

REPORT

The Buck Institute For Age Research
A millionaire's vision becomes reality

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Back in the mid-1970's, a humanitarian and multi-millionaire did something that had a rather unusual result. Beryl H. Buck left behind a fortune-now valued at nearly \$1 billion- for the benefit of her community. In order to properly manage her generous contribution, which multiplied rapidly thereafter, a Foundation was later set up. Among other projects, the Foundation helped to build and support an institute for the purpose of conducting research aimed at understanding the biology of aging and extending the healthy human life span.

Beryl Buck's foresight has resulted in the establishment of a world-class research facility where scientists are aggressively researching the causes of age-related diseases using multi-disciplinary approaches. The following article reveals what has been going on at the Buck Institute for Age Research located in Marin County, California.

by Melissa Block, M.Ed.

The Buck Institute For Age Research is a non-profit, totally independent research center, not affected by political or economic interests. Because of this, the scientists working there are free to do the work they believe is in the best interest of life extension, and are not beholden to large pharmaceutical companies, medical associations, HMOs, politicians or any of the other parties who tend to stifle groundbreaking research.

Dale E. Bredesen, M.D.,
President and CEO

The Institute's headquarters have been called "a magnificent blend of art, architecture and science," and are considered a Marin County landmark. They were designed by famed architect I.M. Pei, with the intent to create the ideal environment for the use of cutting-



edge methods and for the collaboration of scientists in various areas of aging research. Phase I of construction includes 185,000 square feet, including a 238-seat auditorium, administrative offices, three libraries, faculty offices and laboratories. When completed, the complex will measure a total of 355,000 square feet. On the 488-acre property, which includes 128 units of housing for entry-level researchers and visiting scholars, 238 acres are dedicated to permanent agricultural use and 70 acres will be open public space. In such an environment, where brilliant scientists are able to spend one hundred percent of their efforts on research, and where they have complete access to state-of-the-art equipment and research methods, great things are bound to be discovered.

As a freestanding research center, The Buck Institute collaborates on projects with universities, biotechnology firms and other public and private research organizations. In fact, researchers from The Buck Institute collaborated with scientists from Eukarion, Inc. to lengthen the life span of nematode worms with synthetic catalytic scavengers (SCSs). Buck Institute research teams have also collaborated with the University of California, San Diego (UCSD), the University of California, San Francisco (UCSF) and Smith-Kettlewell Eye Institute.

Scientific innovators

The Buck Institute's mission is to find ways to stave off or altogether prevent the degenerative diseases of aging, effectively defusing the upcoming health care crisis expected as the world's population ages. By identifying very early diagnostic markers in people who will eventually develop these diseases, Buck Institute scientists hope to create therapies that will delay the disease's onset for 5, 10, even 50 years. These innovative scientists seek to understand the nature of the aging process—and the disease processes that often accompany aging—at the cellular and molecular levels. In other words, The Buck Institute's quest is to locate the exact triggers of age-associated disease, and to turn those triggers off or delay them from being turned on. What makes

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The Buck Institute truly extraordinary is its research staff. Culled from top universities and research centers in the U.S. and abroad, these dedicated scientists have come together in an unprecedented joint effort to hold back the tide of age-related disease. Unique research is ongoing in each of the Institute's laboratories, and there is a constant exchange of information between researchers in various disciplines that enriches the pursuit of each individual team of scientists. Interns and junior research fellows are an integral part of the facility's staff; senior staff members appreciate the importance of bringing in and mentoring young scientists. Senior staffers also recognize the need for their own continuing education as research methods become more and more technologically advanced.

Present research on age-related neurological disorders

Gerontologist Julie Andersen, Ph.D., studies Parkinson's disease, a hereditary neurodegenerative disease that strikes one out of every 100 Americans over the age of 65. Parkinson's causes progressive stiffness, tremor and loss of control over body movements, and is caused by the destruction of dopamine-producing cells in a part of the brain called the substantia nigra. Dr. Andersen is studying the role of free radicals in the progression of Parkinson's disease; more specifically, whether the age-related decrease in cells' ability to make the antioxidant glutathione is partly responsible for the disease's progression.

Dale E. Bredesen, M.D., the founding president and CEO of The Buck Institute, is a neuroscientist of the highest caliber. He has belonged to the neurology faculty at UCLA and worked as a professor and director of the Burnham Institute's Program on Aging and Cancer in San Diego, California. In his laboratory, a dozen researchers are working towards a complete picture of the molecular and cellular mechanisms that cause the death of nerve and brain cells in diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). Once those mechanisms are understood, the Bredesen lab will use this knowledge to develop techniques for early identification and treatment of these diseases, extending healthy years of life for people predisposed to them.



Vivian Y.H. Hook,
Ph.D.
Professor and
Director of DNA
Sequencing Core,
Co-Director of
Chemistry Core

In an issue of the journal Nature Medicine [Nat Med 2000 Apr;6(4):397-404], Dr. Bredesen and Dr. Edward Koo of UCSD reported on their Alzheimer's research. In the brains of Alzheimer's patients, an abundance of a sticky deposit known as beta-amyloid is thought to be the main cause of nerve cell degeneration. Drs. Bredesen and Koo report that another substance, which they named the C31 peptide, appears to contribute to the progressive brain cell damage and death characteristic of Alzheimer's disease as well. This research could have significant effects on drug development for Alzheimer's, which until recently has focused on affecting the formation of beta-amyloid plaques alone. Further research could lead to better targeted drug therapies for slowing the progression of this disease.



Chemist Lisa Ellerby, Ph.D., is one of the founding faculty members of The Buck Institute. Dr. Ellerby and her research team seek to understand why the cells of the nervous system die off in people with inherited, age-dependent neurodegenerative diseases, including Huntington's chorea (which causes progressive loss of motor control and dementia), Kennedy's disease (a disease of muscle atrophy that only affects males) and Machado-Joseph disease (a Parkinson's-like disorder that strikes mostly people of Portugese descent). Specifically, she is studying how changes in the structure of a neurotransmitter molecule affect the activity of enzymes that spur cell death. Her goal is to identify which of these enzymes are involved in neurodegenerative disease.

Vivian Y.H. Hook, Ph.D., holds a joint faculty position as Adjunct Professor of Neurosciences and Medicine at UCSD. She also directs a pre- and postdoctoral training program in the neurosciences at both UCSD and The Buck Institute. She has received several grants from

government and private sources to further her research. Her research focus is the role of enzymes called proteases—and of specialized molecules that inhibit their activity—in the development of Alzheimer's, Huntington's and other neurodegenerative diseases.

Her research into proteases could have a more general application for age-related problems, as well. Proteases regulate the production of neuropeptides, which, in turn, regulate stress responses, pain, blood pressure and weight gain. Dr. Hook hopes to manipulate proteases with drugs in ways that will relieve pain, downregulate stress reactions and blood pressure, and control the tendency towards obesity often seen in aging people.

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**Lisa M. Ellerby,
Ph.D.
Assistant Professor**



**Julie Andersen,
Ph.D.
Associate Professor**

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The Benz Lab—cancer research at The Buck Institute

Cancer is a disease of aging. While only 207 out of every 100,000 people under age 65 develop cancer, 2,261 out of every 100,000 people over 65 develop some form of this disease. Breast cancer is among the most common and most feared of the cancers.

Christopher Benz, M.D., is an internationally recognized expert on breast cancer research and therapy. Before starting his Benz Lab at The Buck Institute, he worked as a senior attending oncologist at the UC San Francisco Comprehensive Cancer Care Center, where he still holds a position as an adjunct professor. The research Dr. Benz is engaged in today has been built on almost two decades of study directed at finding molecular strategies for improvement of cancer diagnosis and treatment.

Work in the Benz lab seeks to understand an interesting paradox: when we age, our cells age, too, and begin to malfunction and break down more quickly than our bodies can repair them; but when cells become cancerous, as they often do with age, they become immortal and grow uncontrollably. Dr. Benz and his research associates seek to find the common molecular and cellular defects that these seemingly divergent processes (cancer and aging) share.

Modern chemotherapy drugs are incredibly toxic, especially to the less resilient body of an older person, and cancers often develop resistance to chemotherapy agents that initially work to slow disease progression. Research in the laboratory of Michael Ellerby, Ph.D. is focused on finding new, non-toxic therapies for cancer. In order to grow and spread, tumors must develop a network of blood vessels. Dr. Ellerby is researching the potential usefulness of lab-created “Hunter-Killer peptides,” proteins designed to selectively target and destroy the cells that make up tumor blood vessels.

In a study published in the September, 2000 issue of Nature Medicine, Dr. Ellerby describes the biological action of these Hunter-Killer peptides. One component guides the peptide into cells that are in the process of forming tumor blood vessels; research so far has shown that the other component spares normal cells, but kills off the targeted cells. Currently, Dr. Ellerby is engaged in a search for yet more effective and less toxic versions of these peptides.

Free radicals and mitochondrial function

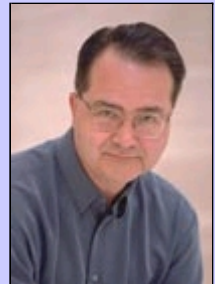


Gordon J. Lithgow,

Before helping to found The Buck Institute, Simon Melov, Ph.D. was an assistant professor at Emory University's Center for Molecular Medicine. Today, he participates in the Gordon Conference on Oxidative Stress and Disease, and is on the editorial board of two peer-reviewed gerontology journals. His research focuses on the mitochondria, tiny “engines” that make energy within cells. Mitochondria create free radicals in the process of metabolizing fuel, and if inadequate antioxidant reserves are present, those free radicals can damage or destroy the mitochondria or the entire cell. The effects of free radical stress—also called oxidative stress, because free radicals can



Christopher Benz, M.D.
Professor and Director of the Program on Cancer and Developmental Therapeutics



H. Michael Ellerby, Ph.D.
Assistant Professor



Simon Melov, Ph.D.
Assistant Professor

Work in the Benz lab

Ph.D.
Associate Professor



David G. Nicholls,
Ph.D.
Professor of
Mitochondrial
Physiology



David Greenberg,
M.D., Ph.D.
Professor and Vice
President of Special
Research Programs

The laboratories at the Buck Institute house some of the most advanced techniques and equipment available for the purposes of medical research. Those labs are directed by expert technologists who support research teams in using these invaluable tools.

only be formed in the presence of oxygen—have been strongly associated with aging and age-related diseases. Dr. Melov's research goal is to determine how much of a role mitochondrial oxidative stress plays. In his most recent work, he examined the effects of synthetic antioxidant compounds on mice incapable of producing the mitochondrial antioxidant SOD (superoxide dismutase). Without the antioxidant compounds, the mice died of heart disease within days of their birth; with the SOD-like antioxidant, they lived much longer.

Gordon Lithgow, Ph.D., is the founding editor of the journal *Ageing Cell*, and has authored and contributed to numerous publications and received prestigious scientific awards for his research. As one of The Buck Institute's newest staff members, he collaborated with Dr. Melov and Eukarion researchers on studies showing that synthetic catalytic scavengers could lengthen the life span of nematodes. His research focus has been on the link between stress and aging; he has found that animals' responses to stress strongly influence the length of their lives.

David G. Nicholls, Ph.D., once the head of the Department of Pharmacology and Neurosciences at Dundee University in Scotland, is a founding faculty member of The Buck Institute. He is one of the world's most respected experts on the subject of mitochondrial physiology. The research he is conducting today builds on the understanding that mitochondrial dysfunction plays an important role in the death of nerve cells in neurodegenerative disease and stroke, as well as in heart damage during heart attack. Dr. Nicholls is also studying the role of excitotoxicity in neurodegenerative disease. Excitotoxicity describes the rapid release of the excitatory neurotransmitter, glutamate, into nervous system tissues, causing nerve and brain cells to be literally excited to death.

Stroke research

Neurologist David Greenberg, Ph.D., is a founding faculty member of The Buck Institute. Prior to beginning his research there, he was an attending neurologist and professor at the University of California, San Francisco and the University of Pittsburgh. His research seeks to understand the cause of cell death during stroke, with the eventual goal of preserving brain function in victims of stroke and similar disorders. His team is also studying how reduction of oxygen supply to the brain encourages the growth of new blood vessels, in hopes of developing a treatment protocol incorporating the administration of VEGF (vascular endothelial growth factor) to reduce the extent of brain damage by re-establishing blood flow to oxygen-starved tissues. Dr. Greenberg's research also incorporates the study of cannabinoids, substances produced by nervous system tissues in response to injury; there is

some evidence that cannabinoids could help prevent stroke. In addition to his research duties, Dr. Greenberg directs the training program for junior researchers and coordinates educational programs for scientists as well as laypeople who live in the San Francisco Bay area.

Cutting-edge laboratory technology

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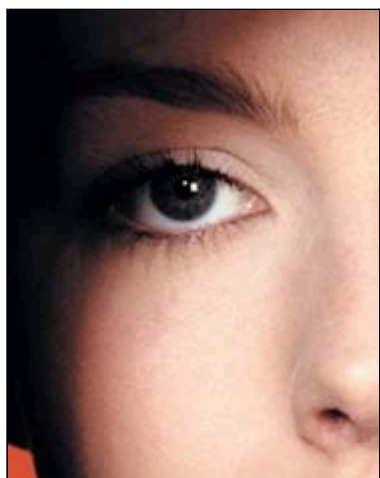
The laboratories at The Buck Institute house some of the most advanced techniques and equipment available for the purposes of medical research. Those labs are directed by expert technologists who support research teams in using these invaluable tools.

Mark W. Eshoo, Ph.D., runs The Buck Institute's Genomics Core Laboratory. In this laboratory, researchers use DNA microarray technology to identify the genes involved in diseases of aging. The technology behind the work being done in Dr. Eshoo's laboratory is incredibly complex, but the end result is an easy-to-read visual representation of genetic activity. Many of the scientists working in the labs of The Buck Institute use Dr. Eshoo's DNA microarray technology in their work.

Bradford W. Gibson, Ph.D., specializes in the fields of mass spectrometry and structural biology. He currently is working with Dr. Vivian Hook, using these techniques to identify biological markers for degenerative diseases.

Paul C. Goldsmith, Ph.D., directs the Morphology Lab. He has been a professor of obstetrics, gynecology and reproductive sciences at UCSF. The Morphology Lab contains equipment—including transmission electron microscopes and computers that can create detailed digital video images—that allows research teams to visualize and study the activity of genes and genetic expression. In his own research, he seeks to better understand the progression of Alzheimer's disease by identifying the exact causes of nerve cell degeneration.

Vision research



Since 1989, Buck Institute re-searchers have conducted a study of residents of the Marin County area aged 55 and older. Data gleaned from this population has been used for research projects on age-related depression, memory, medication use and causes of early death. The aim of the latest of these projects, funded by the National Eye Institute and in collaboration with the Smith-Kettlewell Eye Institute, is to better understand the vision changes that occur with aging. From the results of 16 vision tests given to over 2,000 elderly Marin County residents, researchers hope to better characterize age-related visual changes; to identify lifestyle factors related to vision loss with age; and to find ways to use visual changes to predict general health status.

Helping you age more gracefully

The Buck Institute For Age Re-search is a unique research center, staffed by scientists who are working together to extend the healthy years of the human life span through biomedical research. By doing so, they hope to decrease the financial cost of health care for Americans over 65—approximately \$400 billion in 1999 and rising as more people enter this age bracket. They also hope to reduce other costs of declining health in senior citizens, such as the loss of quality of life that inevitably affects sick people, and the stresses increasingly falling on adults who care for their ill, elderly parents.

The Leonard and Beryl H. Buck Trust generously donated much of the funds needed to start the Buck Institute, and continues to donate \$5.5 million each year towards its operations. The Buck Institute for Age Research is a unique research center, staffed by scientists who are working together to extend the healthy years of the human life span through basic biomedical research.

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Mark W. Eshoo, Ph.D.
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