent cells*. Laberge. 2013.
[SEN8] *Purification to homogeneity and characterization of human B-cell differentiation factor (BCDF or BSFp-2)*. Hirano et. al. 1985.
[SEN9] *The Achilles heel of senescent cells from transcriptome to senolytic drugs*. Zhu et. al. 2015.
[SEN10] *Discovery of N-2-chloro-6-methyl-phenyl-2-6-4-2-hydroxyethyl-piperazin-1-yl-2-methylpyrimidin-4-ylaminothiazole-5-carboxamide BMS-354825, a dual Src-abl kinase inhibitor with potent antitumor activity in preclinical assays*. Lombardo et. al. 2004.
[SEN11] *Studien uber Quercetin und seine Derivate.* Herzig. 1894.
[SEN12] *New agents that target senescent cells – the flavone, fisetin, and the BCL-XL inhibitors A1331852 and A1155463*. Zhu et. al. 2017.
[SEN13] *Identification of a novel senolytic agent, navitoclax, targeting the BCL-2 family of anti-apoptotic factors*. Zhu et. al. 2016.

Remove Protein Damage – Tau/Amyloid Beta

Amyloid Beta and Tau are proteins that aggregate in the brain, creating large chunks of material that cannot be broken down. I don't quite understand the acetylcholinesterase mechanism for alzheimers so I'm leaving it out for now. I believe it has something to do with the symptom – that the plaques inhibit normal activity and preventing degradation of acetylcholine helps with memory. That implies that the drugs currently available only treat the symptom and not the underlying disease. The acetylcholine section is uninteresting as far as this report is concerned.

Figuring a general solution for removing aggregated proteins allows us to prevent a range of damage accumulation, potentially leading to biological immortality.

History:

1907: Alzheimer's disease identified [ALZ1]
1964: Plaques and tangles observed [ALZ2]
1984: Amyloid-beta associated with Alzheimer's disease [ALZ3]
1985: Tau protein associated with Alzheimer's disease [ALZ4]
1987: Amyloid precursor protein identified [ALZ5]

Challenges:

No way of selectively disrupting protein aggregations
No way of measuring protein aggregation in vivo

Development:

Relevant Goals:

Relevant Organizations:

Sources:

[ALZ1] *An english translation of alzheimers 1907 paper Uber eine eigenartige erkankung der hirnrinde*. Stelzmann, Schnitzlein, Murtagh. 1907. {1995}
[ALZ2] *Ultrastructural studies in Alzheimer's presenile dementia*. Terry, Gonatas, Weiss. 1964.
[ALZ3] *Alzheimers disease and Downs syndrome – sharing of a unique cerebrovascular amyloid fibril protein*. Glenner, Wong. 1984.
[ALZ4] *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.
[ALZ5] *The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor*. Kang et. al. 1987.

Remove Protein Damage – Crosslinked Proteins

Crosslinked proteins refers to proteins that have covalently bonded with each other, as opposed to ionic or hydrogen bonding. Crosslinked proteins are implicated in arterial wall stiffness as well as skin aging, but likely have much broader implications since they can affect any tissue that needs to stretch (such as the heart).

History:

1832 – Earliest concept of crosslinking, vulcanization of rubber [SOURCE UNAVAILABLE]
1887 – Observation of accumulation of particles in marine worms [SOURCE UNAVAILABLE]
1900 – Clinkers of metabolism theory of aging [SOURCE UNAVAILABLE]
1952 – Cholesterol deposition in arteries attributed to crosslinking [CRO2]
1955 – Crosslinking theory of aging [CRO1]

Challenges:

Development:

The crosslinking theory has transitioned into a more specific version involving advanced glycation endproducts and amadori products.

Relevant Organizations:

Sources:

[CRO1] *Cross Linking – key to aging?* Bjorksten. 1955. {1957}
[CRO2] *A mechanism of cholesterol deposition on arterial walls*. Bjorksten. 1952.

Remove Protein Damage – 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 or proteolysis but accumulates with age, presumably as a product of degrading proteolytic efficiency.

A lot of papers involving lipofuscin reference a particular review - "Lipofuscin – mechanisms of age-related accumulation and influence on cell function" as a source for lipofuscin being a product of oxidative damage. However, the section on oxidative origin of lipofuscin in that review references yet another review "Lipofuscin – mechanisms of formation and increase with age"

History:

1842 – Description of autofluorescent material in neurons [SOURCE UNAVAILABLE]
1886 – Association of autofluorescent material with age [LIP1]
1912 – Lipofuscin coined [SOURCE UNAVAILABLE]
1959 – Lipofuscin accumulates linearly with age [LIP2]
1984 – Lipofuscin formation tied to oxidative damage [LIP4]
1995 – In vivo measurement of lipofuscin [LIP3]

Challenges:

Lipofuscin is too heterogeneous to characterize it's composition but generally it contains lipids and proteins.

Development:

In vivo measurement of lipofuscin appears to have been developed using fluorescence.
No method of artificially breaking down lipofuscin exists yet.
Lipofuscin apparently accumulates in slow dividing or post-mitotic cells. This brings up an interesting question regarding it's interaction with something like caloric restriction, which elongates life on the basis of slowing growth. Does slower growth mean more lipofuscin accumulation, due to lack of dilution? Can we measure it in vivo – between CR and controls – to find out?

Sources:

[LIP1] *Beitrage zur kenntniss der nervenzellen in den peripheren ganglien*. Koneff. 1886.
[LIP2] *Rate and magnitude of age pigment accumulation in the human myocardium*. Strehler, Mark, Mildvan, Gee. 1959.
[LIP3] *In vivo measurement of lipofuscin in Stargardt's disease – fundus flavimaculatus*. Delori et. al. 1995.
[LIP4] *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.

Reprogramming

Some believe that aging is a result of a breakdown in regulation of the body. As time passes, the complex systems that control the soma begin to spontaneously degrade and the result is poor health. Others believe that these flaws are not flaws at all, but are actually a product of evolution favoring controlled obsolescence. In either case, rather than replacing or repairing the systems that comprise the soma it may be possible to reprogram the body to maintain good health.

Reprogramming may lead to a cascade of downstream effects that keeps the soma alive indefinitely. Natural repair systems, gene expression, and body synchronicity are governed by regulatory systems. By reprogramming these systems, it may lead to indefinite regeneration of the soma.

What we need:

- A list of all programs operating in the human body
- The ability to control each program
- Knowledge of what the optimal setup should be for each program

Reprogramming Body – Klotho

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, leading to biological immortality.

History

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

Development:

Challenges:

No way of measuring Klotho in real time

Relevant Organizations:

RayBiotech

Sources:

[KLO1] *Mutation of the mouse klotho gene leads to a syndrome resembling aging*. Kuro-o et. al. 1997.
[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.

Reprogramming Body – Menopause

Menopause, and to a lesser extent andropause, are the best examples of programmed aging. The prevailing theory for why menopause exists is that offspring of extremely old individuals tend to do poorly when competing against offspring of younger individuals. This mechanism gave rise to an off-switch that increases fitness at the species level by shutting down the reproductive system. Once the reproductive system shuts down, the pressure of natural selection also is removed which prevents longevity developments on an evolutionary scale from taking place post-menopause.

If such a system of programmed obsolescence can arise naturally, what other systems may have also arisen which prematurely truncate our lives?

History

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]
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 observed to undergo menopause [SOURCE UNAVAILABLE]
2015 – Inovium founded [SOURCE UNAVAILABLE]

Relevant Supplements:

Black Cohosh Root
Soy Isoflavones
Magnolia Bark
Melatonin
Ginkgo Balboa
Synetrim CQ
Flaxseed
Angelica sinensis
Vitamin B, D, E
Evening Primrose oil
Milk Thistle
Ashwagandha
Calcium
Curcumin
Coenzyme Q10

Relevant Organizations:

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.

Reprogramming Body – Circadian Rhythm

It could be said that the entire quest for biological immortality falls under the umbrella of chronobiology – because the goal is to discover how to keep **biological systems** operating for infinite **time**. The term chronobiology and circadian biology themselves seem to fluctuate in a rhythmic pattern, when one becomes distasteful (such as when the person who coined the term goes partially insane) the other becomes used. Generally they refer to the same thing. Circadian rhythm, on the other hand, seems to refer to the daily sleep cycle. As people age, their circadian rhythm becomes misaligned not just in relation to the environment but also between individual organs.

Causality is not established yet. It could be that aging causes circadian malfunction, or it could be that circadian malfunction causes aging. If the latter is true, control over circadian rhythm may lead to lifespan extension and be a necessary component for biological immortality.

The circadian rhythm biological clock is implicated in DNA repair, brain metabolite clearance, and SIRT acetylation.

History

350BC – Androsthenes describes diurnal leaf movements [SOURCE UNAVAILABLE]
1729 – First record of circadian oscillation [CIRC1]
1896 – Experiments on sleep [SOURCE UNAVAILABLE]
1918 – 24 hour pattern observed even in absence of light and temperature changes [SOURCE UNAVAILABLE]
1959 – Circadian coined [SOURCE UNAVAILABLE]
1971 – Period gene discovered [CIRC2]
1973 – Frequency gene discovered [CIRC6]
1978 – National Institute on Aging initiative targeting sleep changes and aging [SOURCE UNAVAILABLE]
1989 – Rev-erb alpha discovered [CIRC9]
1994 – Timeless gene discovered [CIRC7]
1994 – ROR alpha discovered [CIRC10]
1994 – Clock gene discovered [CIRC5]
1996 – Cryptochrome gene discovered [CIRC8]
1997 – BMAL1 (ARNTL) gene discovered [CIRC11]
2013 – Glymphatic system discovered [CIRC4]
2013 – Glymphatic system associated with sleep cycle [CIRC3]

Challenges:

Clock knockout mice have been shown to exhibit normal rhythms, indicating that the circadian clock is still not completely correctly identified.

Development:

Need to know when it was discovered that organs have individual circadian rhythms.

Sources:

[CIRC1] *Observation Botanique*. Mairan. 1729.
[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.

Reprogramming Genes – Telomeres

Telomeres are chromosomal endcaps that degrade after each cell replication, creating a hard coded limit (called the Hayflick Limit) on the number of times a cell can divide. Telomerase is an enzyme that extends the lengths of telomeres, and is present in human stem 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. The breakdown in regulation of telomeres is a direct cause of cellular senescence.

History

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]

Challenges:

Early mistakes were made when everyone assumed immortality was an intrinsic property of cells, based on Alexis Carrel's chick fibroblast experiment [TELO1]. It is likely that those cells were either cancerous or had reintroduction of new cells or perhaps malicious intent was involved.

Telomere length has been found to not be associated with age, and it fluctuates quickly. Telomere length in an astronaut lengthened significantly in space then began shortening within days of returning to earth [TELO5].

Development:

Telomere length can be measured. Telomerase can be activated in vivo. It is not known whether elongating telomere length reverses aging. It is likely that telomere length is a symptom, not a cause.

Sources:

[TELO1] *On the permanent life of tissues outside of the organism*. Carrel. 1912.
[TELO2] *A tandemly repeated sequence at the termini of the extrachromosomal ribosomal RNA genes in Tetrahymena*. Blackburn, Gall. 1978.
[TELO3] *Identification of a specific telomere terminal transferase activity in tetrahymena extracts*. Greider, Blackburn. 1984.
[TELO4] *Telomeres shorten during ageing of human fibroblasts*. Harley, Futcher, Greider. 1990.

[TELO5] https://www.nasa.gov/feature/how-stressful-will-a-trip-to-mars-be-on-the-human-body-we-now-have-a-peek-into-what-the-nasa
[TELO6] *Telomerase catalytic subunit homologs from fission yeast and human*. Nakamura et. al. 1997.
[TELO7] *Telomerase activity is restored in human cells by ectopic expression of hTERT (hEST2), the catalytic subunit of telomerase*. Counter et. al. 1998.
[TELO8] https://bioviva-science.com/blog/2017/3/2/first-gene-therapy-successful-against-human-aging

Reprogramming Genes – 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.

Progress:

1942 – Epigenetics [MET1]
1964 – Methylation and acetylation of histones [MET2]
1966 – DNA methylation [SOURCE UNAVAILABLE]
1977 – Ethionine inhibits DNA methylation [MET3]
1980 – 5-azacytosine inhibits DNA methylation [MET4]
1982 – DNA methylation of adenine for DNA repair in prokaryotes [MET5]
19?? – 5-aza-2-deoxycytidine inhibits DNA methylation
1992 – Bisulfite detection of methylation [MET6]

Development Pathway:

Identification of methylation locations and mechanisms → Control of methylation → Induce optimal methylation pattern

So far most work has focused on identification of methylation mechanisms and locations. It is possible to measure methylation and produce reliable data in the form of an epigenetic timestamp and correlations for diagnostic purposes.

We are mostly done with identification and partially moving into control. All control efforts so far have focused on changing methylation rate over long periods of time. Nobody has yet altered methylation on short timescales – such as stripping methylation from a living cell or hypermethylating a living cell via chemical means. Metformin is thought to upregulate the DNA methylation cycling process but has not yet been fully tested.

Attempting to identify or control methylation in other species prior to mammals/humans is generally

considered a wasted effort. Prokaryotes have a different method of methylation which affects adenine as well as cytosine.

Challenges:

It is unknown what the optimal pattern should be at any given age. The pattern at birth is known, but simply returning methylation to birth state has not been tested. Demethylating agents are extremely carcinogenic.

A small but important step would be to figure out how to hypomethylate or hypermethylate either stem cells or tissues in vitro without causing cancer and then watch the effects.

Relevant Goal:

The goal is to control methylation patterns of all DNA anywhere in the body.

Sources:

[MET1] *The epigenotype*. Waddington. 1942. {2012}
[MET2] *Acetylation and methylation of histones and their possible role in the regulation of RNA synthesis.* Allfrey, Faulkner, Mirsky. 1964.
[MET3] *Inhibition of DNA methylation by s-adenosylethionine with the production of methyl-deficient DNA in regenerating rat liver*. Cox, Irving. 1977.
[MET4] *Cellular differentiation, cytidine analogs and DNA methylation*. Jones, Taylor. 1980.
[MET5] *Methyl-directed repair of DNA base-pair mismatches in vitro.* Lu, Clark, Modrich. 1983.
[MET6] *A genomic sequencing protocol that yields a positive display of 5-methylcytosine residues in DNA strands*. Frommer et. al. 1992.

Reprogramming Genes – Acetylation

Histones can be modified by adding acetyl groups to lysine residues on the histone. The addition of acetyl groups opens up the packed histone configuration, making the DNA accessible to translation machinery. Acetyl regulation is modulated by HAT (Histone Acetyltransferase) and HDAC (Histone Deacetylase). HAT's are regulated by Sirtuins in a NAD+ dependent manner.

NAD+ is a vital energy intermediate that powers many different reactions in the cell. NAD+ declines with aging. It is thought that the reason for this is that CD38, an enzyme that degrades NAD+, increases with age. The reason CD38 increases with age may be related to inflammation. Regardless, NAD+ declines with age and adding NAD+ to certain animals extends lifespan dramatically. So far, evidence suggests that NAD+ supplements do work to increase circulating NAD+ levels but no evidence exists for the lifespan extension effect.

The novel concept of sirtuins and acetylation was the idea was that aging is caused by too many genes being turned on over time, which was caused by a breakdown in acetylation regulation. Rather than a loss of function, aging might actually be a gain of function, albeit the wrong type. Imagine a bakery being forced to hire 30 trapeze artists who spend all day getting paid from the bakery gross income to harass the bakers with silly antics. There is more activity going on, but the end result is a loss of efficiency. Such a mechanism might produce the phenotype we associate with aging – a genetic gain of function resulting in more frailty and weakness. Aging could theoretically be reversed by restoring regulation and silencing aberrant genes. This type of reprogramming could produce cascading health effects which lead to biological immortality.

History:

1906 – NAD+ discovered [SOURCE UNAVAILABLE]
1938 – Vitamin precursors of NAD+ discovered [ACE1]
1942 – Epigenetics [MET1]
1964 – Methylation and acetylation of histones [MET2]
1987 – Sirtuins discovered in yeast [ACE3]
2000 – Sir2 discovered to be NAD+ dependent [ACE4]
2014 – Elysium founded, attempts to use NAD+ precursor to raise NAD+ and prevent aging

Development Pathway:

Identification of methylation locations and mechanisms → Control of methylation → Induce optimal methylation pattern

Challenges:

It is unknown what the optimal pattern should be at any given age. The pattern at birth is known, but simply returning acetylation to birth state has not been tested.

End Goal:

The ultimate end goal is to control acetylation of all DNA anywhere in the body. The practical goal is to prevent acetylation change over time.

Relevant Supplements:

Resveratrol
NAD+
NR
NMN

Relevant Organizations:

Elysium
Harvard Medical School

Sources:

[ACE1] *The isolation and identification of the anti-black tongue factor*. Elvehjem, Madden, Strong, Woolley. 1938.
[ACE3] *Four genes responsible for a position effect on expression from HML and HMR in Saccharomyces cerevisiae*. Rine, Herskowitz. 1987.
[ACE4] *The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases*. Landry et. al. 2000.

Reprogramming Genes — Sumoylation

Sumoylation is the process by which Small Ubiquitin-like Molecules attach to various proteins of the cell to trigger activation or deactivation. It is implicated in modulating the behavior of p53, telomeres, autophagy, senescence, apoptosis, IGF, and peroxiredoxin.

History:

1996 – Sumoylation discovered [SUM1]

Sources:

[SUM1] *A novel ubiquitin-like modification modulates the partitioning of the ran-GTPase-activating protein RanGAP1 between the cytosol and the nuclear pore complex*. Matunis, Coutavas, Blobel. 1996.

Reprogramming Genes – Genetic knockout

Turning off genes by disrupting or removing them is one of the simplest methods of genetic engineering. Genetic knockout has produced some interesting longevity results in model organisms. Theoretically, if aging is a product of antagonistic pleiotropy, knocking out genes once they are no longer useful may be a valid strategy to stop aging and attain biological immortality. If aging is a product of gain-of-function resulting from incorrect acetylation, selectively knocking out genes may create the same effect as fixing gene silencing.

History:

1993 – C. elegans lives twice as long with daf-2 knockout [GKN1]

Sources:

[GKN1] *A c elegans mutant that lives twice as long as wild type*. Kenyon et. al. 1993.

Stopping Time

The ability to stop time gives us 'breathing room' so to speak when attempting to become biologically immortal. Any methods that slow or stop change are functionally equivalent to slowing or stopping time.

Cryonics

Cryonics is a product of humans realizing that low temperatures prevent change. If we can prevent all change, we can pause time and prevent the destruction of information – namely, the information contained by the human body when it is in a configuration of being alive. While cryonics itself does not have the capacity to grant immortality, it is a potential shortcut to preserving oneself until biological immortality is discovered.

History:

1720 – Vitrification [SOURCE UNAVAILABLE]
1755 – Artificial refrigeration [SOURCE UNAVAILABLE]
1766 – Cryopreservation of cells in snow [SOURCE UNAVAILABLE]
1866 – Red blood cells die but nuclei preserved when freezing [SOURCE UNAVAILABLE]
1946 – glycerol used to freeze frog cells [SOURCE UNAVAILABLE]
1955 – rats revived from 0C via microwaves with full recovery (no death within 10 days) [CRYO1]
1954 – human eye tissue frozen to -79 C and revitalized [CRYO3]
1956 – experiments on insect supercooling and ice crystal nucleation [CRYO2]
1956 – successful conception w/ frozen sperm [SOURCE UNAVAILABLE]
1961 – ethylene glycol used to freeze and revive eels, clams observed to freeze [SOURCE UNAVAILABLE]
1961 – Embryo chicken hearts frozen to -190C, golden hamsters partially frozen [SOURCE UNAVAILABLE]
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]

Challenges:

DMSO cryopreservant is toxic

Sources:

[CRYO1] *Reanimation of rats from body temperatures between 0 and 1C by microwave diathermy*. Andjus, Lovelock. 1955.
[CRYO2] *Influence of moisture content and temperature on cold-hardiness of hibernating insects*. Salt. 1956.
[CRYO3] *Preservation of corneal grafts by freezing*. Eastcott, Cross, Leigh, North. 1954.
[CRYO4] http://www.alcor.org/Library/html/BedfordSuspension.html
[CRYO5] http://www.cryonics.org/ci-landing/history-timeline/
[CRYO6] *Human pregnancy following cryopreservation, thawing and transfer of an eight-cell embryo.* Trounson, Mohr. 1983.

Biostasis

Biostasis is a DARPA project to slow biological processes of soldiers on the battlefield. The technology involved could be redirected toward non-cryogenic biological time dilation.

History:

2018 – Biostasis initiative [BST1]

Development:

Sources:

[BST1] https://www.darpa.mil/news-events/2018-03-01

Documentation

Documentation of longevity efforts is required for us to know whether progress is being made. Currently, aggregate lifespan is being recorded. Supercentenarians are kept track of by the Supercentenarian Research Foundation, Gerontology Research Group, and 110 club.

Tangible Philosophical Barriers to Immortality

Fertility Cliff

If biological immortality becomes widespread before space travel is cheap enough for mass migration, there may be a population issue due to the lack of death. To compensate, humanity can simply reduce new births. Population growth will trail off logarithmically until only a small number of new people are born to replace those that die from accidents and other causes. However, suppose then that some new threat emerges, some kind of health condition which affects most of the first-wave immortal population. What if it is not possible to 'gear up' reproduction fast enough to compensate for an unforseen health risk that wipes out what will then be the vast majority of the human population? It has been shown in experiments by John Calhoun at NIMH that mice populations experience some kind of population momentum or inertia [GEN3], and that once on a downward trend mouse populations can collapse from thousands to a few dozen members even in the presence of sufficient food, water, and healthcare.

One solution to this problem is to wait until mass migration across space becomes feasible, at which point the population bomb is reduced to a non-issue and fertility doesn't need to be tempered.

Competition Against Birth

In order for biological immortality to be feasible it must overcome the test of economic competition. It must be more profitable to keep an old person alive than to let them die and have a newborn take their place.

The obvious argument in favor of immortality is that when an aged person goes senile or dies, their entire lifetime of experience is lost. This equates to roughly 60-70 years of accumulated knowledge being destroyed, which creates a substantial economic loss. This argument works if immortality turns out to be relatively cheap, like a common drug that boosts natural regeneration. But what happens if it turns out that we absolutely need whole body printing for immortality, and that 3d bioprinters have a high operating price floor?

Societies led by selfish individuals may allow for limited immortality, but they will eventually be destroyed by comparatively efficient natalist societies. This concept was covered by August Weissman in his work “The Duration Of Life” back in 1881 [GEN4]. His observations led him to the conclusion that evolution tends to favor the shortest possible lifespan. Rapid aging is a product of genetic evolution being more important than somatic persistence. Shorter lifespans means more DNA recombinations per time period which allows greater change and ability of the gene to adapt to changing conditions.

The way to escape this is for mechanical or technological evolution to supersede genetic evolution. Once technological evolution becomes the defining characteristic of survival, then the ability to learn

and retain knowledge becomes more important than genetic mutation. Brain persistence must out-compete rapid reproduction in order for biological immortality to be feasible.

Competition Against Death

Whereas immortal humans will have to compete against natalism, so too will they have to compete against deathists. Deathists leverage their life for short term gains as a survival mechanism. This is the essence of being a warrior. Immortality requires not just that it is possible to be immortal, but that everyone believes it is possible to be immortal, otherwise there will exist those who purposefully create life threatening situations for personal gain.

"Immortal dictators" falls under this category – that in a world of immortality all the immortal people are too afraid of death to stand up to those who would seek to control others. A selection bias occurs in which deathists end up at the highest positions of power and then impose their way of life upon the rest of us. A practical example of this behavior is Electronic Arts, a video game company that acts as a dumping ground for dying intellectual property. They consistently destroy the reputation and future of game lineages in order to reap large short term gains. So far, it has been working for them.

Many stories of ignoring death in order to act are held up as pillars for our society – especially here in the US. Movies and games constantly depict heroes who get over their own fear of death and end up achieving greatness, many times by sacrificing themselves for the greater good.

One potential solution to competition against death is to try to get everyone to believe in their own immortality. By making immortality common and robust, the deathist strategy becomes impractical.

Large scale breakdown of engrained social systems

Death has been with the human race for as long as it has existed. Methods of dealing with death exist in every long standing organizational system we have created. While some organizations simply deal with death, other rely on it for their core functionality. We do not know how much of society would collapse if death were removed from the equation.

Think of civilization like a large computer program, with all sorts of various components having their own code. Death is a variable that has been incorporated into every single component of the program since the program has existed. And once immortality is discovered, the death variable will be changed probably within a day of discovery thanks largely to the speed of information transfer over the internet.

If we look through history we can see that civilization is not immune to collapse. Once there is enough complexity in the system, one large perturbation can start a chain reaction which causes the whole thing to break down. The removal of death as a certainty seems like a potential trigger for collapse.

The only solution I have come up with is for immortality to be discovered and practiced in secret until such a time as the risk of collapse can be accurately assessed and ameliorated.

Sources:

[GEN3] *Death squared the explosive growth and demise of a mouse population*. Calhoun. 1973.
[GEN4] *The Duration Of Life*. Weismann. 1881.

Solved Arguments Against Immortality

Overpopulation

Off planet migration or self imposed population control

Boredom

You can always kill yourself whenever you choose.

Unequal Distribution

People undercutting each other is a product of short term logical strategies. Game theory predicts long life will lead to cooperation over backstabbing.

Aging as Achievement

There are certain people in this world whose only accomplishment is that they managed to get older. Rather than being ashamed of the circumstance, they have built it up in their mind as some kind of accomplishment that their taste in food has deteriorated with age, or that they've grown wrinkles. These people can and should be ignored when possible.