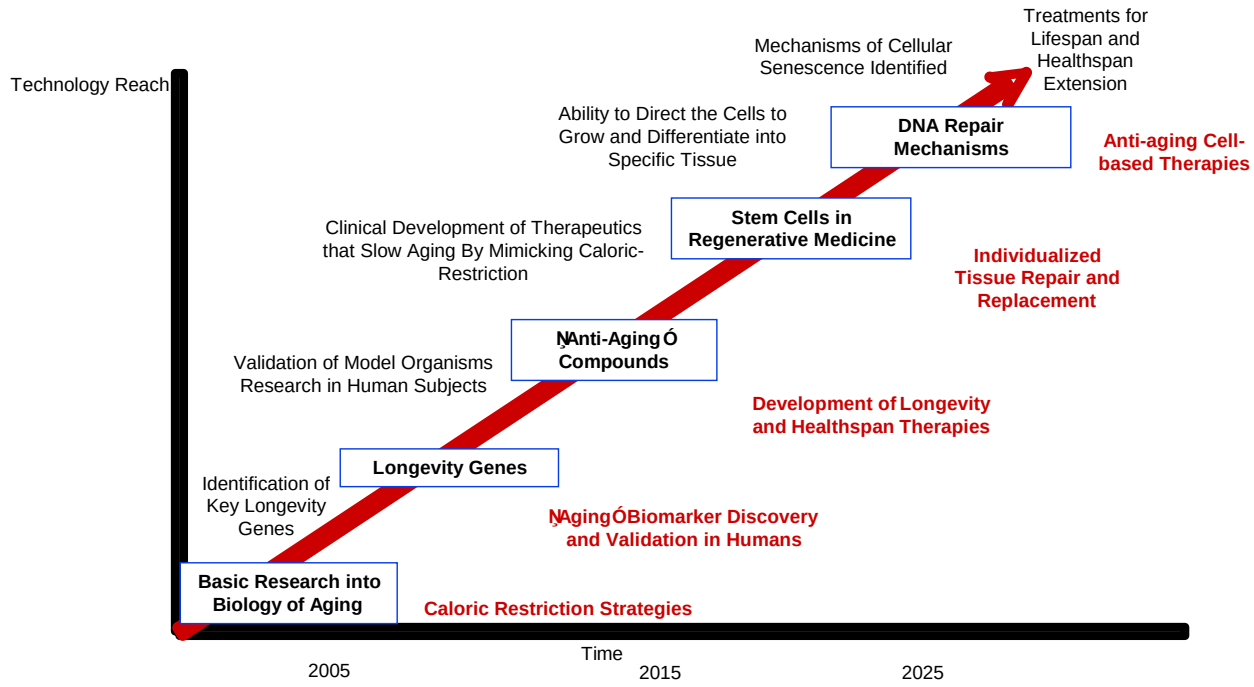
APPENDIX A: BIOGERONTECHNOLOGY (BACKGROUND)

The Technology

Figure 1[1]
TECHNOLOGY ROADMAP: BIOGERONTECHNOLOGY



Source: SRI Consulting Business Intelligence

Biogerontechnology

Biogerontechnology is the concept of applying the science related to the study of the cellular and molecular basis of disease and aging to the development of new technological means for treating diseases and disabilities associated with old age in order to keep an aging population healthy, active, and independent. The real disruptive potential of biogerontechnology is based on a number of key technology areas in molecular biology (such as genomics, proteomics, and metabolomics) and cell biology (such as stem cells, cell signaling, and mitochondrial function). The revolutionary disruptive potential of biogerontechnology is not likely to come from one field alone but most likely from technological synergies through convergence and knowledge creation from the intersection between fields that inform and drive each other.

Humans have forever been preoccupied with the quest to discover the fountain of youth. To date, no single theory as to exactly how and why we age occurs has been universally accepted and

[1] The Technology Roadmap highlights the timing, features, and applications of significant technology milestones that would be necessary for developers of this technology to achieve if successful (equivalent to commercial) application—and possible disruption—is to occur by 2025.

the knowledge from any individual field is far from complete. As a result, technology pathways to the development of anti-aging interventions are not only numerous but differ considerably in strategy and, as a result, should be considered theoretical and highly speculative at present. Researchers tend to break theories of biological aging into two but very often not mutually exclusive categories of theories:

- Programmed theories, which suggest that the biology of organisms follows a programmed development plan, include programmed longevity, endocrine, and immunological theories.
- Error theories, which highlight the role that environmental assaults play in the aging process, include biological wear and tear, crosslinking proteins, free radicals, and somatic DNA damage.

At a general level, scientists are driven in their research to understand the principal process of senescence, which occurs when cells lose their ability to reproduce and to maintain a restorative function in response to accumulated molecular damage over an organism's lifetime. As a result, mechanisms underlying senescence may hold the key that differentiates the more destructive aspects of aging and that increase our risk for disease, disability, and death from some of the more benign physiological manifestations. The enormity of the challenge to understand that biological process is underscored by the fact that senescence for now remains one of the least understood aspects of aging.

Although researchers are confident that human lifespan can be expanded through understanding and influencing biological processes, no scientific proof from research studies involving human subjects that life extension through biogerontechnology is possible exists. Leading scientific research areas offering the greatest potential in biogerontechnology include the genetics of aging and the identification of regulatory pathways important to aging processes; regulation of telomeres and the enzyme telomerase that potentially provides the cell with a capability for perpetual self-renewal; and the potential for tissue regeneration using human embryonic stem cells.

The Enabling Building Blocks

Research studies demonstrating lifespan extension have been conducted primarily in model organisms, such as nematodes, yeast, and fruit flies, where results suggest that delayed aging may produce a genuine compression of mortality and morbidity. Enabling components of the key technology building blocks that have been implicated in extending lifespan in animal models include the identification and manipulation of "longevity" genes, cellular senescence, caloric restriction which aims for a reduction in calorie intake as the means for extending maximum and average lifespans while staying physically healthy and active; and tissue regeneration using embryonic stem cells:

- Reduction of calorie intakes is the only approach that scientists have found to date that increases longevity in mammals. Primates represent the next animal model step towards human validation.
- Genetic manipulation of "longevity" genes in nematodes has also been shown to dramatically extend their natural lifespan. Homologous genes have been identified in humans but scientific validation is far from realization.
- Senescence can lead to changes in important cellular functions, such as those that lead to changes in gene expression, that ultimately increases an individual's vulnerability to disease through unregulated growth and tumor formation.

- Scientific research involving telomeres are an important mechanism in understanding the biology of aging that researchers are seeking to understand how to control and direct in cell replication and cellular aging.
- Human embryonic stem cells offer non-aging and infinitely self-renewing capabilities that are unique and hold great promise as a potentially unlimited and universal source of tissue and organ replacement.

Funding availability is perhaps the single most critical factor affecting research in the field today. Today, the United States government spends several hundred million dollars annually on aging research. Private funds are obviously much larger than that but probably still fall short of the levels needed to advance the field. A group of leading U.S. aging-related researchers recently called on Congress to invest $3 billion annually to this effort and to provide the organizational and intellectual infrastructure necessary to support and advance the field. Of the $3 billion, they recommend that one-third be devoted to the basic biology of aging with a focus on genomics and regenerative medicine as they relate to longevity science; another third should be devoted to age-related diseases as part of a coordinated trans-NIH effort; with the remaining third split evenly between the development of clinical trial studies and a preventive medicine research initiative addressing the reduction of risk factors that lower life expectancy.

Implications of Advancement in Various Technological Capabilities

Biogerontechnology captures leading scientific and technological research efforts in understanding and manipulating the biological basis of longevity. The applications that emerge will not only seek to extend an individual's age but also facilitate their retaining physical and mental functional capacities into old age. Although the research results from animal models have been impressive, not all researchers are convinced that the aging benefits observed in animal studies will be as easily transferred across species. The safety and risks of certain procedures, such as the observation of reduced fertility in calorie-restricted animals, is a good example of the nature of uncertainty that surrounds the field. To resolve these uncertainties and validate the efficacy of experimental treatments that claim to slow, halt or even reverse aging, it is likely that any human safety and clinical evaluation would be best served in younger populations who have aged the least. Such studies are likely to take decades rather than years for meaningful results to be borne out.

Synergistic Technologies

Steady gains that have been realized in human longevity to date are a result of advances through more conventional enabling technologies and interventions, such as public health practices in the form of sanitation, medical interventions in the form of vaccines and antibiotics, and environmental modifications, and these will likely continue to be important in the future. Synergistic technology approaches that target the prevention or treatment of diseases and their associated risk factors will play a synergistic role with biogerontechnology in realizing future longevity gains. However, longevity gains that will be possible through these approaches alone will be incremental as a result of gradual improvements to existing capabilities compared with the anticipated gains possible through the truly disruptive potential for technological innovation that biogerontechnology offers.

Cultural trends also contribute towards disrupting the aging process and countering conventional wisdom as to what aging implies. For example, aesthetic medical practices and lifestyle preferences are just some examples of trends already well underway that seek to delay if not to arrest the aging process. Non-biological variables that are important determinants of the

aging experience (in terms of longevity and proclivity to disease and disability), such as gender, ethnicity, emotional health, social status, lifestyle activities, and personal resources (such as education and wealth), also need to be considered. These factors together with conventional health care practices need to be considered in understanding synergistic technologies and the contributory role that they potentially play in enabling humans to lead longer and healthier lives

- Therapeutics
  - —Small Molecules
  - —Biopharmaceuticals
  - —Vaccines
- Human Augmentation
  - —Prosthetic Limbs
  - —Artificial Organs
  - —Neuroprosthetics
- Electronic Health Care Management
  - —Electronic Health Records
  - —Personal fitness and management
  - —Personal Healthware and Ubiquitous Computing
- Medical Devices
  - —Molecular Diagnostics
  - —Drug Delivery Devices
  - —Implantable Medical Devices
- Lifestyle and Wellness
  - —Nutraceuticals or Functional Foods
  - —Dietary and Health Supplements
  - —Alternative Medicines

Applications

Key Uses and Instantiations of Biogerontechnology

The biological process of aging manifests itself in different ways as evident from observing skin (less elastic and flexible), bone (joint wear and tear), body tissues (accumulated damage to cellular control systems that leads to cancers), muscles (atrophy or wasting of muscles), the senses (gradual decline in quality and fidelity), the brain (neurodegeneration), the endocrine system (hormones become deregulated), and the circulatory system (atherosclerosis and stiffening of the blood vessels). The applications that will emerge through biogerontechnology will not only seek to extend an individual's age but also to facilitate their retaining physical and mental functional capacities into old age. Scientists can accomplish these research goals through a number of different strategies, such as compressing morbidity associated with chronic conditions during old age, decelerating the aging process, and arresting or even reversing the aging process itself.

Although no currently marketed intervention has proven to slow, stop, or reverse the human aging process, the fact that the cost of obtaining biological information is declining by approximately 50% each year suggests that researchers will increasingly be able to acquire and use biological information for knowledge discovery with greater efficiency and cost-effectiveness and apply that more quickly toward product research and development. Today's emerging knowledge can be immediately applied in the form of general strategies for good health maintenance through nutrition, for example. The next-generation of applications will involve the development of medical technologies, such as screening or diagnostics tests and, eventually, therapeutics that delay the onset

of disease and disability, extend life expectancy, or restore vitality and function to aging bodies and minds.

Current Affected Products

Research into the biological mechanisms of aging represent a very promising research approach to the development and realization of anti-aging treatments that go beyond the treatment capabilities of current drugs. Researchers are already forming companies to commercialize their research discoveries in biogerontechnology. However, therapeutic strategies currently tend to focus on drugs that slow the aging process through mimicking caloric restriction. Sirtris and Elixir Pharmaceuticals are two leading companies in this regard. To expedite the clinical review process and increase their chances for commercial success, these companies' first-generation drug candidates target specific, age-related diseases, such as diabetes and cancer, through targeting the DAF-2 and SIR-2 pathways, rather than the aging process itself. Their progress through the clinical development process is important to monitor for validation of the underlying science, which could prove important in advancing products that will extend human healthspans and lifespans. Elixir estimates the market potential for anti-aging could be billions if one considers the current amounts spent on drug treatments for diabetes, cancer and other aging illnesses.

New Capabilities Created by Biogerontechnology

Understanding aging as a biological process that breaks down as the self-capacity for maintenance and repair declines suggests that understanding the mechanisms of keeping things repaired could theoretically result in indefinite operational fidelity. Treatments that may emerge as a result of biogerontechnology may include anti-aging drugs, DNA repair mechanisms, caloric restriction strategies, tissue regeneration, brain rejuvenation, and strategies for metabolic management and maintaining molecular integrity.

Timeline

Acceptance of the feasibility and potential for the malleability of aging is growing in basic research. The current status of knowledge and capabilities in the field suggests, however, that basic and applied research activities are likely to attract the majority of resources dedicated to biogerontechnology through 2025 and beyond. The use of biogerontechnology in pharmaceutical research activities is also likely to occur throughout the time period but the degree to which the science is applied in pharmaceutical research activities will depend greatly on the level, pace, direction of basic research funding and the insights and breakthroughs realized in basic research. Product development applications of the science will probably initially target the treatment of specific conditions. All things considered, the development of drugs specifically targeting anti-aging could start to enter clinical development within the next 15 years, and the first products will not reach the market for at least 25 years.

Issues Determining the Development of Biogerontechnology

From a research perspective, the field of biogerontechnology has a broad base of stakeholders committed to advancing biomedical research to improve health during aging. Although many of the lines of research are formative and remain speculative as to their commercial potential, much of the research is officially sanctioned with government agencies such as the National Institutes of Health

in the United States or the Medical Research Council in the United Kingdom sponsoring research at major academic, public, and private research organizations. Public funding levels are low and private philanthropic organizations and social entrepreneurs currently play a big role in supporting and advancing the field. Possible venture philanthropists with an interest in boosting funding for the field may include Paul Allen, Richard Branson, Larry Ellison, and Steve Jobs. Of course, the theoretical and oftentimes speculative nature of the research also means the field has its fair share of proponents who represent more extreme positions and that operate on the fringes of the scientific communities and technology spectrums.

If the benefits of research demonstrated in model organisms are reproduced in humans biogerontechnology would probably be treated no differently from other medical research areas that seek to accomplish control over and improvement in the human condition. The ability to compress mortality and morbidity would create significant financial gains for the health system that would drive the introduction of reimbursement plans and support quick market adoption. Consumers would also be supportive as they generally seek developments that are aesthetic and life sustaining. But the challenge will be to understand how to apply and mange biogerontechnology in society in a controlled and responsible manner. Ethical, legal and social implications of adoption could act as a brake on rapid market adoption. Monitoring and understanding public opinion will be critical in formulating appropriate policy responses that will dictate investment levels in research, legal frameworks for intellectual property protection, and market regulation governing safety and evaluation.

The broad range of stakeholders will no doubt become engaged on a broad range of issues:

- Public policy interest groups will seek legislators to address the issue that access and control to biogerontechnology needs to be regulated to ensure fair and equitable opportunity for each and every member of society.
- Environmentalists, for example, might question the societal value of biogerontology relative to other population and sustainability challenges, and the earth’s carry capacity for sustaining a growing population through longevity gains.
- Bioethicists will openly debate issues that seek to resolve differences over where biomedical inquiry stops and ethics begins in terms of the means and goals of biogerontechnology,
- Social advocates might be motivated to raise public consciousness around issues that deal with the impacts of biogerontechnology on attitudes and values towards spirituality, evolution, and voluntary life-termination.
- Academics will seek to study how a delay in the onset of aging might affect perceptions to quality of life measures, social aspirations, and financial, moral, social, cultural, consumer, and political lifestyle preferences.
- Policy makers would seek to understand how traditional demographics might be impacted, what changes in reproductive choices might emerge, and how birth rates would be impacted.
- Regulators might deal with ethical science, protecting the public from the scams that claim anti-aging benefits, as well as the ethics of activities undertaken by less mainstream groups such as extropians and transhumanists

- Economists would seek to understand what the impact on health care spending might be, the impact of health and longevity on gross national product growth, and added economic cost from people living healthier and longer lives.
- Industry would seek to understand how older consumer behaviors differ in terms of media preferences, leisure activities, transport, and entertainment, and the impact of health and longevity trends on productivity and innovation.

Items to Watch

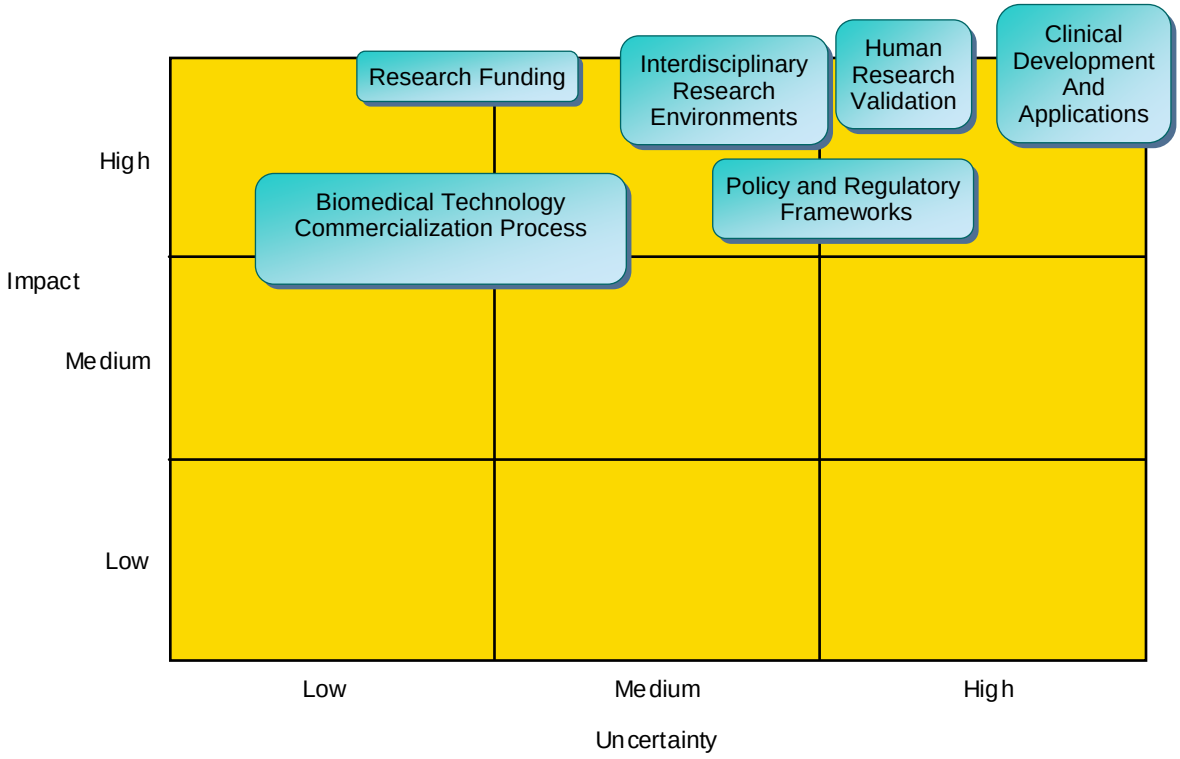


Figure 2[2]
BIOGERONTECHNOLOGY: ISSUES AND UNCERTAINTIES

Source: SRI Consulting Business Intelligence

From Figure 2, the key areas of uncertainty to monitor and better understand their impact on biogerontechnology include:

- *Human research validation*. The scientific knowledge to drive discovery and support product development are limited. Animal research conducted to date has been relatively easy for studying

[2] Figure 2 illustrates major issues and events that will have an impact on the rate or direction of a technology's development and thereby application. The impact of these issues and events is plotted against a measure of uncertainty, where uncertainty implies insufficient knowledge of how (and usually just when) the issue or event will be resolved or be sufficient to drive or hold back development of the technologies. An organization that is able to accurately predict or (better) influence or dictate the outcome (thereby moving the issue/event to the left of the figure), will have a distinct advantage over organizations that are still in the dark or just passively following developments.

the biological mechanisms of aging. However, only human research studies will determine whether the human homologs of genes identified in animal models have similar effects. Understanding the aging process and evaluating the clinical efficacy of anti-aging therapies poses a unique challenge because biomarkers that predictably change in level with age and correlate with longevity are unavailable.

- *Clinical development*. The process of human research validation will be complicated further by the lack of regulatory frameworks and government funding. The position of the FDA, which does not for now recognize aging as a disease and will not approve products claiming to increase longevity, requires that companies need to target the treatment of specific conditions. The availability of standardized biomarkers as identifiers of rates of biological aging, predictors of longevity, and indicators of susceptibility to aging-related diseases may be a prerequisite for a change in position.
- *Research funding*. The money spent by public agencies and private investors is small compared to the total spent by the biomedical research community on specific diseases such as cancer. Research and development timelines will be strongly impacted by funding availability for the biology of aging. Strong political commitment to the funding of basic science will be an important catalyst to drive advances in the field. In addition to more traditional public funding sources for basic research, philanthropic organizations and social entrepreneurs are also likely to play a big funding role for anti-aging science and technology R&D.
- *Interdisciplinary research.* Aging is probably not the result of any individual mechanism but a combination of different processes acting in unison. As a result, no individual field of research is likely to make the breakthroughs that will lead to revolutionary disruptive change, but it is more through the convergence of technologies that inform and drive each other. The availability of research environments for researchers to work collaboratively in multidisciplinary environments and in a manner that supports the need for shared insights and technology convergence will drive the scientific insights and technological innovation that will lead to biogerontechnology breakthroughs.
- *Policy and regulatory frameworks*. Governments that seek not to directly or fully support research in the area, such as the U.S. government has done with human embryonic stem cells, could result in countries restricting research activity or losing critical resources as key research and researchers gravitate to more tolerant and less regulated countries. Ethical, legal and social implications could act as a brake on rapid market adoption. Government regulation to balance commercial interest with public concerns and objections they may have to allowing the market application of biogerontechnologies and under what circumstances may be required.
- *Biomedical technology commercialization process*. University spin-offs are the most likely source for commercialization of the science. But the nature of research and funding timeframes suggest that many companies are likely to fall victim to the funding gap. Because a high rate of commercial failure is a hallmark of the biotechnology sector, companies can mitigate against that through patent strategies and portfolios. Should ventures prove to be successful in anti-senescence research they need to be prepared for the significant resource commitments involved in clinical trials that will seek to validate the anti-aging science in clinical populations and the bioethical requirements that are likely to accompany them.

Directional Signposts

Identifying the major issues that will determine how biogerontechnology will develop and understanding the uncertainty of items important to watch help us to understand better the potential dynamics of development and application that we might see in the future. That heightened sense of awareness is necessary because the United States will want to formulate a policy and act before unambiguous evidence on the drivers and barriers to, and direction of advancement of biogerontechnology is available. Preparation for a watch-and-respond system is essential to identify signposts that would indicate whether the advancement of the technology is proceeding rapidly or not. The following developments are likely to occur near the suggested years, and their outcomes will strongly influence the status of biogerontechnology. Their occurrence would indicate that the above issues and uncertainties were being resolved in the direction of positive development and application of biogerontechnology:

- 2010—The U.S. government launches a major research initiative to study the biological basis of aging and commits $1 billion annually over the next 10 years.
- 2013—The U.S. research initiative leads to the launch of similar initiatives with competitive funding in the European Union, Japan, China, India and Russia.
- 2015—Scientific research studies provide the first evidence that human lifespan can be expanded through understanding and influencing biological processes
- 2018—Follow-on scientific breakthroughs are occurring at a rapid rate globally and concerns mount over the implications of a demographic explosion.
- 2020—The development of drugs targeting anti-aging start to enter clinical development with the first products expected to reach the market after 2030.
- 2025—The first application for market approval of a human embryonic-stem-cell–based therapy is submitted to the U.S. Food and Drug Administration.
- 2027—The average U.S. human life expectancy in 2025 is 81 years and indications are that biogerontechnology could increase this to 89 by 2050.
- 2030—The first application for market approval of an anti-aging therapy could be submitted to the U.S. Food and Drug Administration.

Within the timeline that these developments are likely to occur, some specific signposts will be important to watch for and monitor on a global level in order to understand the direction and pace with which the field is advancing globally, which may influence the U.S. response:

- Scientific evidence that both confirms and disconfirms the current aging theories
- Global public research funding levels and trends for biogerontechnology research
- The establishment of non-U.S. centers of biogerontechnology research excellence
- Successful early models for scientific research and technology commercialization
- The size and nature of biogerontechnology investments worldwide
- Position statements about the ethics and practices of biogerontechnology research
- Consistency in regulatory frameworks governing research and commercialization

- The influence of scientific research and applications on public opinion

Abbreviations

The following abbreviations are used in this Biogerontechnology disruptive technology profile:

DNA	deoxyribonucleic acid
GDP	gross domestic product
OECD	Organization for Economic Cooperation and Development