

Alix VENTURES

Market Deep Dive Report

Longevity Therapeutics

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1. Summary

Aging and longevity focused startups are still in risky and exploratory phases. Most aging science has only occurred in animal models, and the few compounds that have progressed in clinical trials have failed in Phase III or are currently testing. The biology of aging is inconclusive and there are major concerns about side effects including cancer and other quality of life aspects when interventions are given.

The market for aging therapeutics is unique in that the demand is invariably high, yet there has been slow adoption by VC firms and large biopharma companies to partner, invest, and develop such technologies. This may be due to a history of high profile failures and a more sober realization that the current stage of biogerontology research is not mature enough to afford the expenses of clinical trials and the current biopharma R&D lifecycle. Indeed, it seems that the field is in the early target ID stage, driven primarily by methodological scientific progress rather than high throughput screening approaches used to identify most pipeline ready compounds.

Still, there has been a resurgence of interest, powered by the excitement of some high profile clinical trials, ever increasing research spending, and a philosophical shift of many to view aging as a disease rather than an inevitability. The establishment of new longevity focused funds as well as some strong recent funding rounds has encouraged founders to start ventures and commercialize their research. However, due to existing biological complexity and uncertainty, longevity remains a highly turbulent field to invest in. Ultimately, success as a startup is highly dependent on the chosen biological approach, as few if any have developed biology distanced platform approaches to discovery therapeutics.

2. Market Overview

The global longevity and anti-senescence therapies market will grow from \$329.8 million in 2018 to \$644.4 million by 2023 with a compound annual growth rate (CAGR) of 14.3% from 2018-2023. The key growth drivers are increasing funding and progress in aging research and a wealthy aging population.

Life extension is unlike any normal demand curve. There will be a tremendous growth in market opportunity because of an aging Boomer population in the U.S. and the world average lifespan also increasing annually. Using a model of future health and spending in the USA, the effect of delayed aging resulting in 2.2 years additional life expectancy would yield US \$7 trillion

in savings over 50 years. The median wealth of US families aged 62 years or older is over US \$200,000, compared with US \$100,000 and US \$14,000 for middle-aged and young families, respectively. This may in part be responsible for the increase in investment in even non-traditional therapies and DTC products and services aimed at extending healthy lifespan.

Still, the market for longevity therapies has been dampened by the discouragement of past failures. The most prominent example was GSK's acquisition of Sirtris for \$720 million in April 2008, whose leading compound resveratrol was hyped to have unprecedented success in pre-clinical modeling. Five years after the acquisition, GSK shut down Sirtris due to lack of efficacy. This comes with a string of more recent high visibility companies that have failed to reach investor expectations. Human Longevity Inc., founded in 2013 and previously headed by Craig Venter was once worth \$1.5 billion and now has dropped to a post-valuation of \$40 million. AgeX Therapeutics, founded in 2017 was once worth \$68 million and IPOed in late 2018. It currently has a market cap of \$28 million and is in risk of getting delisted by the NYSE.

Aging has received funding from atypical investors. Historically, the field has received interest from tech innovators and billionaire investors including Peter Thiel (Unity Biotech), Jeff Bezos (Unity Biotech), Google (Calico), Adam Neumann (Life Biosciences), Jim Mellon (Juvenescence). The largest aging focused company, Samumed, is worth over \$12 billion and has been funded primarily by private equity investors. Indeed, VCs have only recently viewed aging as a field worthy of investment. In particular, high impact investors including a16z and First Round have recently made investments into early stage aging startups Bioage and Spring Discovery, respectively. Among other deals, Juvenescence got a \$100 million series B in August 2019. Life Biosciences got a \$50 million series B in January 2019.

There has recently been progress made. The first in-human trials of senolytics are ongoing. Nutraceutical and stem cell regenerative medicine trials are ongoing. Samumed is starting Phase III trials for OA. Even more promising for aging becoming an accepted indication, a Nature Aging journal was just set up and a trial for metformin was just approved using aging as a clinical endpoint, which is a tremendous step towards regulatory approval for aging focused therapies.

2.1 Pitchbook Statistics

- Quick stats (All time)
 - No. Companies: 25
 - No. Deals: 82
 - No. Investors: 101
 - Largest deal: \$438 M (Samumed)
- Deal count (TTM): 8
- Most active VCs by deal count: ARCH Venture Partners, Kizoo Technology Capital, Fidelity Management, Bold Capital Partners, EcoR1 Capital,

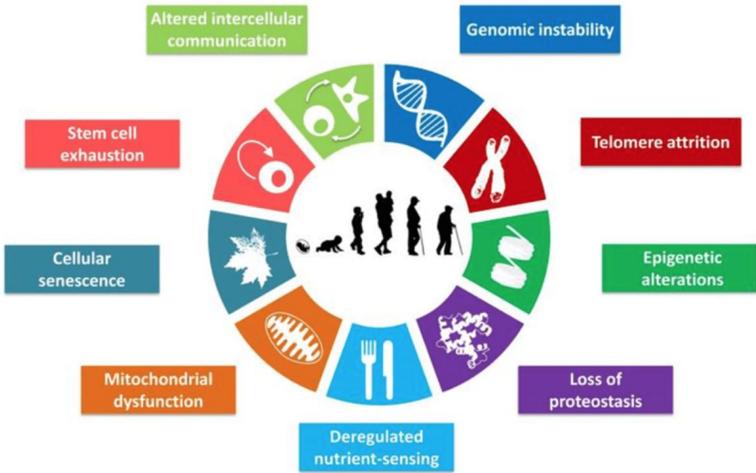
Stage	Average Round Size	Average Post Valuation
Seed	\$1.35 M	\$4.63 M
A	\$9.68 M	\$37.27 M
B	\$48 M	\$255.75 M
C,D,E,F	\$37.52 M	\$259 M

3. Technology Overview

3.1 The Biology of Aging

Most diseases accelerate with age, both in terms of incidence and severity. Cellular damage accrues over time, and as bodily repair mechanisms become worse and worse at fixing such damage, cancers, heart disease, autoimmune diseases, and others become more frequent and eventually cause death. A robust collection of in-vivo data has demonstrated that alleviating age related biological damage decreases risk of diabetes, neurodegenerative disease, and even cancer.

In a [hallmark review](#), researchers have developed 9 ‘hallmarks of aging’, which have been targets of therapeutic interventions. At current stages of research, there are no indications of which are may be more therapeutically promising than others. As a result, a spectrum of companies targeting different aspects of aging biology have arisen.



Hallmarks of Aging

Stem Cell Exhaustion	Activities of the 4 types of stem cells, which all help in regenerating new tissue cells, decline with aging.
Altered Intercellular Communication	Communication between cells is disrupted with age, resulting in inflammation and tissue damage.
Genomic Instability	Throughout one's life, both internal and external factors that cause genetic damage start to build up in the body. This is known to accelerate aging.
Telomere Attrition	Telomeres – the protective “caps” located at the ends of our chromosomes (which house our genetic material) – start getting shorter each time a cell divides. Over time, this results in cells not being able to divide anymore, which can lead to disease.
Epigenetic Alterations	There are changes in gene expression (not changes to the DNA itself) via an individual's life experiences or environmental factors which affect aging.
Loss of Proteostasis	With age, cellular proteins become misfolded and therefore, lose their homeostatic functions. A build up of these damaged proteins is observed with aging or age-related diseases.
Deregulated nutrient sensing	There are metabolism-regulating pathways, whose proteins (e.g. mTOR, sirtuins) are influenced by nutrient levels and also implicated in promoting aging.
Mitochondrial Dysfunction	When the mitochondria (considered the energy powerhouse responsible for regulating metabolism in our bodies) starts to malfunction with age.
Cellular Senescence	“Older” cells can't be cleared out as fast and their build up can lead to harmful health effects.

3.2 Current Approaches

Current approaches to therapies can be segmented into pharmacological treatments and cell and blood based therapies. The industry has favored the more traditional pharmacological approach, but with the applicability of stem cell research in other indications, regenerative cell based therapies have recently been of interest.

Pharmacological

¹ Table from CB Insights

On the pharmacological side, the current iteration of therapeutics have hoped to target molecules and targets that are over or under-expressed in aged individuals. These have ranged from nutraceutical supplements, repurposed diabetic medication, selective elimination of cells, and compounds to make cells live and last longer. The most promising and widely studied options have been rapamycin analogs, which modulate cell metabolism, and senolytics, which selectively eliminate senescent cells.

Starting with the nutraceuticals, [Elysium Health](#) has developed Basis, a pill containing a powerful antioxidant and a precursor to NAD+, which has been demonstrated in lab experiments to promote cellular health and longevity. NAD+ levels decrease with age and boosting NAD+ metabolism has been shown to boost lifespan in numerous model organisms. Basis has been tested clinically to increase NAD+ levels, and Elysium has announced a follow-up study to study the effects of NAD+ levels on epigenetic aging in humans. This study was expected to be finished in May, however no updates have been posted. Basis is sold DTC as a supplement and thus has bypassed most costly FDA regulatory requirements.

Metformin is a diabetic medication that has received interest as a potential longevity compound due to data showing decreased neurodegeneration in humans, as well as increased healthspan in animal models. The onset of diabetes is commonly associated with diet and obesity, but aging is an order of magnitude greater of a risk factor. Repurposing of existing drugs from diseases that are highly correlated with age has thus been an increasing area of study.

Rapamycin has been known to modulate aging for decades. It is an immunosuppressant that has been used to prevent organ rejection and works by inhibiting T cell and B cell activation via the mTORC1 pathway. However, rapamycin has a host of adverse effects including nausea, pain, diarrhea, fever, and hypertension among others. As a result, there has been ongoing work by companies such as resTORbio and Navitor Pharmaceuticals to develop ‘rapalogs’, compounds that mimic the anti-aging effects of rapamycin, without the poor side effect profile.

Drug developers have directly addressed the cellular senescence hallmark of aging by selectively eliminating senescent cells with compounds termed senolytics. Senolytics target senescent cells based on their activity or cell surface markers, and have been shown to alleviate age related symptoms in many animal models. Senolytics are the focus of an industry leader in the space, [Unity Biotechnology](#).

Stem cells have also become a frequent target for pharmacological intervention. Modulating the decline of stem cells with age can be done via a variety of signaling pathways and their receptor molecules. As one example, the highest valued company in this space, Samumed, is targeting the Wnt pathway to impact stem cell differentiation in order to promote rejuvenation.

Cell and Blood Based

Cell based therapies have become popular due to the progress of stem cell research in neighboring fields. Genetically engineering cells and transplanting them to areas with age related damage has been shown to restore healthy phenotypes in animal models. The commercial leader in this approach has been [Celularity](#), which develops allogeneic cell therapies engineered from post-partum placentas.

Finally, blood based therapies are being developed, stemming from animal experiments demonstrating that blood transfusions alleviate age related symptoms and extend healthy lifespan. Exploring the plasma proteome for proteins that contribute to this effect is the strategy of [Alkahest](#), a startup that hopes to develop therapies for neurodegenerative disease.

3.3 Late stage privates & publics

[Unity Biotechnology](#): Unity Biotech was founded in 2009 and IPOed in 2018 with a current market cap of \$360 million. It is a leading developer of senolytics, with its leading compound for osteoarthritis in Phase II trials with results expected in the second half of 2020.

[Samumed](#): Samumed is the largest aging focused company, worth over \$12 billion and funded primarily by private equity investors. They develop Wnt pathway based small molecule therapeutics and their furthest programs have reached Phase III trials in osteoarthritis and androgenetic alopecia.

[resTORbio](#): resTORbio was founded in 2016 and IPOed in 2018. It was once worth over \$450 million, but after a Phase III failure for its leading rapalog compound, shares plummeted and its current market cap is \$76 million.

[Calico](#): Calico is a research and development company under Google and employs some of the top scientists in the aging field. However, Calico is primarily a research endeavor and has not developed a therapeutic pipeline.

[Celularity](#): Celularity was founded in 2016 and raised a \$250 million series A in February 2018 and another \$77.7 million round in November 2018. The company develops allogeneic cell therapies, engineered from the postpartum human placenta, for cancer immunotherapy and functional regeneration. Their furthest therapies are for cancer immunotherapy, with two Phase II programs. Regeneration therapies are at preclinical stages.

5. Historical Context, Key Trends, & Future Development

5.1 History

Longevity and aging research has long been a topic of research interest, but until recently has failed to demonstrate meaningful advances. Only recently have researchers approached aging with a genuine scientific and evidence based approach. The National Institutes of Aging was founded in 1974, and since then, scientists have characterized a variety of ways to increase lifespan and healthspan in mice and a variety of other small model organisms.

The industry however has been plagued by bad science and regulatory pushback. Hope driven consumerism has led to the development of an array of supplements, treatments, and nutritional plans that are ‘anti-aging’. None have been backed by a regulatory agency or have any confirmed utility.

5.2 Present day status

Currently, there are a wide array of promising human clinical trials ongoing for aging interventions. On the senolytics end, Unity Biotech has a Phase II compound for osteoarthritis. There is also currently a combination study of two widely studied and cheap senolytics dasatinib and quercetin (D+Q) for tolerability and senescent cell removal that should report clinical results in the next year. Initial results for this trial were favorable, demonstrating that D+Q were indeed able to eliminate senescent cells. The significant question to answer will be whether the elimination of senescent cells has any QOL or healthspan benefit, and also to characterize the side effects of senescent cell elimination.

The most promising results will come out of Samumed’s pipeline in the next year. These are Phase III trials for osteoarthritis and androgenic alopecia, utilizing Wnt signaling to modulate stem cells. Success here would greatly increase interest in stem cell therapies for regenerative medicine applications.

At present stages, aging and longevity companies can best be characterized as coming from the East coast philosophy, that is, robust understanding of biology leading to the development of therapeutic assets. There are few platform technologies that can be adapted for different use, largely due to inconclusive biology and the range of factors that impact one’s biological age.

5.3 Top People and Labs

The major aging research centers are the National Institutes of Aging in Baltimore, Maryland, the SENS Research Foundation in Mountain View, California, and the Buck Institute in Novato, California, but all major research universities have now established labs dedicated to the study of aging. The following scientists have reached the status of being thought leaders in the field.

Michael West: Founder of Geron and CEO AgeX Therapeutics. He has written 7 books on stem cells and the biology of aging.

David Sinclair: Leads a genetics lab at Harvard studying sirtuins. Scientific founder at Life Biosciences and 7 other biotech companies including Sirtris which sold to GSK for >\$700 million.

Judith Campisi: Professor of biogerontology at the Buck Institute for Aging Research. A founder of Unity Biotechnology, Campisi is widely known for work on senescent cells and the senescence associated secretory phenotype (SASP).

Aubrey DuGrey: Largely known as a public advocate for aging research. CSO at SENS Research Foundation, VP of Technology Development at AgeX Therapeutics. Known for contributions to the mitochondrial theory of aging.

Laura Deming: Thiel Fellow who founded the Longevity Fund, a Seed and A Series VC with \$37 AUM.

5.4 Top VCs and Funding Sources:

The longevity and aging space has attracted an atypical group of funders. There has historically been a lack of venture financing, and in replacement companies have been funded via non-traditional sources such as grants, wealthy individuals, tech innovators, successful businessmen and investors, and private equity investors. Notable individual investors have included Jeff Bezos, Peter Thiel, Larry Ellison, Sergey Brin, and Jim Mellon. From a VC perspective, there are three funds that invest exclusively in longevity and aging focused companies: [Longevity Fund](#), [Methuselah Fund](#), [Longevity Vision Fund](#).

Another phenomena has been holding companies such as [Juvenescence](#) and [Life Biosciences](#). These companies function as a management and business development aid to portfolio companies so that they can focus on R&D. Entry into these holding companies typically comes via spinouts from existing companies within the portfolio or new collaborations with research labs.

5.5 Future Predictions

Progress in understanding aging biology has been difficult for three reasons: (i) aging is a complex process; (ii) although there are numerous theories of aging with vocal advocates, there is no consensus among scientists regarding the underlying causes of aging; and (iii) aging can be manipulated in short-lived model systems by genetic, dietary, and pharmacological intervention, but have poor translation thus far. This leaves many open questions, so the uncertainty concerning human anti-aging approaches remains very high.

Catalyst events that will drive the industry forward:

1. **Aging as an indication:** A major hurdle to development of aging specific therapeutics has been the FDA's reluctance to allow age to be used as an indication. This may be on the verge of changing however, as the TAME trial for Metformin with much negotiation was allowed to use aging related biomarkers for endpoints.
2. **Efficacy and safety data from a therapeutic:** Thus far, no aging specific therapeutic has made it through clinical trials. An approval and subsequent strong sales performance would spur additional investment. Additionally, this would allow the collection of large amounts of post-approval data that would inform side effects and additional biological impacts. Large scale clinical data that could be collected post-approval is a large missing barrier that is crucial for further development.
3. **Reliable epigenetic clock / standard biomarkers to use as endpoints:** A reliable epigenetic clock with standard biomarkers has yet to be developed. Such a development would vastly improve efficiency of aging clinical trials, as endpoints could be switched from death or physical or cognitive tests to more easily measurable and quantifiable endpoints.

6. Opportunities

6.1 Startups to Watch

Life Biosciences: Life Biosciences is funded by Adam Neumann and headed by aging researcher, David Sinclair. The holding company has raised a total of \$93 million since its founding in 2017 including a \$50 million series B in 2019. Life Biosciences' research efforts are focused on developing therapeutics in the commonly cited areas of mitochondrial dysfunction, chromosomal instability, metabolism, epigenetic alterations, loss of proteostasis, altered communication and inflammation, and stem cell exhaustion. Each of Life Biosciences' eight start-ups, referred to as daughter companies, are focused on analysing at least one of the eight commonly cited areas that account for ageing and age-related diseases. Life Biosciences is planning to have at least three clinical trials this year from its various daughter companies.

Juvenescence: Juvenescence is another portfolio based holding company. It is funded by billionaire investor Jim Mellon and has raised a total of \$165 million since its founding in 2016, including an \$100 million series B in 2019. Daughter companies are typically formed via partnerships with existing labs or companies, since no R&D is performed by Juvenescence itself. Notable portfolio companies include Insilico Medicine, AgeX Therapeutics, and LyGenesis.

Spring Discovery: Spring discovery is applying machine learning to accelerate aging research and has raised a total of \$22.3 million through series A from investors including First Round, General Catalyst, Felicis, Sam Altman, and the Longevity Fund. While there is no technical information on their website, the team is very strong and was valued at a \$78 million post.

Rejuvenate Bio: Rejuvenate Bio is approaching the longevity problem by developing gene therapies for dogs. The company was founded out of George Church's lab and has its initial focus on mitral valve disease, with a trial that is currently recruiting.

Juvena Therapeutics: Juvena is a Seed stage company that has raised \$4.3 million from investors including Liquid 2, Felicis, and Refactor. Juvena is developing protein-based tissue rejuvenation therapeutics by combining quantitative proteomics with computer vision analysis of high throughput microscopy.

Fountain Therapeutics: Fountain is a series A stage company that has raised \$11 million at a \$26 million post valuation from investors including Khosla and Eshelman ventures since their founding in 2018. The company has developed a model of aging that re-creates many of the complex hallmark features of aging, but in a laboratory dish. This cellular model is combined with artificial intelligence and computer vision to develop an unbiased platform for the identification of novel targets and potential therapeutics.

Rubedo Life Sciences: Rubedo is a Seed stage company founded in 2018 that has raised \$5 million from investors including the Longevity Fund and Refactor. The company claims to have developed an intelligent discovery platform combined with recombinant chemistry to selectively target specific cell types of the body (senescent cells), without toxicity or side effects.

Genome Protection: Genome Protection is a Seed stage company founded in 2018 that has raised \$10.5 million to develop drugs against retroelements, non-coding DNA that harbors ancient viruses. By silencing their activity, the company hopes to prevent the DNA damage and inflammation associated with cancer and age-related diseases.

Revel Pharmaceuticals: Revel is a Seed stage company that is developing designer enzymes to degrade the molecular damage that accumulates with aging. The technology comes out of 10 years of research at Yale and the SENS Research Foundation.

Oisin Biotech: Oisin is a Seed stage company that was founded in 2014 and since has raised \$5.6 million to develop their proprietary SENSolytics platform for age related disease. The

platform delivers a caspase-9 suicide gene that selectively causes senescent cells to undergo apoptosis.

6.3 Industry challenges

The aging and longevity space suffers from significant clinical and biological challenges, as well as some ethical pushback. This report identifies four major risks in the longevity space.

1. The FDA does not consider aging as an indication. As a result, companies have needed to pursue alternative indications to test therapies. This is partly because there are few widely accepted biomarkers of aging to use as endpoints, but also because aging is not currently viewed as a treatable disease. Eventually, as the scientific perception of aging as a disease changes and robust epigenetic clocks or biomarkers of aging are developed, the FDA may decide to allow aging to be used as an indication for regulatory approval. This would be a significant win for companies in the space because it would grant access to a much larger clinical market. Currently, companies have needed to carefully select an indication, which may involve significant pre-clinical testing risk. Common choices have included osteoarthritis, androgenetic alopecia, pulmonary fibrosis, neurodegenerative diseases, and age-related macular degeneration.

2. Clinical trials are particularly expensive and difficult to run. The clinical population that aging interventions target are inherently older and thus have more pre-existing conditions and are more difficult to recruit to join clinical trials. Many older adults have care plans focused more significantly on palliative care and are less likely to participate in a potentially risky clinical trial. Older adults are frail and thus more difficult to manage as part of a clinical trial without at home monitoring. Finally, since the primary goal is to restore function, not to regress a disease, the timescale of the endpoints is more long term in nature, meaning that clinical trials in the aging and longevity space take longer than other indications.

3. The biology is complex and currently poorly understood. Aging interventions have not yet been tested in humans and have only had limited and inconsistent data in primates. Increasing healthspan is possible in simple animal models, but when taking into account quality of life aspects, these interventions still do not seem applicable at scale in humans. Furthermore, aging pathways often share biological processes with the development of cancer. For example, increasing telomerase restores the ability for cells to continuously divide healthily, but is also a modification typical of rapidly dividing cancer cells. Regulators will be very careful to ensure that aging interventions do not increase the occurrence of cancer or other conditions.

4. There are ethical concerns about longevity therapies. In some circles there has been a strong negative reaction towards aging therapies due to concerns about overpopulation, the value of life, and accessibility. Unlike a specific disease, aging is a ubiquitous process that

happens to everyone. Therefore, the costs and accessibility of aging therapies will be an ethical issue to consider. While some consumers are willing to pay exorbitant amounts of money for an extension of healthy living, most are unable, so there is concern that regulators may impose pricing controls.

7. Conclusions

Overall, the longevity therapeutics market has significant biological and clinical risk, but sits in a market that has fast growing funding interest. Since currently, unapproved by the FDA as an indication, top companies in the space have taken three strategies to commercialize their research: 1. Go after an age related indication like osteoarthritis 2. Attack the longevity problem in dogs 3. Use a DTC nutraceuticals approach. Human therapeutic approaches have been highly capital intensive yet still have not produced a compound that has passed clinical trials. Meanwhile, the jury is still out on whether nutraceuticals like NAD+ will have clinical efficacy, though studies are ongoing. Finally, therapeutics for dogs have attracted interest recently due to an increasing willingness for consumers to buy expensive therapies for their pets as well as the ease of testing that animals provide.

7.1 Vertical Strengths

- Strong funding interest
- Rapid pace of research development
- Unique demand curve, can price therapies high

7.2 Vertical Weaknesses

- Shaky science with potential off targets effects including cancer
- FDA has not formally recognized aging as an indication
- Clinical trials are especially expensive and difficult to run
- Low rate of adoption by large biopharma

7.3 Opportunity Cost of Capital

At the current stages, the longevity field does not appear conducive to a venture scale business approach. Human therapies are unproven, operate in crowded and small indications, and have proved especially expensive and risky to develop. At this stage, longevity therapeutics will be relegated to niche fields such as applications for pets or nutraceutical supplements. Specific companies who are able to generate high quality clinical data may be considered. However, due to our inconclusive understanding of aging biology in complex mammals, this

report recommends deferring on longevity focused startups until more robust clinical results arise.

7.4 Investment Thesis Areas

1. **Animal health:** The FDA approval and regulatory process for longevity therapeutics is unfavorable and is unlikely to improve in the years to come. The animal health market provides a testing ground not as strictly regulated, that is already utilized by startups including Celevity and Rejuvenate Bio to develop therapeutic pipelines that may one day translate to human use.
2. **Well characterized aging associated diseases:** Aging associated diseases that are well characterized and can stand as an FDA approved indication are another area where aging therapeutics have potential applications. The development of platform technologies that can target these indications can begin to set the groundwork for anti-aging interventions, whenever the FDA is able to approve aging as a targetable indication.

8. References

1. [Crunchbase Report](#)
2. [Laura Deming Explainer](#)
3. [ElderTech Market Map](#)
4. [The Hallmarks of Aging](#)