

THE BUCK INSTITUTE STUDY GUIDE

Following are some key messages, facts, stories and answers to frequently asked questions about the Buck Institute to support conversation and fuel interest and engagement:

What is The Buck Institute?

The Buck Institute is the world's first biomedical science institution devoted exclusively to research on aging. For the past 22 years, everything we do has been focused on our mission to help people live healthy longer. We have pioneered the study of aging, even developing the terminology of geroscience.

The Buck's scientists differentiate themselves by collaborating across disciplines to bring a wholistic exploration to the study of aging – sharing thinking, approaches and outcomes that enrich and extend the study of aging.

The outcomes of the research breakthroughs created by the Buck Institute have the very real potential to transform the global health landscape, dramatically reduce human suffering, and alter the focus, economics and practice of medicine in the future.

The Buck Institute is a non-profit organization, initially funded by a generous bequest, but now reliant on government research grants and generous philanthropic donations from corporations and individuals. Charitable contributions are essential to the Buck – they form the seed capital that allow Buck scientists to think outside the box, innovate without strings attached, and create research that will lead to scientific breakthroughs.

What does research on aging mean?

The Buck focuses on aging as the root cause of age-related disease – the impact that aging has as the #1 risk factor for diseases like Alzheimer's, Parkinson's, stroke, heart attack, cancer, osteoarthritis and more.

The Buck's goal is to slow down the aging process to prevent, delay or even reverse these horrible diseases. We are researching ways to intervene in key aging mechanisms and pathways.

What surprises most people about the science of aging?

- Aging is not fixed; it can be altered. It is plastic, malleable.
- Lifespan and longevity are not primarily driven by the genes you inherit. In fact, research shows that genes may only be responsible for about 7% of your life expectancy. The remaining 93% is determined by personal behaviors and lifestyle choices – like how much and what type of exercise you do, how much sleep you get, what and WHEN you eat, how you manage stress, and what drugs and supplements you take.
- Aging itself is the root cause of many chronic diseases.

- Healthspan is different than lifespan. While lifespan is simply how long you live, healthspan is how many *healthy* years you live. Healthspan is the number of years you live free of disease and chronic illness.

Why healthspan, not lifespan?

Today it is believable to live to be 100. But the critical goal to maximize healthy aging is not increasing lifespan. No one wants to live longer if it means suffering with chronic illness or disease. The target should be maximizing healthspan, or the healthy years of life. Making it possible to live longer with healthy minds, healthy bodies, making contributions to the world around us, and enjoying our lives well into our 90's and beyond.

What do we know now about aging science that we didn't 10 years ago?

- Aging is the root cause of many chronic diseases.
- The Buck has been part of developing interventions that exist today to capture another 15-20 years of healthspan.
- We've learned that it is possible to compress morbidity – the period of time that one suffers from a disease or medical condition – and we are learning how to achieve that through direct intervention.
- We can harness human biology to maintain and repair aging mechanisms and pathways that lead to chronic disease.
- Aging can not only be slowed but may even be reversed.
- The technological advances made in deep learning, data analysis and artificial intelligence is transforming biomedicine. We are exponentially accelerating the evaluation of data – ranging from imaging to molecular make-ups to protein analyses – to routinely discover connections, patterns and pathways that would have been unrecognizable before. AI is also democratizing science – completely eliminating bias in its evaluation of raw data to encourage unforeseeable breakthroughs, open new insights, and encourage opportunities to advance and accelerate science.

You might know a little about The Buck – but what most people don't know is....

- The Buck Institute is internationally renowned for doing cutting edge research – leading the way on the global interdisciplinary study of aging.
- Aging is the Buck's sole focus – which has had a huge payoff in our collaborative approach to the complex study of aging.
- Collaboration is baked into the DNA of the Buck. The commonality of purpose, to extend human healthspan, is unique and speaks to the strength of the Buck. Lack of silos mean everyone, from grad students to senior faculty, can suggest new projects and get buy-in to move science forward.
- Private charitable giving provides Buck Institute scientists the freedom and flexibility to follow promising leads and quickly launch new studies before they would ever be eligible for funding from traditional government sources such as the NIH (National Institutes of Health) and NIA (National Institute on Aging).

- The Buck’s breakthroughs and scientific discoveries hold the promise of changing the future of medicine, moving away from a model based more on treatment of disease and sick care, to one focused more on the prevention of disease and true health care. As our understanding of human biology deepens, we envision the emergence of precision medicine and medical practice delivering highly personalized interventions and treatments based on each individual’s unique biology, biomarkers and genetic profile.
- Buck scientists are also working on cures for specific diseases such as cancer, heart disease, Alzheimer’s and diabetes. The difference is that we view each disease through the lens of aging and seek to focus upstream to prevent the disease before it develops in the first place.
- The Buck is developing compounds and drugs that are entering human clinical trials now.
- Many of the Buck’s discoveries, inventions and intellectual properties (97% of which have been patented) have led to partnerships or been licensed to commercial organizations elevating outcomes of research to human therapies and treatments.

Facts/Stats on The Buck

- The Buck is home to more than 200 scientists from more than 30 countries representing widely varied ages and stages of career, a broad scope of disciplines – but all sharing a unifying belief in the role aging plays in driving chronic disease.
- The Buck has inspired scientific study from high schoolers to post-doc researchers.
- The Buck is the birthplace of geroscience and the world leader in senescence research.
- At any one time, there are hundreds of collaborative research studies under way in Buck Institute labs.
- The Buck is now standing up on average two new companies a year that bring its science and inventions to market and the general public.
- The Buck is committed to bringing its discoveries and interventions to humans and is currently launching its first human clinical trials.
- The Buck must raise millions of dollars each year from donors to advance and accelerate our science. Donations provide the critical seed and bridge capital for scientists to pursue innovative high risk/high reward research.

What kind of future can we look forward to if we to explore the science of aging?

- The prospect of healthy, productive lives full of vitality well into our 90’s.
- Improved medical and healthcare practices and interventions, with focus on disease prevention rather than disease treatment.
- Dramatic reduction in end-of-life medical and healthcare costs.
- Alleviation of chronic disease and associated disabilities and suffering for billions of people.
- Benefits to society from engaged, healthy, productive seniors.

Are there any discoveries and interesting stories about Buck scientists?

- We strongly recommend a viewing of the eight short videos – each less than 2 minutes long, in the “Next Generation Scientists” section of the new “Discover the Buck” portal.

What is considered difficult or "hard" about this field?

- Aging has not been considered a disease, so funding for aging research is limited. For example, most NIH funding tends to be disease specific.
- Aging is a complex system, with thousands of interrelated and interdependent biological pathways, mechanisms and molecules. Researching aging requires expansive knowledge, long time horizons, and a high-level of collaboration across multiple disciplines and areas of expertise.
- Basic science – fundamental or bench research that encourages invention, curiosity and innovation as it explores the unknown – provides the foundation for knowledge for applied science to follow. This evolution takes time. However, with its deep history and experience, the Buck is now in the process of translating its most promising science into new interventions and therapeutics that benefit humans and combat chronic disease.
- Moving basic science to humans is a difficult process. It is challenging to study human aging because we live so long. There are also obvious ethical and practical concerns involved. In many cases, we can't test/study directly with humans. We need to rely on good animal models to identify potential targets and interventions – some of which will not translate to humans.
- Scientific research is expensive, and by nature, very risky. Most studies don't lead to new breakthrough discoveries.
- Yet there are financial and time pressures to show positive results/outcomes and to bring solutions to humans. There are also pressures to commercialize intellectual property.
- The financial and academic pressures on Principal Investigators can influence the direction and type of research and place limits on scientific freedom, curiosity and exploration. P.I.s under pressure, might miss out on moments of scientific serendipity.
- The best, most radical or promising research might not get funded or ever get a chance.

What interesting, unique organizational challenges does The Buck have?

- Being a small, independent institute is both a blessing and a curse. We can pivot quickly and pursue new opportunities or directions as they emerge – as we did in support of COVID research. However, we don't have large institutional backing, so we need to constantly raise money to support and grow our science.
- Solving aging requires identifying and hiring the best and brightest minds across many different fields/disciplines and bringing them all in under one roof. There is magic in collaboration. However, it can be challenging to foster and expensive to operate. The tremendous success of the Buck Institute is due to its collaborative culture and the fact that Buck scientists routinely bring together different areas of focus and expertise to solve biology's most challenging problems.
- Most people view aging as fixed and predetermined and don't appreciate or understand that aging is malleable and can be changed. They tend to direct their focus and support on the treatment of specific diseases, rather than on aging research. They miss that aging itself is the root cause driving chronic disease and that investing and supporting in aging research has the best potential of curing the entire spectrum of age-related chronic disease.

How is The Buck approaching/thinking about these challenges?

- The Buck is leveraging opportunities to create partnerships, joint ventures and scientific collaborations with other research institutes, universities, industry and biopharma companies, venture capital firms, and donors/venture philanthropists.
- The Buck keeps lean, flexible and nimble, so that we are in a position to opportunistically pivot and pursue promising new directions.
- We seek out, attract and retain world-class scientists who bring both a collaborative mindset and belief in aging research.
- The Buck invests in state-of-the-art technology and shares it across all labs.
- The Buck is committed to collaborating across the globe – leading with openness and transparency.

As an organization, what are the people of The Buck most proud of?

- The Buck is considered the global leader in research on aging.
- The Buck coined the phrase “geroscience,” which describes the intersection of the biology of aging and chronic age-related diseases. The term has been adopted by the NIH and is now shaping the field.
- The Buck established the world’s first PhD program in the Biology of Aging.
- The Buck’s focus is on educating/mentoring young scientists and preparing the next generation of scientists.
- CEO Eric Verdin is an accomplished, charismatic and visionary leader – as well as a working scientist in the study of aging with his own lab at the Buck.
- We have a 20-year head start on the rest of the aging and longevity research field.
- We are working every day toward translating our research into interventions that can help people live better longer.

Timeline of Buck Impacts

<u>YEAR</u>	<u>BUCK ACHIEVEMENTS</u>
1999	The Buck Institute officially opens its doors.
2000	Simon Melov, PhD., and Gordon Lithgow, PhD, report the first successful use of a drug-like compound to extend lifespan in an animal.
2003	Julie Andersen, PhD, links iron to Parkinson’s disease.
2006	Christopher Benz, MD, in partnership with the Marin Health and Human Services, helps launch the Marin Women’s Study.
2007	Buck receives a \$25 million federal grant that establishes a new field of research called “geroscience.”

- 2008 The California Institute for Regenerative Medicine (CIRM) awards the Buck \$20.5 million to build a new facility to house stem cell research.
- 2009 Judy Campisi, PhD, identifies SASP in senescent cells which propels research on “inflammaging.”
- 2011 Gordon Lithgow, PhD, reveals a common laboratory dye profoundly extends lifespan and slows the disease process in nematode worms with Alzheimer’s-like pathology.
- 2012 Buck researchers correct for the Huntington’s disease mutation in induced pluripotent stem cells.
- 2013 The Melov and Kennedy labs show that rapamycin reverses heart disease in mice.
- 2014 Buck partners with USC to launch the nation’s first PhD program in the Biology of Aging.
- 2015 Buck partners with Calico to develop the science of aging therapeutics
- 2016 Unity Biotechnology, based largely on cellular senescence research from the Campisi lab, incubates at the Buck.
- 2017 The Verdin lab publishes in *Cell Metabolism* that a ketogenic diet protects memory in aging mice.
- The Buck partners with Astellas Pharma to develop drugs that target cellular senescence.
- 2018 A \$6 million gift from Nicole Shanahan establishes the world’s first Center for Female Reproductive Longevity & Equality.
- Unity Biotechnology treats the first osteoarthritis patient in clinical trials.
- 2019 The Buck spins off three new companies: Napa Therapeutics, BHP Therapeutics and Gerostate Alpha.
- The Bia-Echo Foundation partners with the Buck to launch the Global Consortium for Female Reproductive Longevity and Equality
- Buck researchers discover how cellular senescence leads to neurodegeneration.
- 2021 The Buck is awarded more than \$26 million in a series of prestigious grants by NIH to study cellular senescence and Alzheimer’s disease.
- Astera Institute and Buck Institute announce a \$70 million collaboration to redefine the field of research on aging.

Four Buck professors, Eric Verdin, PhD, Judy Campisi, PhD, Martin Brand, PhD, and Claudio Hetz, PhD, are recognized as among the most highly cited researchers in the world.

BHP Therapeutics launches its first commercial product, Metabolic Switch, a ketone-ester drink that puts the body into a state of ketosis without the restrictive diet.

2022 The Tracy lab uncovers new findings for the function of tau in neurodegenerative disease.

Buck Fellow, Kai Zhou, PhD, discovers a new mechanism of how mitochondria begin to malfunction, which opens new doors for researchers seeking to fix the problem.

Buck researchers in the Kapahi lab uncover intriguing connection between diet, eye health and lifespan.

The Buck Institute initiates its first human clinical trial called Bike: Buck Institute Ketone Ester. This study will explore whether inducing nutritional ketosis through consumption of ketone esters affect any blood biomarkers of aging. The aim of the study is to demonstrate that ketones can alter aging in humans.

Researchers in the Andersen lab design a smart cell-based delivery system to treat multiple pathologies of Alzheimer's disease all at once and receive a \$2.4 million Transformative Research Award from the NIH, only one of nine in the nation. NIH considers the effort as high risk/high reward with the potential to change how we treat multiple diseases.