making connections
2013 ANNUAL REPORT
Senescence and cancer link

Cellular senescence typically occurs after 50 cell divisions.

Senescent cells can account for 15% of cells in mammalian tissues.

There are 75 to 100 trillion cells in an adult human body.

Kidney disease

In the U.S., 8.8% of the population, or 1 in 11 people, have had a kidney stone.

Kidney disease is the 8th-leading cause of death in the U.S.

Between 1994 and 2006, the prevalence of chronic kidney disease in people age 60 and older jumped from 18.8% to 24.5%.

Nearly 60% of adults age 50 and older are at risk of breaking a bone.

1 in 2 women and up to 1 in 4 men age 50 and older will break a bone due to osteoporosis.

Genetic factors may determine as much as 50% to 90% of bone mass.

Environmental factors account for the remaining 10% to 50%.

Osteoporosis

Osteoporosis is responsible for 2 million broken bones each year in the U.S.

About 1 in 8, or 12%, of American women will develop invasive breast cancer during their lifetimes.

Most cancer cells have 60 or more mutations.

Tumor samples were collected and analyzed from over 800 patients.

Over 30,000 genomic mutations were found, 35 of which were significantly mutated genes.

Breast cancer

In 2009, 40,676 American women died from breast cancer.

In 2009, 211,731 American women were diagnosed with breast cancer.

Huntington’s disease

More than 250,000 Americans are at risk of inheriting it from a parent.

Approximately 30,000 Americans have it.

The Cancer Genome Atlas

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Genetic factors may determine as much as 50% to 90% of bone mass.

Environmental factors account for the remaining 10% to 50%.
Each liver cell contains 1,000 to 2,000 mitochondria, which in total occupy about 20% of cell volume.

There are at least 20,000 different protein-encoding genes in humans, some of which are studied by the Buck Chemistry and Mass Spectrometry Core.

Mitochondrial DNA contains 37 genes, all of which are inherited from your mother.

The Buck Genomics Core processed 148 samples this year from zebra fish, mice, tardigrades (water bears), and human skeletal muscle.

The Buck Genomics Core processed and analyzed over 6 billion sequencing reads and over 1 terabyte of data this year.

There are at least 20,000 different protein-encoding genes in humans, some of which are studied by the Buck Chemistry and Mass Spectrometry Core.

The Buck Bioinformatics Core collaborated with 9 faculty members, and published 6 articles last fiscal year.

There are 100 million bits of data in the sequenced human genome.

The Buck Morphology Core processed 1,497 paraffin samples this year.

This past year the Buck Morphology Core processed 756 cryostat (frozen) samples.

24-month-old mice are the human equivalent of 70 to 75 years old.

A mouse heart beats every 10 milliseconds.

Rapamycin is a naturally occurring compound that extends lifespan in mice by up to 14%.

The Buck Mouse Phenotyping Core’s ultrasound machine captures more than 700 frames per second.

Fruit flies live longest when eating a diet featuring a relatively high carbohydrate-to-protein ratio of 16:1.

More than 70% of human disease loci have been found to have a homolog in the fruit fly genome, including 68% of genes linked to human cancers.

Mitochondrial DNA contains 37 genes, all of which are inherited from your mother.

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The Buck Institute is making tremendous progress and generating new discoveries about how aging enables chronic disease. Each year we advance our unique mission to extend healthspan, the healthy years of life, while contributing to a deeper understanding of how we can and should be treating the debilitating conditions suffered by increasing numbers of people around the world. In 2013 the accomplishments of Buck scientists were particularly impressive:

- Dr. Chris Benz’s lab, in collaboration with scientists at UC Santa Cruz, made major contributions to studies conducted by The Cancer Genome Atlas, which were published in Nature.
- Martin Brand’s lab zeroed in on free radicals, finding that their production in muscle causes insulin resistance and Type 2 diabetes.
- Dr. Dale Bredesen’s lab developed evidence that Alzheimer’s stems from an imbalance in nerve cell signaling that can be ameliorated by a new therapeutic system now set for human clinical trials.
- Scientists in the Ellerby lab corrected the genetic mutation responsible for Huntington’s disease in cell culture.
- The California Institute for Regenerative Medicine awarded Deepak Lamba $1.5 million to make a 3-D model of the retina that will enable studies of retinitis pigmentosa, an inherited disease that usually blinds its sufferers by middle age.
- Simon Melov and Brian Kennedy published a study showing that rapamycin reversed age-related heart disease in elderly mice.
- Xianmin Zeng’s lab, in collaboration with the New York Stem Cell Foundation and City of Hope in Los Angeles, cured Parkinson’s disease in rats using dopaminergic neurons generated in the lab.

But even as 2013 was an inspired year for many of our labs, it was also a year of decreased federal support for research caused by the sequester, which greatly increased the pressure on the Buck and other research institutes across the country to develop new sources of financial support.

The Buck met this mounting challenge in 2013 by redoubling its global outreach and fundraising efforts in all areas. Our Board of Trustees provided significant help with a major increase in contributions led by a $5 million gift from Arthur and Drue Gensler coupled with a $250,000 challenge grant from Dick and Barbara Rosenberg that was fully matched. In addition, a gift of $500,000 from Trustee Larry Rosenberger and his wife Diane added a new learning center to deepen and expand our commitment to K–12 STEM education. Our global outreach is also building momentum; initiatives led by the Buck Advisory Council generated more than $800,000 for research and operations in the past year.

As government funding of research continues to decline, the Buck must continue to grow and diversify its income streams through philanthropy and by monetizing our intellectual property through corporate-sponsored research, licensing, and new ventures. We need your help now so that we can continue to support the groundbreaking research that has made the Buck Institute the global leader in research on aging. Please call us. We welcome the chance to explore with you the areas in which your support would have the greatest benefit.

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Chair, Board of Trustees

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President and Chief Executive Officer
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BUCK FACULTY

Buck researchers are unraveling new connections between the science of aging and the causes of chronic disease. Across our labs, dedicated scientists are pursuing unique collaborations, exploring biological links, and decoding pathways that will lead to breakthrough treatments for a host of age-related maladies.
“We now have proof that senescent cells in the brain contribute to age-related neurodegenerative diseases.”

Julie Andersen
PhD, Professor

Julie Andersen is bringing her expertise in neurodegenerative diseases to a new collaboration focused on the aging brain. This past year she began a major project with Judith Campisi, PhD, who studies senescence in relationship to cancer and aging. Senescence occurs when damaged cells stop dividing. The process suppresses cancer but also results in inflammation, which drives the aging process.

Internationally recognized for her research in Parkinson’s disease, Andersen says very little is known about senescence in the brain. Using a mouse model of Parkinson’s, she and Campisi removed senescent cells and saw improvement in the animals. Andersen has also started a collaboration with the Bredesen lab to explore the role of senescence in mild cognitive impairment. All of the work is fueling efforts to ask basic questions about senescence-driven inflammation in the aging brain.

Andersen’s lab continues to develop animal models and to explore therapeutic options for Parkinson’s disease. She and her staff are also involved in collaborative projects aimed at understanding the impact of metals—specifically lithium and manganese—on Parkinson’s, age-related neurodegeneration, and lifespan. Andersen is participating in the new BAIT (Buck Aging Interventional Testing) project as well, which involves screening compounds that have the potential to increase healthspan and lifespan in mice.

www.buckinstitute.org/AndersenLab

“The silos in cancer research are coming down. Someday patients will no longer be diagnosed with cancer based on its tissue of origin, but rather on its genetic and molecular characteristics.”

Christopher Benz
MD, Professor

This year, the Benz lab, in collaboration with UC Santa Cruz computer scientists and bioengineers, made major contributions to studies done by The Cancer Genome Atlas (TCGA), which were published in *Nature*. TCGA involves a national network of researchers working to understand the molecular basis—and resulting genetic similarities—of 20 types of cancer. One of the TCGA’s goals is to be able to repurpose existing cancer drugs for wider use.

In addition to working on TCGA, the Benz lab continued its research involving two major pathways linked to breast cancer. The work is aimed at developing personalized treatments for patients. In tumor cells making excess amounts of the estrogen receptor (ER) protein, scientists are pursuing a therapeutic target that could improve the endocrine treatment approach for the most common form of breast cancer in women over 50. Researchers are also looking at cancers caused by a genetic abnormality that results in excess production of the ErbB2/HER2 receptor protein, facilitated by an unexplored cancer-driving mechanism within protein-producing polysomes. This work is yielding a new “preclinical rationale” expected to enhance and individualize treatments against clinically resistant HER2-positive breast cancers.

www.buckinstitute.org/BenzLab

“We have worked out how we might be able to prevent Type 2 diabetes.”

Martin Brand
PhD, Professor

This year Martin Brand has been intensely focused on activities within the mitochondria of muscle cells. He says free radicals produced in the energy-converting mitochondria impede the signaling pathway for insulin, ultimately rendering the muscle unresponsive to this hormone, which regulates glucose in the blood. Basically, free radical production in muscle causes insulin resistance and Type 2 diabetes.

A chain of electron transport proteins within the mitochondria is involved in the production of both free radicals and the energy essential for life. The challenge is to stop the free radicals without shutting down the cell’s ability to release energy. Brand’s lab has zeroed in on three sites within that chain that make the radicals. His group is currently working with the Genomics Institute of the Novartis Research Foundation to screen 600,000 compounds to find those that shut down radical production at just those sites.

As director of the Institute’s Morphology and Imaging Core, Brand and his lab collaborate with many Buck scientists on projects involving aging and age-related disease. Brand is a co-principal investigator on a new project involving osteoporosis. Researchers will be studying gene expression and the bioenergetics of osteoblasts—cells that maintain bone.

www.buckinstitute.org/BrandLab
"We now know that chronic diseases usually involve imbalances in entire networks; they are not typically caused by a simple virus or gene mutation. Optimal treatment will therefore take more than a simple drug—as well as a number of things that aren’t drugs."

Dale Bredesen
MD, Professor

Dale Bredesen’s laboratory studies the mechanisms underlying neurodegenerative disorders such as Alzheimer’s disease and works to develop therapeutics for this devastating disorder. The lab has developed System 1.0, a system of therapeutics that addresses the network of abnormalities driving Alzheimer’s disease.

On the molecular level, Bredesen has discovered evidence that Alzheimer’s stems from an imbalance in nerve cell signaling. In the normal brain, there is a balance between signals that support memory formation and those that support memory reorganization, allowing irrelevant information to be forgotten. In the Alzheimer’s brain, however, the network imbalance supports forgetting over new memory formation and maintenance. Fortunately, this network imbalance can be ameliorated by a new therapeutic system, which is now set for human clinical trials. The research has also led to a novel class of drugs for Alzheimer’s disease that block the production of a key part of the abnormal network without interfering with the normal functioning. The first drugs in this new class are now in pre-clinical trials in a mouse model of the disease.

www.buckinstitute.org/BredesenLab

"We know senescent cells fuel cancer metastasis and are at least partially responsible for why patients feel so ill after chemotherapy."

Judith Campisi
PhD, Professor

Judith Campisi’s pioneering work on senescence—a tumor suppressor mechanism that also drives the aging process—took a major leap forward this year with discoveries that will likely impact clinical practice.

Badly damaged cells permanently stop dividing—a process termed cellular senescence, which prevents cancer in young organisms. But senescent cells accumulate with age and also secrete inflammatory cytokines, thereby causing “inflamming”—a process implicated in many age-related diseases.

The Campisi lab’s recent discoveries point to senescence-driven inflammation as a driver of late-life cancer metastasis—the process primes tissue distal to the primary tumor to be welcoming to errant cancer cells. Chemotherapy causes both cancer and healthy cells to senesce. While successful in the short term as a cancer treatment, Campisi says chemotherapy can induce “early aging” and supports the proliferation of cancer metastasis. She says chemotherapy also induces senescence-associated inflammation, which causes acute, debilitating side effects.

Many discoveries in the Campisi lab come from mice that are genetically engineered to “eliminate” senescent cells. Her team is screening compounds for drugs that accomplish the same effect in humans. The aim is to develop therapeutics that slow inflammaging and ameliorate the devastating side effects of chemotherapy.

www.buckinstitute.org/CampisiLab

"Now that we have proof-of-principle that we can correct the Huntington’s disease mutation in a petri dish, my lab is focused on moving this research into animals as quickly as possible."

Lisa Ellerby
PhD, Associate Professor

Scientists in the Ellerby lab have corrected the genetic mutation responsible for Huntington’s disease using a human induced pluripotent stem cell (iPSC) that came from a patient suffering from the incurable, inherited neurodegenerative disease. Scientists are now attempting to transfer that know-how from the petri dish to a mouse model of Huntington’s, using viruses and other technologies that allow for genetic corrections in living animals.

Huntington’s disease stems from a mutation in the huntingtin gene, which encodes a protein that goes by the same name. Mutations in the huntingtin protein and the generation of toxic fragments gradually damage cells in the brain.

The iPSCs used in the Ellerby lab are reverse engineered from diseased human cells, such as skin, back to an embryonic-like state where they can be coaxed into becoming any type of cell. Ellerby makes the correction before the iPSCs are induced to become neural stem cells. Scientists replace the abnormal huntingtin protein with a normal protein using homologous recombination—a type of genetic recombination where two molecules of DNA are exchanged. In this case, the diseased DNA sequence is exchanged for the normal DNA sequence.

www.buckinstitute.org/EllerbyLab


Bradford Gibson
PhD, Professor

Typically, someone builds a career studying one or two of these proteins. We’ve identified hundreds of them; the big question is ‘how do we deal with this?’

This year Gibson and collaborators from Harvard University and the Gladstone Institute made a major contribution to aging research by identifying hundreds of new proteins active in networks and metabolic pathways that are regulated by SIRT3, an enzyme that has previously been linked to aging. Published in the prestigious Proceedings of the National Academy of Sciences, Gibson says researchers are now poised to understand the biological and pathological consequences of misregulation of SIRT3, which is impacted by diet and other lifestyle choices.

As the Director of the Institute’s Chemistry and Mass Spectrometry Core, Gibson is focused on understanding the biological and chemical processes common to both aging and age-related diseases. His lab is actively involved with other Buck scientists studying cancer, diabetes, Huntington’s and Parkinson’s diseases, and the role of protein aggregation and protein turnover in aging.

Gibson has also begun a major collaboration with Arvind Ramanathan. The two faculty members are establishing the Center for Integrative Metabolomics and Proteomics of Aging. Gibson says the new center will allow side-by-side analysis of changes in protein structure and metabolic flux—a systems biology approach to understanding aging that has never been done before.

www.buckinstitute.org/GibsonLab

David Greenberg
MD, PhD, Professor

Our aim is to be able to intervene earlier to prevent stroke.

This year Greenberg and his team are looking at dysfunction in the endothelial cells that line the blood vessels in the brain. When healthy, these cells regulate the function of the blood vessels and help prevent inflammation and clotting. One consequence of endothelial dysfunction is the deposition of atherosclerotic or fatty plaques within the blood vessels, which can be the precursor to stroke. Working in cell culture and in mice, researchers want to understand the early steps that lead to endothelial injury, which usually occurs at particular sites within the arterial tree in the brain.

Greenberg says that stroke is not primarily a disease of the brain but rather a disease of the blood vessels. The origins of atherosclerosis have been well studied in relation to heart and cardiovascular disease, but not in relation to brain and related cerebrovascular disease.

Our lab shows there are clear defects in cell movement due to the disease mutation’s impact on RRAS. This defect also makes it more difficult for developing neurons to make normal synaptic connections. Hughes is exploring methods for modulating the RRAS pathway using drugs and drug-like molecules.

The Hughes lab has a diverse portfolio of projects. This year researchers collaborated with other Buck labs investigating systems that maintain the ability of proteins to fold into the shapes that best support healthy functioning. Optimal protein folding is compromised both in aging and disease. Lab members are also engaged in studies focused on protein–protein interactions involving the nutrient-sensing mTOR pathway, particularly in embryonic stem cells. A collaboration with the Lamba lab is aimed at understanding how mTOR activity controls the differentiation of embryonic stem cells into neurons.

www.buckinstitute.org/GreenbergLab

Robert Hughes
PhD, Associate Professor

This year we’ve focused on altered cell motility as a feature of Huntington’s disease; we’ve discovered that the pathways that impact cell motility in HD cells are druggable.

Following up on genome-scale research that identified hundreds of potential drug targets for Huntington’s disease (HD), the Hughes lab has zeroed in on RRAS, a gene involved in cell motility and neuronal development. Hughes says defects in the RRAS gene, which helps drive the “machinery” involved in cell movement, are conferred by the inherited mutation responsible for Huntington’s. Research in the lab shows there are clear defects in cell movement due to the disease mutation’s impact on RRAS. This defect also makes it more difficult for developing neurons to make normal synaptic connections. Hughes is exploring methods for modulating the RRAS pathway using drugs and drug-like molecules.

www.buckinstitute.org/HughesLab
What is most exciting is that we’re learning how we can shape the community of bacteria in the gut of simple animals to influence tissue health and lifespan.

Heinrich Jasper
PhD, Professor

Heinrich Jasper wants to enhance the function of adult stem cells—tissue-specific cells that self-renew and spring into action when tissues are damaged. These stem cells also become less vigorous with age. Over the past year Jasper and his team have become interested in exploring the condition of adult stem cells in the gut, specifically asking if and how the bacterial community in the gut changes with age and whether the so-called “health” of this community is connected to chronic inflammation—which helps drive the aging process.

Much of this work is focused on adult stem cells that line the gut in Drosophila, the fruit fly. Jasper and his team have been able to shape the immune response in the gut of these animals, improving it and extending lifespan.

Jasper also moved his work into mammals this year. His lab is studying the impact of lifespan-extending compounds on stem cells in the trachea of mice. These cells are very similar to gut stem cells in fruit flies.

Jasper is involved in many collaborations with other Buck faculty—in projects that involve macular degeneration and global epigenetics, among others.

www.buckinstitute.org/JasperLab
“We now know physical activity is essential for simple animals to reap the benefits of dietary restriction—we think there’s a good chance the same axiom will hold true in humans.”

Pankaj Kapahi
PhD, Associate Professor

In a paper published in *Cell Metabolism*, the Kapahi lab showed that fruit flies on dietary restriction shift their metabolism toward increasing fatty acid synthesis and breakdown, specifically in muscle tissue. The flies need to move those muscles in order to get the lifespan-extending benefits that come from eating a Spartan diet. The research suggests that humans practicing caloric restriction in hopes of living longer need to make sure they eat enough in order to avoid fatigue, which limits physical activity.

In addition to studies focused on nutrition and energy metabolism in lifespan and disease, Kapahi’s team is engaged in diverse projects aimed at finding clues to longevity. Other projects involve metals and aging, the impact of circadian clocks on metabolism, efforts to modulate senescence using rapamycin, and the calcification that leads to kidney stones and vascular diseases such as atherosclerosis. Kapahi, who first identified the connection between the nutrient-sensing TOR pathway shift their metabolism toward increasing fatty acid synthesis and breakdown, specifically in muscle tissue. The flies need to move those muscles in order to get the lifespan-extending benefits that come from eating a Spartan diet. The research suggests that humans practicing caloric restriction in hopes of living longer need to make sure they eat enough in order to avoid fatigue, which limits physical activity.

Kapahi is also collaborating on the BAIT project aimed at testing potential healthspan-extending drugs in mice.

www.buckinstitute.org/KapahiLab

“This year we started asking ‘what’s the right way to study macular degeneration?’ We are concentrating on chronic stress—something that no one else has done.”

Deepak Lamba
MBBS, PhD, Assistant Professor

This year scientists in the Kennedy lab identified a promising lead in the development of rapamycin—an FDA-approved drug that dramatically increases healthspan in middle-aged mice and cardiac function in elderly mice, but that can cause adverse reactions in humans. The new class of molecules is more specific for its primary target and is predicted to have efficacy at least equal to that of rapamycin, with reduced side effects.

The lab also got more heavily involved in studying Hutchinson-Gilford progeria syndrome, a genetic condition characterized by the dramatic, rapid appearance of aging beginning in childhood. Researchers engaged in a project showing that the natural product resveratrol was effective in a mouse model of the debilitating disease.

Kennedy’s team also initiated an expanded program in yeast aging. Kennedy says the simplicity of yeast lends itself to a holistic understanding of how the genetics and molecular biology of aging interact within a whole organism. Studies in yeast have played a big role in identifying pathways that affect mammalian aging.

As CEO, Kennedy lent institutional support to the new BAIT project and helped establish a new Mouse Phenotyping Core that facilitates *in vivo* functional imaging of a variety of tissues and organs.

www.buckinstitute.org/KennedyLab
I am convinced that in order for us to effectively understand what’s going on in aging, we need to understand the process at the level of the single cell. “

Simon Melov
PhD, Associate Professor

Simon Melov says this may be the year when it all comes together. After studying various facets of aging in whole organisms and tissues for more than 20 years, Melov has begun focusing on unraveling the complexity of the aging process in single cells—and developing technologies that help illuminate a field of age research where little is known. His initial studies involve cardiomyocytes, the cells that constitute heart muscle, and osteoblasts, the single cells responsible for bone formation.

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In addition, Melov is also taking a “satellite” view of aging—asking essential questions of how discoveries in single cells relate to physiology and the development of meaningful therapeutics for age-related disorders. To that end, he is leading the new BAIT project, which involves a collaboration with the Andersen, Lithgow, Kennedy, and Kapahi labs to screen compounds that have the potential to increase healthspan and lifespan in mice.

Melov, who heads the Institute’s Genomics Core, and his team are also continuing studies involving the FDA-approved drug rapamycin. This year his lab published a study showing that the lifespan-extending drug reversed age-related heart disease in elderly mice.

www.buckinstitute.org/MelovLab

No one knows when aging starts. We have zeroed in on novel, unreported epigenetic changes in the DNA packaging mechanism that allow us to estimate the efficiency of DNA repair and predict the rate of adult stem cell aging.”

Victoria Lunyak
PhD, Associate Professor

Epigenetics is the study of how gene activity can be altered without actual changes in DNA sequencing. The Lunyak lab is focused on epigenetic changes in adult stem cells in order to understand why their regenerative function declines with age, leading to frailty and an increased susceptibility to cancer.

Aging impacts the proper organization of genetic information within adult stem cells. The packaging of this information (chromatin) is indispensable for controlling when and where our genes are expressed. Chromatin is formed by wrapping DNA around sets of specific proteins, which serve as the “epigenetic memory” of cellular identity. The Lunyak lab has identified age-related changes in chromatin and created a set of unique reagents that can be used to identify aging stem cells in clinical settings. This new finding allows researchers not only to visualize human adult stem and somatic cells with broken DNA repair mechanisms, but also to estimate the rate of organ-

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The goal is to understand the molecular mechanisms that trigger changes in chromatin and to identify pharmacological compounds that can efficiently combat these DNA packaging abnormalities.

www.buckinstitute.org/LunyakLab

“We now know that vitamin D profoundly affects longevity and healthspan in simple animals.”

Gordon Lithgow
PhD, Professor and Director of Interdisciplinary Research

This year the Lithgow lab initiated a major project involving vitamin D, finding that the “sunshine” vitamin extends both lifespan and healthspan in the nematode *Caenorhabditis elegans*. Lithgow’s team is focused on understanding how vitamin D impacts protein shape and aggregation, offering a possible explanation of why vitamin D deficiency is associated with many age-related diseases.

Expanding on earlier work with the Andersen lab that explored the link between the accumulation of excess iron and Parkinson’s disease, Lithgow’s team is now involved in a major collaboration with the Andersen and Kapahi labs and external partners targeting metal homeostasis and aging. “We’ve known that metals play a role in disease development,” said Lithgow. “What we didn’t know is that metal accumulation drives the aging process and that the interaction between metals plays a major role in aging.” The initial investigation involves iron, copper, and manganese. Compounds that clear those metals in nematodes will eventually be tested in mice.

Lithgow is also a principal investigator in the new BAIT project, which will examine the impact of normal aging in mice and involve screening drugs that could impact longevity and healthspan.

Lithgow, who initiated the Buck’s program in Geroscience, became the Institute’s Director of Interdisciplinary Research this year.

www.buckinstitute.org/LithgowLab

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www.buckinstitute.org/LithgowLab
“This past year my lab focused on expanding human genome annotation and clinical interpretation.”

Sean Mooney
PhD, Associate Professor

The Mooney lab uses computers and computer science to both generate new hypotheses and make biomedical research easier. This year the lab constructed a web-based tool that substantially broadens the type of information that researchers can glean about a particular gene or protein. Gene ontology, which is used to describe the characteristics of individual genes, has traditionally focused exclusively on function—what a gene does in the body. The tool created by Mooney and his team enriches that ontology by including information on drugs, diseases, and physiology associated with individual genes. “Researchers at the Buck and elsewhere want that information,” says Mooney. “It will help us take full advantage of information stemming from the explosion of genome sequencing.”

As director of the Buck’s Bioinformatics Core and a leader in the field, Mooney is involved in many collaborations both internal and external to the Institute. This year his team worked on The Cancer Genome Atlas project with the Benz lab and contributed to publications focused on inherited cancers, Down syndrome and heart disease, and DNA variants in mitochondria associated with dementia. His lab is also heavily engaged in ongoing Huntington's disease research in the Ellerby and Hughes labs.

www.buckinstitute.org/MooneyLab

“It is essential for us to understand how the body—in particular, skeletal muscle—responds to anti-aging interventions.”

Arvind Ramanathan
PhD, Assistant Professor

This year Arvind Ramanathan built an analytic platform that enables an in-depth understanding of how small molecules impact cell metabolism and function—initially in skeletal muscle. This “metabolomic” undertaking will help inform the development and testing of drugs and the discovery of biomarkers of aging.

Ramanathan is working with Buck faculty member Brad Gibson to establish the Center for Integrative Metabolomics and Proteomics of Aging. This unique effort, involving skeletal muscle, takes a systems approach to the biology of aging in which the analysis of protein expression and protein–protein interaction is done in tandem with the mapping of metabolic pathways and metabolic flux. The comparison of old vs. young, normal vs. diseased, with and without drug treatment will result in important mechanistic insights into the diseases of aging and the aging process.

Ramanathan’s lab is also involved in projects focused on stress and cell metabolism. How does a cell—in particular, a cancer cell—remember its biochemistry when it divides? This basic exploration could lead to interventions that would disrupt cancer cell replication. Ramanathan is also engaged in several collaborations with Buck faculty looking at metabolomic changes in simple animals and in stem cell models of human diseases, including macular degeneration and Huntington’s disease.

www.buckinstitute.org/RamanathanLab

“With our collaborators, we cured Parkinson’s disease in rats this year using dopaminergic neurons generated in my lab. Now that efficacy has been established, we are awaiting results of long-term safety studies in the animals.”

Xianmin Zeng
PhD, Associate Professor

The Zeng lab takes a two-pronged approach in its efforts to find treatments for Parkinson’s disease. Researchers are focused on replacing dopaminergic neurons damaged by Parkinson’s with dopamine-producing cells generated from embryonic and induced pluripotent stem cells. Dopamine is a chemical neurotransmitter produced in the midbrain that helps deliver the brain’s orders to the muscles.

Scientists in the Zeng lab are also creating patient-specific stem cell lines from people who have either the familial or sporadic form of Parkinson’s. These cell lines are genetically identical to the patients and provide an excellent model to study the mechanisms of a disease that is diagnosed in 60,000 Americans each year. This “disease-in-a-dish” research model also allows scientist to screen compounds to find therapeutic interventions that could treat or prevent the disease.

Zeng receives funding from the California Institute for Regenerative Medicine and the National Institutes of Health. She collaborates with researchers at the New York Stem Cell Foundation and City of Hope in Los Angeles.

www.buckinstitute.org/ZengLab
Art Gensler gives a toast to celebrate the naming of the Arthur and Drue Gensler Building.
“It’s an honor to support scientists who care so much about improving the health of people everywhere, and it’s a thrill to witness the progress that has been made since the Institute opened its doors just 14 years ago.”

—M. Arthur Gensler Jr.

Arthur and Drue Gensler
In November 2012, M. Arthur “Art” Gensler Jr. and his wife Drucilla Cortell Gensler donated $5 million to the Buck Institute. In recognition of that gift and the roughly $2.5 million the Genslers have previously given to the Buck, the new administrative facility was rechristened the “Arthur & Drue Gensler Building.”

The Genslers’ commitment to the Buck Institute can be seen throughout the Institute’s buildings and labs. Their support, combined with Art’s stature in the worlds of architecture and construction—Gensler is the world’s largest architectural design firm—has been instrumental in opening doors to others who have helped the Institute grow and thrive.

Drue is president of the Gensler Family Foundation. She was one of the Buck’s early supporters and served on the first Buck Advisory Committee. Art joined the Buck Institute as a trustee in 2000 just as the Institute’s first two research buildings were coming on line. Over his 11 years with the Institute, he has served as Chair of the Construction Committee, where his experience and expertise have helped shape both the operations and the esthetics of the Institute.

Art played a crucial role in the development of the open laboratory plans, which have been incorporated into the Institute’s scientific expansion, and he was actively involved in the planning and construction of the new Regenerative Medicine Research Center, which opened in April 2012. He also championed the new geothermal heat exchange program, which enables the Institute to cut $436,000 per year from its energy bills.
Pursuing a Revolutionary Therapeutic—Testing the Link Between Old Cells, Inflammaging, and Disease

Buck professor Judith Campisi has embarked on what promises to be the most exciting stage of her scientific career—and that’s saying a lot because her pioneering work already underpins a leading hypothesis for why we decline with age. The idea is that as cells age, they eventually stop dividing and start secreting compounds that cause “inflammaging,” a state of chronic inflammation that leads to frailty and a myriad of age-related diseases.

This year, the theory that Campisi’s work helped establish is being put to the test. “If we’re right, our findings can revolutionize the way people think about age-related diseases,” says Campisi. “Our research opens the possibility that a single intervention can simultaneously prevent or postpone multiple age-related pathologies. The goal is to extend our healthspan.”

Cells that stop dividing are termed senescent, which derives from a Latin word meaning “to grow old.” We should be grateful for the process because senescence has a life-saving upside. Cells that can divide accumulate damage over time—and the more damage, the greater the risk of cancer. Senescence nips tumors in the bud by keeping cancer-prone cells from dividing.

But as we age these cells begin to pile up and the darker side of senescence begins to dominate. The Campisi lab has found that the ongoing secretion of inflammatory compounds by senescent cells fuels tissue degeneration and even the development of late-life cancers and metastases.

“It’s ironic because senescence probably evolved as a defense against cancer,” Campisi says. “Yet, as senescent cells accumulate with age, their inflammatory processes promote the development of malignancies by priming tissues to be welcoming to cancer. But this apparently paradoxical behavior of senescent cells fits with a major theory of aging.” This theory, termed antagonistic pleiotropy, holds that some biological processes can be good for you when you’re young but bad for you when you’re old.

**SENESCENCE AND AGE-RELATED DISEASE**

In addition to promoting late-life cancers, senescence-driven inflammaging may also contribute to diseases as varied as atherosclerosis, arthritis, Alzheimer’s, diabetes, and the muscle-wasting sarcopenia at the root of age-related frailty.

Campisi was the first to formally link cellular senescence, inflammaging, and age-related disease. “Judy has led the field in many ways,” says James Kirkland, a physician who directs the Mayo Clinic’s Robert and Arlene Kogod Center on Aging. “She was one of the few working on senescence before it became topical.”
In recognition of her outstanding contributions to the field of aging research, Campisi has received awards from the National Institute on Aging of the NIH, the Gerontological Society of America, and the American Federation for Aging Research, as well as the Longevity Prize from the IPSEN Foundation. She was also elected as a fellow to the American Association for the Advancement of Science, which reflects the stellar quality of her work as well as the high regard other researchers have for her.

But no one has yet shown that senescence actually causes frailty and age-related diseases. To test the connection between senescence and these downsides of getting older, Campisi is collaborating with Kirkland and others on a $10 million, 5-year Program Project Grant funded by the National Institute on Aging.

WORKING WITH MAYO COLLABORATORS

The Buck-Mayo component of the team can now definitively connect senescent cells to aging because, for the first time, they can eliminate senescence in laboratory mice. “We and the Mayo group have mouse models that let us kill senescent cells at will,” Campisi says. The mutant mouse model ages prematurely, but killing their senescent cells reduces signs of aging, including cataracts and loss of skeletal muscle and subcutaneous fat. In addition, killing senescent cells in normal mice had no obvious deleterious effects even after 2 years of treatment, which is a long time for these short-lived rodents. “We haven’t seen much in the way of side effects, and function has been enhanced,” says Kirkland, who’s also on the Buck’s Scientific Advisory Board.

Now, the team is testing whether eliminating senescent cells in young mice will prevent functional decline as they get older, thus extending their healthspan. The team is also testing whether eliminating senescent cells in old mice will restore function, thus reversing frailty. Functional assessments will initially include muscle, skin, and the immune system, and will later be extended to the brain, bone, heart, and kidney—and to the development of late-life cancer.

The researchers will use their mouse models to connect the dots between cellular senescence, chronic inflammation, and age-related diseases. “We will capitalize on
these mice to determine the molecular pathways that enable senescent cells to drive inflammation,” Campisi says. A molecular pathway is a series of sequentially dependent events in a cell that result in a biological outcome—in this case, cells’ senescence and their ability to cause inflammation. Delineating the pathways by which senescent cells cause inflammation will reveal targets for drugs that could break this connection. Keeping senescent cells from making the molecules that cause chronic inflammation could, in turn, increase our healthspan by reducing frailty and a host of age-related diseases.

Intriguingly, the team found that cellular senescence is connected to two pathways that are involved in aging, and they are now testing whether inhibiting these pathways also increases the healthspan in mice. One of these aging pathways is called Jak/Stat. The other is called mTOR, and this pathway is inhibited by a naturally occurring compound called rapamycin. This drug extends the lifespan and healthspan of mice and other lab animals (see page 25). The researchers found that inhibiting this pathway also decreases the inflammation caused by senescent cells.

**THE GOAL: DRUGS THAT TARGET SENESCENT CELLS**

Ultimately, the researchers want to be able to eliminate senescence in people, just as they can in the mutant mice. “Our goal is to get drugs that kill senescent cells, not just to reduce the inflammation-causing compounds they produce,” Kirkland says. This could be a bit tricky, though, because cellular senescence continues to have an upside as we age. For example, Campisi recently discovered that senescent cells are vital to wound healing. “The idea would be to give the drug to people while they’re healthy and to kill the senescent cells over a day or two,” says Kirkland, adding that the process works this quickly in the mutant mice.

The researchers are excited at this prospect. “If we get a drug that eliminates senescent cells in people, it will transform treatments for age-related diseases,” Campisi says. “This is a way to simultaneously prevent or postpone multiple maladies associated with aging.”

Kirkland is pleased to be working with Campisi and other Buck researchers. “The environment there attracts people who like to work together, and collaboration is necessary because the aging field is technically complex and is moving quickly,” he says. “We’ll be much more successful with collaborative networks than with people working individually.”
A New Breakthrough in Breast Cancer Research

In a landmark study from The Cancer Genome Atlas (TCGA) published in Nature in September 2012, research collaborators from the Buck Institute and UC Santa Cruz (UCSC) helped demonstrate the existence of four main classes of breast cancer—a disease that causes 450,000 deaths worldwide each year.

After doing multiple types of genomic analysis from samples from 825 breast cancer patients, some 200 collaborators from around the country identified the molecular pathways that are different among the four classes. The Buck-UCSC team made a significant contribution by identifying pathways common to one particularly aggressive class of breast cancer and an aggressive type of ovarian cancer.

“This transformative paper also identified at least 40 possible drug targets, many of which would not have been considered breast cancer targets but are instead borrowed from other areas of oncology,” says Buck professor Christopher Benz, MD, the co-principal investigator of the UCSC-Buck Institute Genome Data Analysis Center (GDAC) and a practicing oncologist at UC San Francisco’s Carol Franc Buck Breast Care Center.

Dr. Benz says the unprecedented analysis, which required the integration of information across six different technology platforms, allows researchers to go beyond genetic mutations associated with breast cancer. “We’re now able to delve into the downstream molecular pathways that may or may not be activated in a particular tumor—this will lead to personalized, precision medicine where we can tailor treatments to very specific breast cancer types.”

Being part of TCGA has connected Buck scientists with leading cancer researchers across the nation. Buck staff scientist Christina Yau, PhD, who has expertise in both molecular biology and bioinformatics, was instrumental in identifying pathways highlighted in the study.

David Haussler, PhD, UCSC distinguished professor of biomolecular engineering, and co-principal investigator Josh Stuart, PhD, associate professor of biomolecular engineering, brought computing power and bioinformatics expertise to the effort. Their team, which is pioneering methods in bioinformatics for TCGA, established the Cancer Genomics Hub, a large-scale data repository and user portal for TCGA and the National Cancer Institute’s other cancer genome research programs.
The Buck-UCSC study is part of TCGA’s sweeping effort to generate comprehensive, multidimensional maps of the key genomic changes in major types and subtypes of at least 20 different cancers over the next 5 years. According to Dr. Benz, the Buck’s collaboration with UCSC is a unique synergy of expertise. “There’s still a lot of work to be done, but it’s a very exciting time to be involved in cancer research. The silos are coming down. Someday patients will no longer be diagnosed with cancer based on its tissue of origin, but rather on its genetic and molecular characteristics.”

ABOVE Cytoscape plot representing an interconnected network of genes that distinguishes squamous cell carcinomas of the head and neck and the lung from 10 other types of cancers arising from different organs, including breast cancer. Squamous cells are flat and closely packed to form a single layer of epithelium, the tissue that covers internal and external body surfaces.
LEFT A heatmap display that shows molecular pathway activation patterns among the four different sub-types of breast cancer. Red signifies high pathway activity, while blue reflects low pathway activity.

LEFT Christina Yau, Staff Scientist, Benz lab
Emmeline Academia, a research associate in the Kennedy lab, checks fittings on cages that measure multiple metabolic metrics in mice.
New Buck Research on a Promising Anti-Aging Drug: An Update on Rapamycin

Rapamycin is a naturally occurring compound that extends lifespan in mice by up to 15 percent. The drug, approved by the FDA to suppress the immune system in transplant patients, is being tested in labs around the world—including those at the Buck, where research involves Parkinson’s disease, human skeletal muscle, inflammation, and cancer.

“What’s really exciting about rapamycin is that it extends healthspan as well as lifespan,” says Buck CEO Brian Kennedy. His lab studies the drug and was involved in two publications that revealed rapamycin’s potential to help us all live healthy, longer lives. “This is where everyone at the Buck wants to go—we have no interest in just living longer.”

The first Buck study, from the Kennedy lab, showed that rapamycin extends survival and improves muscle function in mice with a mutation that mimics muscular dystrophy, which weakens skeletal muscles, and dilated cardiomyopathy, an associated disorder that weakens the heart. Feeding rapamycin to these mutant mice improved heart function as well as balance and coordination, which also decline with age.

The second study focused on age-related heart dysfunction in mice that were 24 months old—the human equivalent of 70 to 75 years of age. Like many seniors, the mice had hearts that had gotten bigger, thicker, and stiffer with age. They didn’t pump blood as efficiently. After just three months of treatment with rapamycin, the rodents saw a significant improvement in cardiac function—in some cases rapamycin even reversed the heart disease.

“Surprisingly, when you give rapamycin to old mice, it makes them more like young mice,” says Buck faculty member Simon Melov, who led the second study. Rapamycin also made the old mice friskier. “They ran much more, and this indicates their overall health was improved.”
The Buck’s First Spin-Off: Delos Pharmaceuticals Builds on the Promise of Rapamycin

The ultimate goal of aging research is to develop therapeutic treatments that extend healthspan. This year, for the first time, the Buck spun off a company to do just that. Called Delos Pharmaceuticals, the new company is developing highly specific rapamycin-based therapeutics.

Rapamycin is a challenge. Along with its positive effects on many diseases, the drug also induces significant side effects, including impaired glucose tolerance, insulin resistance, and high levels of lipids. “People have tried to produce better versions of rapamycin for decades, but no one has been able to reduce these side effects” says Stelios Tzannis, PhD, CEO of Delos Pharmaceuticals.

Can the two sides of rapamycin be separated? Based on its groundbreaking findings, Delos believes they can. Rapamycin acts on two versions of a protein complex called mTOR. One is linked to the drug’s therapeutic efficacy, while the other appears to be responsible for most, if not all, of its adverse effects. “Owing to our unique and proprietary chemistry platform, which we licensed exclusively from the Buck Institute, we are developing rapamycin analogs that have the ability to bind specifically to only one mTOR complex or the other,” Tzannis says. “We can also shift binding ratios between the complexes to achieve the desired balance of therapeutic properties.”

Delos, a Delaware corporation, is a wholly owned subsidiary of the Buck Institute. The company was founded on the basis of discoveries at the Buck and a unique chemistry technology acquired from Biotica Technologies, which allows synthesis of unique rapamycin analogs (rapalogs). “Translating research into medical products is a natural extension of what the Buck does,” says Buck Institute CEO Brian Kennedy. “We anticipate that Delos will be the first of many new companies that leverage our resources and expertise.”

Delos plans to develop its tailored rapalogs for the treatment of age-related diseases. The company’s most advanced program, aimed at treating the autoimmune disorder systemic lupus erythematosus, has successfully completed pharmacology and preliminary toxicology assessments and is ready to enter Investigational New Drug-enabling preclinical studies in the United States. The company has also initiated discovery programs in neurodegenerative diseases, specifically targeting Alzheimer’s and Huntington’s diseases. “This is an entirely new approach to treating age-related diseases,” Tzannis says. “Instead of developing a single compound, we are building an arsenal of targeted treatments tailored to address the needs of each disease separately.”
Choosing the Buck Institute for California’s Stem Cell Bank

In April 2013, Cellular Dynamics International Inc. (CDI), a company that pioneered stem cell technology, selected the Buck Institute as the site for California’s stem cell bank for human induced pluripotent stem cells (iPSCs). The Wisconsin-based developer and producer of stem cell lines won a $16 million award from the California Institute of Regenerative Medicine (CIRM) to establish the stem cell bank.

Robert Palay, CDI’s chairman of the board and CEO, says his company searched California for location options and chose the Buck in a highly competitive process, impressed by the number of CIRM grants the Buck has won and by the Buck’s intelligent utilization of CIRM dollars. “We intend to build the world’s best stem cell manufacturing facility, and this is a terrific location for it,” says Palay. “The Buck Institute is not only a world-class research facility but showed the flexibility we needed, and its great stem cell scientists were very welcoming.”

CDI signed a lease for up to 5 years for approximately 4,000 square feet of laboratory space in the Buck’s Regenerative Medicine Research Center and will sublet a portion of that space to the Coriell Institute for Medical Research. CIRM awarded Coriell nearly $10 million to store and distribute the stem cell lines generated by CDI. Coriell will build and operate a biorepository—a stem cell bank—using proven methods for managing sample collection, safe storage, and worldwide distribution of iPSCs. CDI is Coriell’s primary subcontractor for growing and freezing the stem cell lines.

CDI manufactures iPSCs in industrial quality, quantity, and purity from any individual’s stem cells taken in a standard doctor’s office blood draw. The iPSCs can then be used for drug research and testing, for stem cell banking, and for researching cellular therapeutics.

In its new stem cell center, CDI will create iPSCs from blood and skin samples taken from 3,000 patients suffering from 11 different diseases, including Alzheimer’s disease, cardiovascular diseases, diseases of the eye, and liver disease. Using proprietary technology, CDI will reengineer the samples into 9,000 stem cell lines—3 identical copies of the original 3,000 samples. Their ultimate goal is to create “disease-in-a-dish” research models that can lead to cures.

Buck president and CEO Brian Kennedy says CDI is a perfect tenant for the Regenerative Medicine Research Center. “Their work has the potential to revolutionize the treatment of a myriad of diseases—we are looking forward to collaborating on new research.” And Tom Novak, CDI’s vice president of strategic partnerships, says, “We see this as a great opportunity to not only interact and collaborate with the top scientists in the field of aging research but also to draw top talent to this, our second, laboratory facility.”
“Do join in, at whatever level you can. Help the Institute find cures and the key to healthier living for future generations!”

—Marylin Wanlass

Marylin Wanlass

Marylin Wanlass once dreamed of entering the medical field, but her childhood during the Great Depression made that dream impossible. Now, as a supporter of the Buck Institute, she is helping advance our understanding of the aging process, with the aim of improving the quality of life for people all over the world.

“It’s a very rewarding feeling, helping others, giving back to humanity,” says Wanlass, who watched the Institute being built as she traveled Highway 101. Touring the Institute when it first opened, she decided that the Buck Institute was where she wanted to focus her energy and resources.

After the death of Art Wanlass, her beloved husband, friends encouraged her to get involved and make a difference. She is now a vital member of the Institute’s family and regularly attends seminars and presentations.

In the local community, Marylin acts as an effective ambassador for the Institute. Learning everything she can about the science of aging and the Buck’s research is central to that. “I get a sacred, uplifting feeling when I meet scientists and participate in what is happening within these walls,” she says. “This was the perfect kite to lift me up.”

Since becoming involved with the Buck Institute, Wanlass has made several generous gifts to the Institute. The Wanlass Classroom is named after her late husband, and the Brune-Harris Conference Room is named in honor of her parents and their families. The ground floor of the new Regenerative Medicine Research facility is now named after Marylin.
Solving the Riddle of Osteoporosis, Cell by Cell

Simon Melov, a Buck faculty member and head of the Institute’s Genomics Core, studies the physiological changes that come with age, including the skeletal muscle loss that makes us frail and the heart muscle thickening that impairs our circulation. To extend this work to include how bones alter with age, he connected a world-class team with the right mix of expertise to tackle osteoporosis. This year they won a $457,000 2-year grant from the National Institutes of Health to study the bone-thinning disease in mice.

The research will focus on gene expression and cell function in single osteoblasts, the cells that make bones hard and strong. It’s a unique approach for a disease in desperate need of new therapeutics.

The team’s bone expertise comes from Clifford Rosen, a world leader in bone biology and a practicing clinician at the Maine Medical Center Research Institute. Melov and his Buck colleague Martin Brand bring their expertise in cutting-edge techniques to study single cells to the effort. “We were very interested in this because bone is so heterogeneous, with lots of different cell types,” says Rosen, who focuses on translating the results of basic research into therapies for people.

THE RESEARCH PLAN

To figure out what goes wrong in osteoporosis, the team will investigate osteoblasts in female mice that have had their ovaries removed. This decreases estrogen, which leads to bone loss in mice, just as it does in older women. Osteoblasts lay down calcium and other minerals that give bones their strength. But until now, researchers have only been able to study these bone-building cells in batches. The problem is that when you look at a lot of osteoblasts at once, you get results that are an
average for all of them. This could obscure cell-to-cell variations that keep old bones from laying down new bone. “Let’s say 20 percent of the cells are ‘bad’—we need to know whether that weakens the whole tissue,” says Melov. “Knowing this could help us fix it.”

The team will get that level of detail because Melov recently pioneered a way to measure the gene expression of individual cells. “Bone is a calcified matrix of cells. It’s always been a bit mysterious,” he says. “Now we can deconvolute the biology of aging one cell at a time to see if aging leads to changes in gene expression that cause variation in function—it’s a powerful approach.” This new method is also fast, and speed is critical when assessing cells one by one.

**INCLUDING ENERGETICS**

Laying down minerals in bone takes energy, and osteoblasts in old bones don’t use energy very well. But no one knows why, and that’s where Brand comes in. He’s a world leader in studies of mitochondria, the parts of cells that metabolize nutrients to provide energy. Brand determines the energy status of mitochondria by using a fluorescent microscope. This is partly because the more energy they have available, the more of a fluorescent dye they take up. “Mitochondria shine when they accumulate dye, and we can quantify the brightness,” he says. “For the first time, we can quantify the energetics of single living osteoblasts, even in unseparated, complex mixtures of cells.”

The energetics imaging will let Brand compare how well osteoblasts metabolize glucose and other sources of energy. The team hopes to determine why these bone-building cells have trouble using energy. Is it that they can’t use the nutrients in aging bones anymore? Or is it that they no longer use these nutrients efficiently? “If we knew this, we could develop new therapeutics that, for example, would deliver a different substrate to generate energy for laying down new bone,” says Rosen, who helps advise the U.S. Food and Drug Administration when they consider approving new endocrine and metabolic drugs.

Right now, the researchers can’t assess energetics and gene expression in the same cell. But that is their goal. “It could tie everything together,” Brand says. “We would know if the changes in energy metabolism are due to the expression of specific genes.”

**ABOVE** Martin Brand and Simon Melov meet in Melov’s office to discuss the need for new therapeutics for osteoporosis.
While calcium is essential to strengthening our bones and teeth, this mineral can also end up in the wrong places as we age. This leads to problems like kidney stones and vascular diseases such as atherosclerosis, or hardening of the arteries. "Understanding the fundamental biology of calcification in kidney stones could help us get a handle on vascular disease," says Buck faculty member Pankaj Kapahi, who studies fruit flies to find ways of increasing human healthspan.

But there was no good way to study the basic biology of kidney stones until Kapahi teamed up with Marshall Stoller, a surgeon who heads the urinary stone division at the University of California, San Francisco (UCSF). "We met through a common friend, Arnie Kahn, a UCSF epidemiologist who’s now a visiting professor at the Buck," Kapahi says.

Researchers used to simulate kidney stones in fruit flies by feeding them toxins like antifreeze, but this process obviously has little to do with the abnormal calcification in people. So Kapahi and Stoller joined forces to find a biologically relevant way to induce kidney stones in fruit flies.

FRUIT FLIES AND PEOPLE HAVE A LOT IN COMMON

Like humans, fruit flies make urine in tiny tubules. “The renal physiology of flies is very similar to that of people," Stoller says. So the team decided to see if genes linked to kidney stones in people also caused calcifications in the fruit fly tubules. They found that flies with a mutation in one of these genes, called xanthine dehydrogenase, did indeed get kidney stones.
The parallels between kidney stones in people and flies go even further. Eating a lot of protein makes people more susceptible to kidney stones, and the researchers found that the same is true of the mutant flies. Moreover, a high-protein diet accelerates aging in these mutant flies, shortening their lifespan from about 8 to just 2 weeks.

Now, Kapahi, Stoller (who is now an adjunct faculty member at the Buck), and Kahn are part of a team with a 2-year federal grant of $527,000 to use the aging-accelerated mutant flies to find compounds that reduce abnormal calcification. The team also includes researchers from Children’s Hospital in Oakland and the Lawrence Livermore National Laboratory. “We want to identify drugs that will prevent kidney stones in people,” Kapahi says.

A PAINFUL AFFLICTION

Kidney stones, which cause excruciating pain, afflict about a tenth of the population in the U.S. Current medical treatments are limited to surgery or using shockwaves to break up the stones. Knowing the early steps in kidney stone formation could help the Buck team find better treatments. This could also lead to new therapies for other disorders where calcium accumulates in the wrong places as we age, including Alzheimer’s.

In addition, because abnormal calcification underlies so many age-related diseases, the researchers will test whether compounds that reduce abnormal calcification also extend the lifespan of normal fruit flies.

“Major changes in our basic understanding of these processes will require cross-disciplinary work,” Stoller says. “Putting it all together can lead to quantum-level advances.”
Richard and Barbara Rosenberg

Richard “Dick” Rosenberg, retired chairman and CEO of Bank of America, is well known for his philanthropic activities in the San Francisco Bay Area. Dick’s wealth of experience and financial expertise were a major asset to the Buck in its formative years. During a time of great institutional transition and expansion, he was a steward of the Buck’s financial stability and a committed supporter of its growth.

Dick chaired the board’s Finance Committee and also served as board treasurer. In December 2012, he concluded his final term as a Buck trustee. In winding up his board responsibilities, Dick wanted to underscore his long-term commitment to the Buck Institute. He and his wife Barbara offered the Institute a challenge gift of $250,000.

Given the dramatic decline in federal funding for scientific and medical research, the timing of the dollar-for-dollar matching gift was especially critical, and the Institute is deeply grateful that, by June 2013, the Rosenbergs’ offer was successfully met by other donors. The $500,000 raised as a result of the Rosenbergs’ generosity will enable the Institute to support its research scientists as they develop and test new theories to unravel the connection between normal aging and chronic disease. The Buck’s newly expanded education program will also greatly benefit from the funds raised through the Rosenberg Challenge Gift.

“Barbara and I believe that good fortune should be shared with the community. We have worked very hard, but have had very good fortune, so it is a great feeling to be able to share some of that good fortune with outstanding institutions like the Buck.” —Dick Rosenberg
(clockwise from top right) Sean Mooney, Bioinformatics Core Director; Brad Gibson, Chemistry and Mass Spectrometry Core Director; Simon Melov, Genomics Core Director; Martin Brand, Morphology and Imaging Core Director; Simon Melov and Brian Kennedy, Mouse Phenotyping Core Co-Directors
Sharing Resources to Slow Aging and Prevent Disease

The names of our five core services—mass spectrometry, morphology, genomics, bioinformatics, and phenotyping—may sound intimidating, and the technology that drives them may be hard to fathom for non-scientists, but everyone can understand the benefits these shared resources bring to Buck research in terms of expertise, state-of-the-art equipment, efficiency, and cost savings.

The cores are the engines that power most of our discoveries about aging and disease. These state-of-the-art technologies allow us to validate novel hypotheses, make new and unexpected discoveries, and develop strategies for future experiments. The cores are where the Buck’s collaborative environment shines—because every core leader has expertise in aging.

“Our core directors are the best of the best in their fields,” says Buck CEO Brian Kennedy. “The fact that all of them are passionate about the field of aging research, and that each of them is committed to applying the best resources possible to every project that comes their way, makes the Buck what it is—the premier institute for solving the biological mystery of aging.”

ABOVE Buck research associate Kylie Mitchell prepares samples containing metabolite extracts from human skeletal muscle treated with longevity-enhancing drugs metformin and rapamycin.

ABOVE Buck Institute Core Technologies making connections to

ABOVE Brad Gibson and Arvind Ramanathan run a set of mass spectrometry experiments designed to identify novel secreted factors that are key regulators of skeletal muscle function.

RIGHT Shannon O’Hare at the confocal fluorescence microscope, studying the interaction of the cytoskeleton and the huntingtin protein gene in a cell model of Huntington’s disease.
Where Biology Comes to Life

Imaging reveals the cellular and subcellular structures of living things. In research, a picture is often worth a thousand experiments, showing clearly what other technologies can only hint at. Using powerful microscopes and imaging software, the Morphology and Imaging Core enables a deep understanding of structure and activity within living tissues and cells.

Images from this core have shed light on biological processes involved in wound healing, senescence, stroke damage, and kidney stone formation. They have visualized brain cell connections in mouse models of Alzheimer’s disease as well as the protein aggregation that is a hallmark of neurodegenerative diseases.

“I am extremely proud of the range and level of service that my team provides to the Institute,” says core director Martin Brand. “We enjoy helping other researchers answer challenging scientific questions—everything from localizing a specific DNA sequence or protein molecule in a section of tissue or a single cell to providing whole-body fluorescent images of simple animals.”

The core also offers unparalleled expertise in bioenergetics, thanks to Brand—a recognized world leader in mitochondrial function. Mitochondria are the parts of the cell that metabolize nutrients to provide energy. Brand and his team have collaborated on bioenergetics studies ranging from embryonic stem cells and skeletal muscle to breast cancer, diabetes, and osteoporosis.

**RIGHT** (top to bottom) Akos Gerencser, Assistant Research Professor, using a two-photon microscope to measure calcium levels in pancreatic islets isolated from mice; O’Hare at confocal fluorescence microscope; Morphology Core staff, including Gerencser, O’Hare, research associate Taki Te Koi, and Professor Brand. Te Koi assists in studies of the bioenergetics of bone cells.
Expertise in Gene Expression and Aging

Genes provide the set of instructions that lie at the heart of every cell, orchestrating the expression of proteins—the building blocks of life.

But gene expression changes with age. The Genomics Core, led by core director Simon Melov, uses a suite of technologies to interrogate the fundamental processes of aging at multiple levels—from the complete set of genes in a simple organism, down to gene expression in tissues and single cells in multiple species.

This year the Genomics Core worked with investigators to process samples ranging from zebrafish and the ultra-hardy tardigrade (water bear) to aging mouse hearts and human skeletal tissue. The core also did gene expression studies on stem cell function in Huntington’s disease as well as a novel model of cancer. Its aim is to facilitate science for other investigators.

“Scientists want to know how to maximize the information contained in genomic data,” says Melov. “It’s an unusually collaborative environment.”

Melov also pioneers new genomics technologies. For example, conventional genomics methods involve grinding up tissue, yielding results from a mix of cells, potentially hiding subpopulations of variant cells that drive aging and diseases. But Melov has developed a way to look at gene expression one cell at a time, facilitated by an instrument that can run 10,000 samples in a single run.

“Single-cell genomics is cutting-edge,” says Melov. “It positioned us to do things no one else could do—labs across the country are tapping into our expertise.”

LEFT Melov and research associate Brittany Garrett run a gene expression experiment in the Genomics Core.

BELOW Quantification of senescent genes in many single cells. DNA amplifies and melts at known temperatures. The graph on the left shows the target DNA amplifying. The graph on the right is a melting curve and denotes specificity of gene expression.
State-of-the-Art Analysis of Proteins and Other Biomolecules

Aging and disease involve complex molecular processes. To enable a deep understanding of these mechanisms, this core elucidates the structure and function of proteins and other biologically relevant molecules—no small task. These biomolecules have intricate chemical structures that determine their overall role, shape, location, and interacting partners.

The core includes several mass spectrometers that provide an array of information on an assortment of small to large molecules, along with systems that separate biomolecules from complex samples—such as tissues, blood, or protein mixtures—prior to analysis.

The core also provides expertise. Core director Brad Gibson helps Buck researchers shape their work. “It’s highly interactive,” he says. “We help clarify and expand research goals, and make sure the best technology is used to maximize results.”

Among many projects, core collaborations have helped illuminate basic aging research in proteomics, including secretory processes in senescence as well as the impact of longevity drugs on human muscle cells. The core has also furthered the understanding of protein aggregation in normal aging and in neurodegenerative diseases, the role of protein acetylation in metabolic regulation and diabetes, and protein turnover changes in several organismal models of aging and age-related diseases. Gibson’s team also participated in a national effort to identify protein biomarkers for breast cancer.

Gibson’s core also analyzes carbohydrates and lipids as well as small-molecule drugs. Soon, this work will be extended to include metabolomics, or metabolite analysis, under the direction of Buck faculty member Arvind Ramanathan.

Arvind Ramanathan. To build on this combined expertise, the Institute plans to establish a new Center for Integrative Metabolomics and Proteomics of Aging in the coming year. Ultimately, the two researchers want to find molecular biomarkers of aging, which would help monitor the anti-aging effects of drugs and lifestyle changes.
Reaping the Benefits of the Genomic Revolution

Advances in gene and protein analysis have led to an explosion of biological data. The Buck’s Bioinformatics Core helps researchers make sense—and take advantage—of the resulting deluge of information.

This core provides Institute labs with data management and analysis. Current projects include evaluation of clinical interpretation of human genome sequences and analysis of active genes in aging model organisms. The core is also highlighting genetic pathways that are relevant to Huntington’s disease and cancer.

“My team is also focused on generating hypotheses from large publicly available databases,” says core director Sean Mooney, who had the biggest “a-ha” moment of his career this year when one of his scientists identified a “druggable” molecular pathway involved in a genetic mutation linked to Parkinson’s disease. Mooney took the finding to the Andersen lab, where the drug is currently being tested in cell culture. “It’s particularly rewarding when data can be used to generate new possibilities for therapeutics,” he says.

The bioinformatics team also consults with Buck scientists to design experiments that use high throughput technology. The team then aids the interpretation of data, using pathway analysis and systems biology. “Many experiments generate long lists of genes and proteins,” says Mooney. “We connect the data back to reality.”

The core also develops computer models to anticipate the outcomes of experiments. “Predictive modeling uses artificial intelligence,” says Mooney, who collaborates with researchers worldwide. “If a model reproduces experimental results, that could tell us which of hundreds of genes to focus on in the next experiments.”

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The Mouse Phenotyping Core gives researchers an unprecedented view of aging. "Instead of just looking at how long animals live, we can measure changes in the function of specific organ systems as they age," says Buck CEO Brian Kennedy, who championed the new core this year. “This tells us about healthspan, which is where our interest lies. The core provides a critical step in our efforts to take discoveries in yeast, worms, and flies and move them to mice—and then to people.”

In addition, metabolic cages track mouse activity along with the oxygen, water, and food they consume and the carbon dioxide they produce. And other instrumentation measures body composition changes with age, including an increase in fat and decrease in muscle mass.

“We already have collected the largest data set on aging mouse physiology in the world, including the heart, vascular system, skeleton, metabolism, and fat-to-lean mass,” says Melov. “It’s this type of effort that sets the Buck apart.”

The core houses the new Buck Aging Interventional Testing (BAIT) project, which entails screening anti-aging compounds for longevity effects and monitoring organs in mice to assay functional changes.

Core instrumentation includes a CT scanner for a close look at bone and an ultrasound machine that can be used to measure heart function, capturing up to 10,000 frames per second and imaging living tissues in real time. “We can see blood swirling in a mouse heart, which can beat up to 600 times a minute!” says Simon Melov, who directs the BAIT project and co-directs this core with Kennedy. “Mice get age-related heart disease similar to humans—we can measure functional changes in the heart with astonishing detail.”

Kristin Koenig, a graduate student from Dominican University, reviews data from a mouse ultrasound, which is used to measure blood flow velocity within the carotid artery.
The Cores in Action: A Case Study

The combined power of the cores is fueling efforts by Buck faculty members Lisa Ellerby and Robert Hughes to understand and treat Huntington’s disease. This adult-onset inherited disorder causes the progressive loss of muscle control over movement and cognitive impairments—and ultimately death.

Huntington’s is caused by a mutant protein, and fragments of this protein build up in brain cells. Because protein accumulation is common to many neurodegenerative diseases, work on Huntington’s could also be relevant to Alzheimer’s and other age-related dementias.

Ellerby is investigating how the mutant huntingtin protein affects the brain. “Chemistry and mass spectrometry let us label the protein and track it,” she says. “The Morphology and Imaging Core gives us brain images that show where this protein is localized, and then we can look for altered function in those areas.”

Ellerby and Hughes were part of a Buck team that identified hundreds of potential druggable targets involved in Huntington’s. “Genomics gave clues to the pathways that the mutant protein affects,” says Ellerby. A pathway is a chain of biochemical reactions that carries out a common function. In addition, bioinformatics narrowed a large genomics data set into a list of genes that alleviate Huntington’s-like symptoms in human cells, and then highlighted pathways and functions that were common to those genes.

By combining genomics and proteomics with bioinformatics, the team zeroed in on a protein called R-Ras, which is involved in cell movement. Images of living cells then rounded out the picture. Compared to normal cells, Huntington’s cells are far more active and look like they’re spending more time searching for targets. This could mean they have trouble forming synapses, the connections between neurons essential for muscle control and thinking ability. Drugs that target the pathway associated with R-Ras could correct the devastating effects of the mutant huntingtin protein, preserving or restoring brain function in people with this disease.
“We knew there were no funds in the operating budget to pay for the expansion of the Buck’s educational programs, yet it was obvious there was superb talent with great ideas ready to move forward.”

—Larry Rosenberger

Larry and Diane Rosenberger
Providing access to high-quality education is one of the pillars of Larry and Diane Rosenberger’s philanthropic strategy. With their donation of $500,000 to build a learning lab and fund its launch in April 2013, they became key champions of the new Buck Learning Center—the heart of the Institute’s efforts to address the country’s achievement gap in science education.

“We knew there were no funds in the operating budget to pay for the expansion of the Buck’s educational programs, yet it was obvious there was superb talent with great ideas ready to move forward,” says Larry, a Buck Trustee since 2011 and the former President and CEO of Fair Isaac, a pioneering credit score company now known as FICO. “Once we understood the goals of the program and knew how much CEO Brian Kennedy was focused on educational outreach and growth,” says Larry, “the new center became an obvious focal point for our support.”

Thanks to the Rosenbergs, when school children arrive at the Institute, a 1,400-square-foot, fully equipped demonstration and training space chock-full of scientific equipment awaits them.
Expanding Programs in Science Education—Outreach and the Buck Learning Center

The Buck Institute is nurturing a new generation of scientists—and educational outreach is the key. Challenging economic conditions continue to face public educational institutions in the San Francisco Bay Area. Some local schools have been forced to reduce or eliminate science courses, extracurricular science activities, and teacher training. And so it is increasingly important for institutions with scientific expertise to partner with schools to deliver science programming.

For the past 3 years, the Institute has been reducing barriers and expanding access to science education. This past year the Buck introduced diverse populations of students and adults to scientific inquiry and discovery—sometimes for the first time. More than 3,000 students participated in field trips after school and in weekend programs at the Buck and off site.

Creating opportunities for Bay Area children to see science in action—introducing them to its wonders and possibilities—is the Buck’s core education strategy. The Institute made a permanent commitment to its Community Education Program by hiring Julie Mangada, PhD, a former stem cell researcher, as its first full-time K–12 Education Outreach Coordinator. Board Trustee Larry Rosenberger describes Mangada as “the pied piper of getting children excited about science.”

In April of 2013, the Institute took a giant leap forward with the opening of the long-awaited Buck Learning Center. The launching of the Center was made possible by a gift of $500,000 from Larry and Diane Rosenberger. Located on the ground floor of the Gensler Building, the new facility has 30 seats, microscopes, a 3-D printer, and movable lab workbenches that instructors can reconfigure at will. The floor comes alive with a rendering of a DNA double helix and a blue circle that represents a cell. Students will be able to place components of the cell within the structure—and thus experience cell biology physically. The Center will also provide a training space for the high school Summer Scholar interns supported by the Winifred Johnson Clive Foundation and master’s students from Dominican University’s biological sciences program.

With its unique programming, the Center will enable local schools, teachers, and students to augment their science curriculum with a range of hands-on activities. The outreach and educational programs for middle and high school students are especially crucial. Through them, the Institute aims to entice students to try out experiments that underpin the groundbreaking research occurring daily in the labs—all under the supervision of Buck faculty and staff.

Kristen Gates, EdD, Director of Postgraduate Education and Chief Academic Officer at the Institute, says that the Learning Center will provide unique programs not just for young people, but for lifelong learners in the community, as well. She hopes that K–12 students will be inspired to pursue careers in the STEM disciplines—science, technology, engineering, or mathematics—but also aims to offer opportunities for the general public and Institute members to engage with Buck scientists.
The floor of the Learning Center features a rendering of a DNA double helix. Licensed architect, Sherri Corker, a Buck Advisory Council member and volunteer, designed the new Learning Center at no charge.

**INSET PHOTOS**

*(top)* Julie Mangada  
*(bottom)* Young volunteers help guests at the open house with sample DNA arrays.
The Buck Institute receives support and guidance from a noncompensated Board of Trustees. These recognized leaders from the business, science, and nonprofit communities set policy, approve financial plans, and help shape the strategic direction of the Institute.

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Chairman of Layalina Productions, Inc.
Managing General Partner of VMS Group
General Manager of Bodman Oil & Gas, LLC

G. Steven Burrill
Founder and CEO of Burrill and Company, a life sciences company involved in venture capital and merchant banking
Serves on the boards of the National Health Museum, Kellogg Center for Biotechnology Management, and Catalyst Biosciences

Nathaniel “Ned” Eames David, PhD
Partner, Arch Venture Partners

James Edgar
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Co-author of The Deciding Factor: The Power of Analytics to Make Every Decision a Winner

Mary C. Sauer
Co-founder of Accanto Partners
Co-founder, Senior Vice President, and Director of Sonic Solutions

The 2013 board of trustees
New trustees are helping to transform the Buck in exciting ways. In the past year, five new board members have added a truly international depth in corporate finance, government relations, science, and investing to the Buck.

Richard Bodman is currently the Chairman and CEO of PurThread Technologies, Inc., Managing General Partner of VMS Group, and General Manager of Bodman Oil & Gas, LLC. He serves on a variety of corporate and philanthropic boards. Bodman was a CPA and former Partner of Touche Ross & Co., served as Assistant Secretary of the U.S. Department of the Interior and Assistant Director of the Office of Management and Budget, President and CEO of Comsat General Corporation, President of Satellite Television Corporation, President of Washington National Investment Corporation (a private equity firm), and Senior Vice President for Strategy and Development at AT&T.

G. Steven Burrill is the CEO of Burrill & Company, the venture capital and merchant banking firm he founded in 1994. Prior to that, Burrill spent 28 years with Ernst & Young, directing and coordinating the firm’s services to clients in the fields of biotechnology, life sciences, high technology, and manufacturing worldwide. Burrill has received numerous awards for his work and serves on a variety of corporate and philanthropic boards.

Nathaniel David has devoted himself to building companies that create disruptive technologies to address global-scale problems. He has co-founded five technology companies—Syrnx, Achaogen, Kythera Biopharmaceuticals, Sapphire Energy, and Kilimanjaro Energy—and holds numerous pending and issued patents in fields such as nanovolume crystallography, antibiotic resistance, and aesthetic medicine. He serves on corporate and philanthropic boards, and was named one of the top 100 innovators in the world under age 35 by the MIT Technology Review in 2002.

Edward Lanphier, the founder of Sangamo BioSciences, Inc., has served as President, CEO, and a member of the Board of Directors since Sangamo’s inception in 1995. Mr. Lanphier has more than 25 years of experience in the pharmaceutical and biotechnology industries. He was Executive Vice President and Commercial Development and Chief Financial Officer at Somatix, President and CEO of BioGrowth, Inc., Vice President of Corporate Development at Biotherapeutics, Inc., and Vice President of Corporate Development at Synergen Inc.

Ambassador Fay Hartog Levin was the 65th U.S. ambassador to the Netherlands, serving from 2009 to 2011. Prior to that, Ambassador Levin held positions as a senior consultant at Res Publica Group and as Vice President for External Affairs at Chicago’s Field Museum. Ambassador Levin began her career as a legal advisor to the Illinois State Board of Education and was an attorney in private practice for 15 years before joining the law firm of Seyfarth, Shaw, Fairweather and Geraldson, representing school boards, private and public colleges, and social service agencies.
Crawford Cooley

Since 1991, A. Crawford Cooley has lent his exceptional guidance, support, and wisdom to the Buck Institute as a member of the Board of Trustees and as an outstanding chair for three consecutive terms. Crawford was instrumental in developing the mere possibility of a research institute into a reality—hiring Carla Dingillo, our first executive vice president, and Alzheimer’s researcher Dale Bredesen, our founding president and CEO. He kept the Buck Institute on a steady course with his certainty of ultimate success and his unfailing enthusiasm for fulfilling our mission and the wishes expressed in the will of Mrs. Beryl Buck.

As a pioneer venture capitalist in Silicon Valley since 1959, he learned the importance of basic research in creating economic and societal value through entrepreneurial action. In addition to continuing to invest in this field, Crawford manages approximately 21,000 acres of family vineyard and cattle-grazing properties in Marin, Sonoma, and Mendocino counties, including his great-great-grandfather’s Cloverdale vineyard.

In addition to the Buck Institute, Crawford’s other nonprofit interests include Stanford, Filoli, the Marin Agricultural Land Trust, and the Cloverdale Historical Society.

Even though his “official” association with the Buck is over, Crawford has stayed involved as a Buck Advisory Council member. Endlessly generous in his gifts and in making his home and garden available for meetings and functions, he even nourished the Institute’s local deer population by digging up native ferns from his ranch to plant in the Institute’s front garden.

“The diseases of aging concern us all as we grow older. The Buck is researching exciting leads that may someday help us stay healthy as we grow older. Too many of us have someone in our own family who suffers from one of these devastating diseases. The Buck’s broad-ranging research is leading to new understandings, and Buck scientists are getting ever-increasing recognition for their work.”
Phyllis Faber

Phyllis Faber came on the Board of Trustees in 1992 and served as its chair for two years before retiring in 2007. The Buck Institute is deeply grateful for her outstanding leadership in guiding the Institute since its inception and for her many years of commitment and wise counsel.

For Phyllis, it’s been a remarkable journey. “As chair of the Construction Committee, I saw the transformation of the Novato site from dirt and trailers to a prestigious organization that is now recognized globally for scientists who are exploring new boundaries in science with unusual interdisciplinary zeal—it is a lively and stimulating place.”

Phyllis worked as a wetland field biologist monitoring wetlands in the San Francisco Bay for over 30 years. She has written two wetland field guides for plant identification and *Design Guidelines for Tidal Wetland Restoration in San Francisco Bay*. Phyllis was a founder of the Environmental Forum of Marin and has been an instructor at both the College of Marin and the University of California extension program. Author of several books, including *California’s Wild Gardens* (1997), she is a series editor for the University of California Press’s Natural History Guides.

Co-founder of the Marin Agricultural Land Trust (MALT), which has protected nearly 50 percent of Marin’s farmlands through conservation easements that run in perpetuity, Phyllis currently serves on the MALT board.

“Crawford and I share a great optimism for the Buck’s future and the importance of its work as it relates to our own aging. Marin has a great treasure located on Mount Burdell in Novato, and the aging public an important partner. Do come visit and even play an active role in the Buck’s future and in its success.”
The Scientific Advisory Board (SAB) consists of leading scientists in the fields of aging research and age-related diseases, such as Alzheimer’s disease and cancer. Members of the SAB provide guidance on the Institute’s scientific and educational programs.

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Professor and chairman, Department of Neurology, University of Massachusetts Medical School

Steven A. Carr, PhD
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The Buck Advisory Council (BAC) is a global network of diverse individuals committed to extending advocacy for the Buck Institute and its mission to increase healthspan through research and education. The BAC includes leaders in government, business, finance, pharmaceuticals, law, philanthropy, and other fields, many of whom have served as advisors to governments, universities, public commissions, and nonprofit organizations.

The BAC takes an active role in promoting the Institute as the first nonprofit, independent research facility in the United States that is focused on Geroscience, and as a global leader in research on aging and age-related diseases. These leaders advise the Buck on strategic priorities, serve as informal ambassadors to raise the visibility of our achievements, set the pace for philanthropy at the Institute, and present awards recognizing exceptional individuals whose work directly or indirectly contributes to our mission.

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Brian Kennedy and Raja Kamal, PhD, Senior Vice President for Institute Relations, greets Dr. Ahmed Mohammed Obaid Al Saidi, the Omani Minister of Health, who spoke to the Buck Advisory Council about health care in the Middle East and North Africa during the November 2012 meeting in Muscat.
“Jack adored the Buck and was determined to make it his legacy. As an architect, he greatly admired the buildings designed by I.M. Pei. He loved the science and was most enthusiastic about making a gift that could help the lives of people—both now and for generations to come.”

—Donna Seid, friend and executor

Jack Bissinger
John W. “Jack” Bissinger, a retired Marin County architect, was known and admired throughout his life for his elegance and style. So it is not surprising that he was initially drawn to the Buck Institute by the beauty of its I.M. Pei design. But after learning about the Institute’s research and its focus on the diseases of aging, Jack’s attention was quickly diverted to the extraordinary science under way in its labs and to the Institute’s mission of adding healthy years to human life.

Jack became a dedicated member of the Institute, attending many of its lectures and events. A seat in the Drexler Auditorium bears his name in recognition of his passionate support for the Institute and its research scientists.

Jack lived a full and exciting life marked by international travel, adventure, and motorcycle and automobile collecting. He passed away in March of 2013. A man of quiet grace and generosity, Jack remembered the Buck Institute with a substantial gift through his estate. To honor the legacy of this remarkable man who will be missed by so many, the Institute plans to establish the Bissinger Family Library in 2014.
Operating and Capital Revenue for FY2013

- Contributions 23%
- Government Grants 46%
- Foundation and Other Grants 11%
- Buck Trust 15%
- Corporate Research Agreements 3%
- Interest and Other 2%

Operating Expenses for FY2013 (includes Building & Equipment Depreciation)

- Research 68%
- General and Administrative 23%
- Fundraising 5%
- Bond Interest and Related Costs 4%

Buck Trust Income as Percentage of Total Revenue (includes CIRM Infrastructure Grant)

<table>
<thead>
<tr>
<th>Year</th>
<th>Buck Trust Allocation</th>
<th>Other Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY2008</td>
<td>18%</td>
<td>82%</td>
</tr>
<tr>
<td>FY2009</td>
<td>24%</td>
<td>76%</td>
</tr>
<tr>
<td>FY2010</td>
<td>22%</td>
<td>78%</td>
</tr>
<tr>
<td>FY2011</td>
<td>15%</td>
<td>85%</td>
</tr>
<tr>
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<td>12%</td>
<td>88%</td>
</tr>
<tr>
<td>FY2013</td>
<td>15%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Grant Revenue (in $millions)

- FY2008: $21.4
- FY2009: $17.8
- FY2010: $18.9
- FY2011: $23.4
- FY2012: $24.1
- FY2013: $22.2

CIRM Infrastructure Revenue
- FY2008: $21.4
- FY2009: $17.8
- FY2010: $18.9
- FY2011: $23.4
- FY2012: $24.1
- FY2013: $22.2
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