


Buck@20

2019 ANNUAL REPORT




Discoveries and Achievements


1999–2019



SEPTEMBER 30, 1999
The Buck Institute officially opens its doors.



2003 Julie Andersen, PhD, links iron to Parkinson's disease in the cover story of *Neuron*.



2000 Simon Melov, PhD, and Gordon Lithgow, PhD, report the first successful use of a drug-like compound to extend lifespan in an animal.


2006 Publishing in the *Proceedings of the National Academy of Sciences*, the Bredesen lab engineers mice that have normal memory despite having Alzheimer's disease-related plaques in their brains.

2006 The Buck's first patent is awarded to Dale Bredesen, MD, for a method that modulates excessive cell death.

2006 Christopher Benz, MD, in partnership with the Marin Health and Human Services, helps launch the Marin Women's Study.

2007 The Buck receives a \$25 million federal grant that establishes a new field of research called "geroscience."

2008 The California Institute for Regenerative Medicine (CIRM) awards the Buck \$20.5 million to build a new facility to house stem cell research.



2009 Judy Campisi, PhD, identifies the SASP (senescence-associated secretory phenotype) in senescent cells, which propels research on "inflammaging."


2009 Publishing in *Cell*, Pankaj Kapahi, PhD, shows that a low-protein diet extends lifespan in fruit flies.

2011 Publishing in *Nature*, the Lithgow lab reveals that a common laboratory dye profoundly extends lifespan and slows the disease process in nematode worms with Alzheimer's-like pathology.



2012 The Buck celebrates the April 14 opening of its third, new research building.

2012 Board member M. Arthur Gensler, Jr. and his wife, Drue, donate \$5 million to the Buck. The Buck's administrative building is renamed in their honor.



2012 The Institute spins off its first company, Aeonian Pharmaceuticals.



2013 The Learning Center opens. Its mission is to foster young scientists and encourage lifelong learning.


2013 The Melov and Kennedy labs publish research in *Aging Cell* that shows the drug rapamycin reverses heart disease in elderly mice.

2014 The Buck Institute and the University of Southern California launch the nation's first PhD program in the Biology of Aging.




2015 The Buck partners with Calico to develop the science of aging therapeutics.


2016 The Board of Trustees raises \$11.5 million to support new leadership and growth.



2016 The Lamba and Jasper labs harness an innate repair mechanism that enhances the success of retinal transplantation in blind mice.


2016 Unity Biotechnology, based largely on cellular senescence research from the Campisi lab, incubates at the Buck.





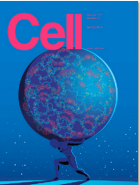
2017 The Verdin lab publishes in *Cell Metabolism* that a ketogenic diet protects memory in aging mice.

2017 The Buck partners with Astellas Pharma Inc. to develop drugs that target cellular senescence, a major driver of age-related disease.



2018 A \$6 million gift from Nicole Shanahan establishes the world's first Center for Female Reproductive Longevity and Equality.

2018 A drug based on Buck research produced by Unity Biotechnology treats the first osteoarthritis patient in clinical trials.



2018 The Benz lab brings precision to breast cancer diagnosis and care with big data, and publishes results in *Cell*.

2019 The Bia-Echo Foundation partners with the Buck to launch the Global Consortium for Female Reproductive Longevity and Equality.

2019 The Buck spins off three new companies: Napa Therapeutics, BHB Therapeutics, and Gerostate Alpha.





WELCOME

As we mark our 20th anniversary, we are pleased to confirm that the Buck Institute for Research on Aging really was ahead of its time! Perusing the scientific literature today reveals that research on aging is one of the most interrogated fields in all of the life sciences.

The field has never been so vibrant and full of possibilities and optimism.

It is edifying to recall that when the Buck opened its doors two decades ago, research on aging was often derided and not taken seriously. We are happy to claim our role as pioneers, and even happier to embrace our role as leaders.

The field of research on aging is at a true inflection point, where laboratory discoveries are being translated into therapeutics and interventions that can help people lead longer, healthier lives. Indeed, the first drug in history explicitly developed for an indication focused on impeding aging (Unity Biotechnology's UBX0101) is now in clinical trials. That drug, we are proud to say, is based on Buck science.

The Buck, for twenty years now, has been at the forefront of this exciting field, and we intend to keep it that way.

We approach our 21st year with incredible momentum. Over the past 18 months, we added six new faculty members and opened our new Center for Female Reproductive Longevity and Equality. During this period, grant revenue has increased significantly and our budget has grown by 19 percent. Three companies have been launched based on Buck research.

Most importantly, breakthrough discoveries into the underlying biology of aging are happening every day. We are steadily gaining new insights into preventing age-related diseases, such as Alzheimer's, Parkinson's, and cancer.

As in previous years, Buck scientists continue to garner national and international acclaim.

For the first time in our history, we have a member of the National Academy of Sciences. Judith Campisi, PhD, a pioneer in the study of cellular senescence, is so deserving of this honor, which is considered among the most prestigious distinctions a scientist can receive.

Gordon Lithgow, PhD, another longtime Buck faculty member, received the American Aging Association's Denham Harman Award, which is presented annually to honor lifetime achievement in the field of research on aging.

Because we never know when the next breakthrough discovery will happen, fully predicting where the field will be in the next twenty years is not possible.

What we can assure you is that some of the most important advances are fast approaching, and the Buck will be a part of them.

Our individual donors, foundations, and federal funding sources are all critical as we work every day to help us all live better, longer. We thank you for joining us on this amazing journey.

Eric Verdin

Eric Verdin, MD
President and Chief Executive Officer

Bill R. Poland

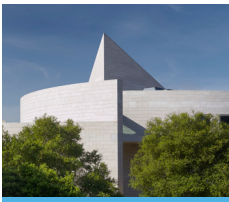
Bill R. Poland
Chair of the Board of Trustees

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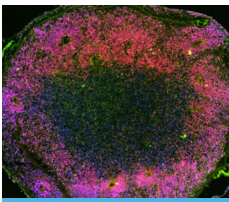
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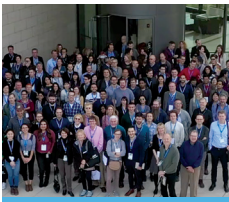
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Buck President and CEO Eric Verdin, MD builds on the past to talk about our future

When the Buck opened its doors twenty years ago, many scientists were dubious about research on aging. Suddenly it's one of the hottest fields in the life sciences. What are your thoughts about the field and the Buck's place in it?

I couldn't be more optimistic, both about the field in general, and the Buck's role specifically. Breakthroughs are happening every day. I think a lot of them will happen here because we've been thinking about this for twenty years now. That's a huge head start, and we have a foundational knowledge base no one else can match.

Another reason I believe the Buck will lead this field is because of the spirit of the place. It has always been built on disruption, and I think this is why I'm having so much fun here. The kind of people we attract see disruption as a badge of honor. Right now, about 85 percent of people at age 65 have at least one chronic disease of aging; most have more than one. A lot of the medical community has the attitude of "That's just the way aging works." The spirit of the Buck says, "Hell no, let's change that!" So, it's the legacy, the spirit, and the true expertise of our folks thinking deeply about how to disrupt aging. A real revolution is going to happen, and I think it's going to happen here.

Twenty years from now, where would you like the Buck to be?

I would love for there to be treatments, based on Buck science, in the clinic for the delay or reversal of age-related conditions, and I firmly believe that

this will be the case. I would love for us to have a clinical center on our campus where people can come and be studied, be evaluated, where we can actually measure all kinds of markers that determine how well they're aging. At this center, we'd be able to tell them what they have to change, and then, ideally, a year later be able to tell them, "You've actually changed your markers, and you look like you're on a better trajectory."

"Bottom line—and this is ambitious but why be anything but—I want the Buck to be at the forefront of rewriting the way medicine is practiced based on personal, quantitative assessments of the aging process."

It sounds like you are talking about a new paradigm of healthcare?

That's right. It is a new model, or a new way of thinking about people's health. Now, typically, a lot of people go see their doctor perhaps once a year. The physician will check blood pressure, cholesterol, blood sugar level—those types of things. So, there's some minimum preventative healthcare, but basically it's built around four or five diseases. There's nothing that tells you how well you're aging. I think there's got to be a way that by age 40, or even 30 ideally, you should know whether you're at risk, for example, for a short lifespan. And some people are. So can we actually measure this? How? To me, that would be the vision, right? And then based on this, make a whole series of recommendations saying, "Based on our measurements, here is what you're at risk for and here's what you should be doing." You shouldn't have to wait to have your first

heart attack before your doctor talks to you about what you could have been doing to prevent it.

These types of advancements are premised on biomarkers. That is the holy grail, right?

Yes, and we will have them. Physicians already intuitively know that biological age is different than chronological age. What we don't have yet is a set of predictive biomarker signatures that will tell us who is at risk for certain age-related diseases, so we can intervene long before symptoms become apparent. We're making tremendous progress and this is an area where new advances in technology—artificial intelligence, proteomics, metabolomics—are critically important. We are, of course, not going to be able to do this by ourselves, but I would love for the Buck to be the conscience of this field, a place about which people say, "Well, they were talking about all of this long before it was popular."

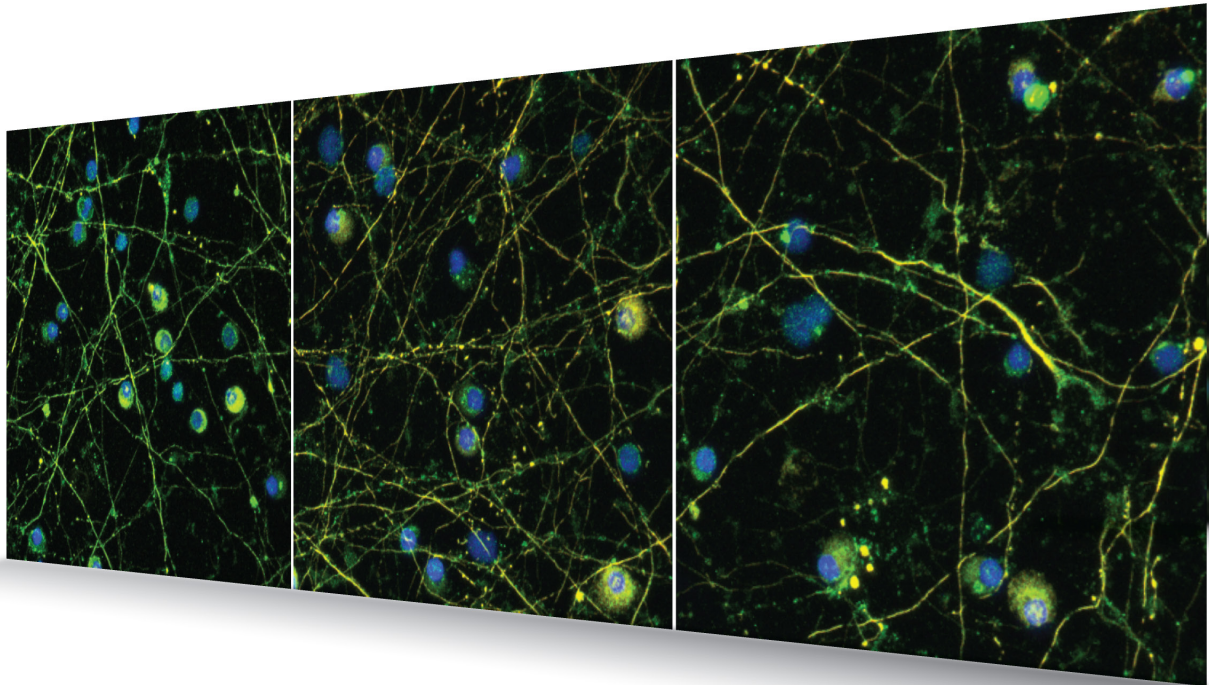
What are you most proud of about this place?

I think the fact that we're tackling such a big problem, and that we're not accepting the status quo—the idea that aging is just something that happens to everybody, you get used to it, that's the way it is, we're all going to die anyway. Being willing to take something that's accepted—that chronic illness is just an inevitable part of growing old—and saying that's not good enough, we're going to do something about it. We're attacking it head on, because we know there's a better way. That's what I'm most proud of.

Federal grants go to Buck researchers tackling Alzheimer’s disease from new angles

Two Buck faculty members have received major federal grants to look outside the box for new ways to treat or prevent Alzheimer’s disease.

The awards were made as the research community comes to grips with the fact that decades of traditional research—looking into the toxic amyloid plaques that are a hallmark of the disease—have yet to result in any successful treatment for the memory-robbing disease that affects an estimated 5.8 million Americans.



GABAergic inhibitory neurons from human induced pluripotent stem cells with variant APOE alleles.

Lisa Ellerby, PhD, received \$4.4 million to research exploiting ApoE2, a gene that protects against Alzheimer’s disease. ApoE2 is a variation of the apolipoprotein E protein that combines with fats in the body to form lipoproteins, which are responsible for packaging cholesterol and other fats, and carrying them through the bloodstream.

While having two copies of the gene variant ApoE4 increases the risk of developing Alzheimer’s by 12 times, carrying even one copy of ApoE2 appears to reduce the risk of developing Alzheimer’s by up to 40 percent.

“ApoE2 has lots of beneficial properties,” says Ellerby. “Those who carry the allele are likely to be exceptionally long-lived, and there is evidence that E2 has positive, direct impact on brain health. There are theories about why that occurs, but no one really understands what E2 does in the body. My focus is to find out what’s special about ApoE2, so that we can use it therapeutically for Alzheimer’s.”

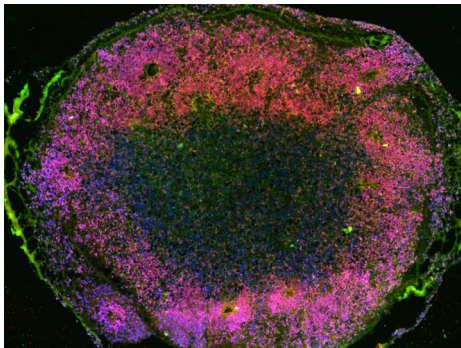
Utilizing stem cell technology to hone in on differences

The E2 allele is the rarest form of ApoE, present in only seven percent of the population. Ellerby’s team is using the latest stem cell technology to tweak apart its characteristics. They are creating isogenic cell lines by reprogramming skin cells from individuals with genetic backgrounds involving E2/E2, E3/E3, and E4/E4 to identify their cellular and functional differences.

“This would not have been possible five years ago.”
– Lisa Ellerby

Researchers will also grow brain cells—neurons, astrocytes, and microglial cells—from the stem cells in order to determine whether ApoE2 enhances stress response and survival in the cells, and if it does, to identify the molecular pathways relevant to the protection. “The latest generation of

stem cell tools and technology are enabling this research,” says Ellerby. “This would not have been possible 5 years ago.”



A cerebral organoid developed from stem cells. (C116-organoid, stain with DAPI, Pax6 and Tuj1.)

Looking at a fruit-derived metabolite as a possible treatment for Alzheimer’s disease

Julie Andersen, PhD, received \$3.4 million to determine if a gut metabolite produced from dietary ellagic acid, which is abundant in strawberries, blackberries, cranberries,

pomegranates, and walnuts, could help prevent or reverse Alzheimer’s. The production of that metabolite, urolithin A, decreases with age due to microbial imbalances in the gut. Her team will determine if rejuvenating the microbiome of older mice enhances the production of ellagic acid, and whether that, in turn, increases urolithin A’s neuroprotective properties in lab animals.

The microbiome, which includes the vast collection of microorganisms that inhabit our gut, is a hot topic of research with imbalances linked to many disease processes, including neurodegeneration.

“Most researchers are comparing individual microbiomes, trying to identify

particular risk factors for Parkinson’s and other neurodegenerative diseases,” Andersen says. “We’re adding changes associated with aging and looking at whether this is one of the links between the brain and the gut.”

Autophagy: the mechanism at the heart of this study

Preliminary research in the Andersen and Lithgow labs involved testing several compounds, including urolithin A, which increased activity in the major pathway involved in autophagy, a process whereby cells recycle damaged proteins and use them for nutrition. Given that

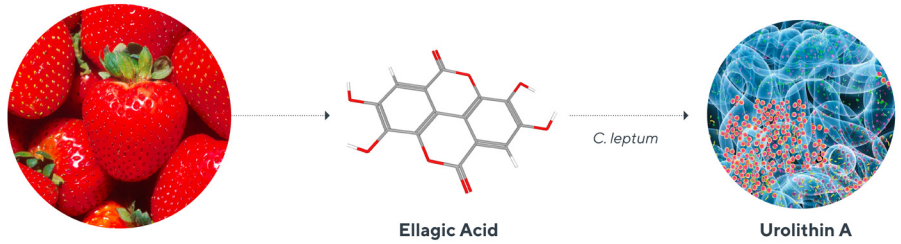
Alzheimer’s disease pathology involves the accumulation of damaged proteins and that there is an age-related decrease in autophagy in the brain, Andersen says many researchers are looking at ways to boost the recycling process.

“We like the idea of boosting something that inherently protects the cells.”

–Julie Andersen

Some of the tested compounds prevented Alzheimer’s, Parkinson’s, Huntington’s, and Lou Gehrig’s disease symptoms in worm models of the diseases. These drugs also prevented Parkinson’s in middle-aged mice who were genetically fated to develop the disease.

“We were particularly impressed with the efficacy of urolithin A,” says Andersen. “And we like the idea of boosting something that inherently protects the cells. Now we’re focused on unravelling its full mechanism of action.”



Will rejuvenating the microbiome enhance the effects of urolithin A? Produced by gut bacteria breaking down ellagic acid, urolithin A protects neurons, but decreases with age.

We celebrated 30 years of research on aging, and then kept the momentum going



In December 2018, nearly 400 people attended a symposium at the Buck marking the beginnings of research on aging.

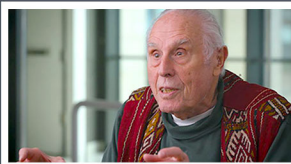
Gloating was allowed! Early pioneers recounted the skepticism they faced from those who viewed the field as pseudoscience and shared their excitement of working in what is now one of the hottest and most promising areas of biomedical research.

Six leading scientists. Six once-in-a-lifetime conversations.

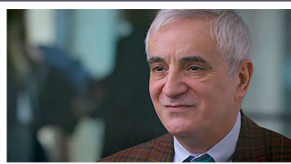
Following the symposium, six of the presenters took part in the Live Better Longer online conference. More than 3000 people viewed the conversations. The videos are available at buck.extendedsession.com.



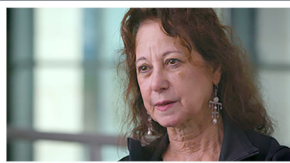
Eric Verdin, MD
President and CEO, Buck Institute



George M. Martin, MD
Professor, University of Washington



Luigi Ferrucci, MD, PhD
Scientific Director, National Institute on Aging



Judith Campisi, PhD
Professor, Buck Institute



Steven N. Austad, PhD
Professor, University of Alabama, Birmingham



Victor J. Dzau, MD
President, National Academy of Medicine

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REVIEW

<https://doi.org/10.1038/s41586-019-1365-2>

From discoveries in ageing research to therapeutics for healthy ageing

Judith Campisi¹, Pankaj Kapahi¹, Gordon J. Lithgow¹, Simon Melov¹, John C. Newman¹ & Eric Verdin^{1*}



Published in *Nature* in July, six Buck faculty members highlighted discoveries that have moved the field forward.

The story suggests that research on aging is entering a new era with unprecedented medical, commercial, and social implications.

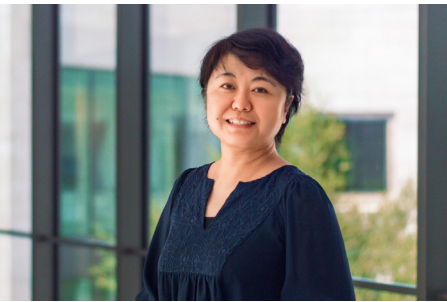
Faculty on board for the Center for Female Reproductive Longevity and Equality

Lei Lei, PhD, Shiyong Jin, PhD, Francesca Duncan, PhD, and Jennifer Garrison, PhD, are the first faculty members to join the groundbreaking new center.

The center, the first of its kind in the world, focuses on preventing or delaying ovarian aging, a subject that has been woefully understudied in research on aging.

The new center was established with a \$6 million gift from Bay Area tech entrepreneur, attorney, and philanthropist Nicole Shanahan and the Sergey Brin Family Foundation (see page 38).

Both Lei and Jin come to the Buck from the Department of Cell & Developmental Biology at the University of Michigan Medical School.



Lei, appointed as associate professor and scientific director of the center, focuses on understanding how the biological clock of ovarian aging is initially set, and the

fundamental differences between young and old oocytes—the cells in the ovary that are capable of forming ova.

One of Jin's main interests is to establish effective approaches for female fertility preservation before the initiation of ovarian aging.



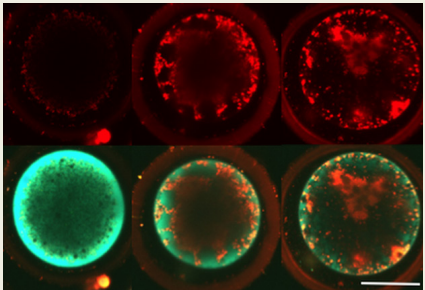
Jennifer Garrison, a Buck neuroscientist, has also joined the center. The Garrison lab is exploring the role of inter-tissue communication between the brain and reproductive organs in ovarian aging.

Francesca Duncan, an internationally recognized leader in ovarian aging in the Department of Obstetrics and Gynecology at Northwestern University Feinberg School of Medicine, has joined the center as an assistant professor in residence.



WHY WE CARE

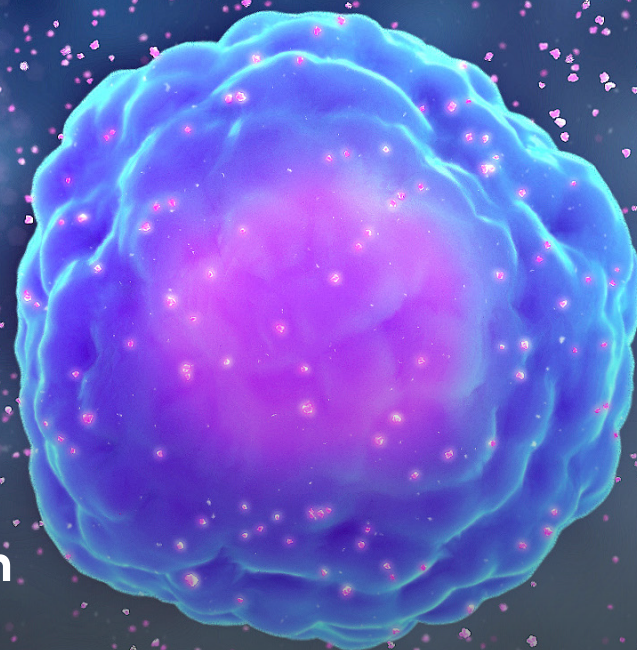
In females, oocytes that develop in the fetal ovary serve as the only source for sustaining ovarian function. Although a baby girl has over 1 million oocytes, over 90 percent of the potential ova remain quiescent and undergo cell death. Drastic declines in oocyte quality and quantity lead to ovarian aging and a significantly increased chance of infertility and birth defects.



Oocytes stained with markers of metabolism.

Beyond losing the ability to reproduce, the end of female fertility sets off a cascade of negative health effects, and early menopause has been shown to correlate with early morbidity.

New faculty hires focus on bioinformatics, inflammation and immunity in aging



It was a very busy summer getting new lab benches ready as the Buck welcomed four new faculty members within three months.

In addition to Lei Lei, PhD, and Shiyang Jin, PhD, David Furman, PhD joined the Buck on August 15 as associate professor and director of our new Center for AI and Data Science of Aging.



A native of Argentina, Furman comes to the Buck from Stanford University's Institute for Immunity, Transplantation and Infection. His work focuses on data science applied to inflammation and aging. He is also the director of Stanford's 1000 Immunomes Project, the largest ever conducted longitudinal population-based study of immunology and aging that provides benchmark metrics for health and disease.

At the new center, Furman and his team will conduct state-of-the-art analyses on the 1000 Immunomes Project dataset to catalyze knowledge generation in the field, as the Buck furthers its collaboration with Stanford.



The Buck is also delighted to welcome Daniel Winer, MD, who joined the Buck faculty on August 1 as associate professor. Winer's

research focuses on the role of inflammation and immunity in metabolism and aging.

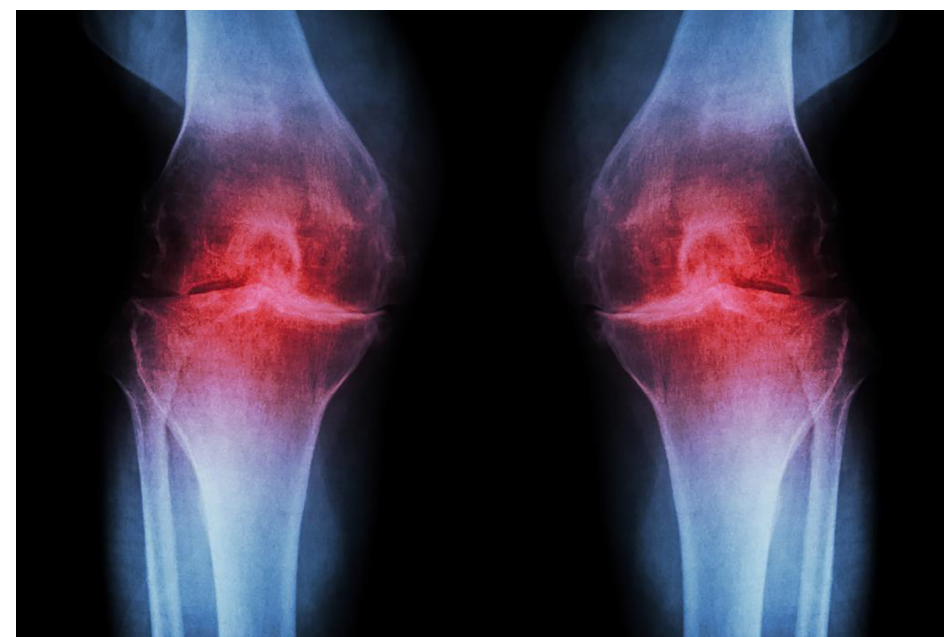
He comes to the Buck from the faculty of the Department of Laboratory Medicine and Pathobiology, University of Toronto, where his laboratory studied how the immune system influences physiological processes and contributes to disease, with the aim of using this information to develop new translational diagnostics and therapeutics.

At the Buck, Winer will use his expertise in cellular immunology and pathology to study how aging and the environment, including dietary choices, impact immune system function. Moreover, the lab will look into how inflammation affects aging and chronic diseases of the elderly, such as diabetes.

Above: Cell secretion of cytokines. Cytokine signaling is an important part of the immune response. Longitudinal studies revealed that the cytokine signaling response of older adults is systemically altered.

Judith Campisi signs the membership book after being inducted into the prestigious National Academy of Sciences in April 2019.

Campisi has received international acclaim for her work on cellular senescence, which is associated with aging and tissue degradation. The NAS election puts Campisi in great company—Abraham Lincoln was the first person to sign the book!



Unity Biotechnology announced promising results from its first-in-human Phase I clinical trial of a senolytic drug in patients with moderate to severe osteoarthritis of the knee.

This experimental drug (UBX0101) is primarily based on pioneering research by Judith Campisi. Unity Biotechnology is now preparing for Phase I trials of a drug treating age-related eye disease.

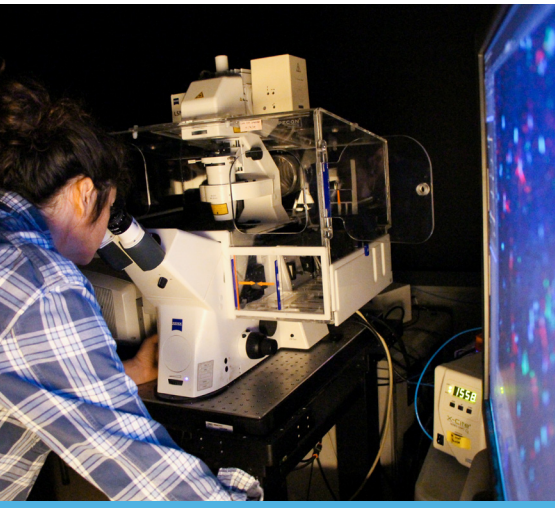
Our first Lifelong Learning Course on the Biology of Aging was launched from our Learning Center in the spring of 2019.

The six-week program, which was fully booked within days of being announced, was taught by Buck scientists.



There are more than 45 ongoing, internal collaborations at the Buck. Here we highlight a few of them. The lab pages that follow provide a deeper dive into specific projects and give a sense of what each principal investigator brings to the table.





ANDERSEN LAB

The Andersen lab concentrates on understanding the underlying age-related processes driving neurodegenerative diseases in order to identify novel therapeutics that slow or prevent them from occurring.

Challenging paradigms: senescence, inflammation, and neurodegeneration

One of the central dogmas of neurobiology, namely that the neurons in the human brain are post-mitotic and incapable of dividing, is being challenged in labs across the country.

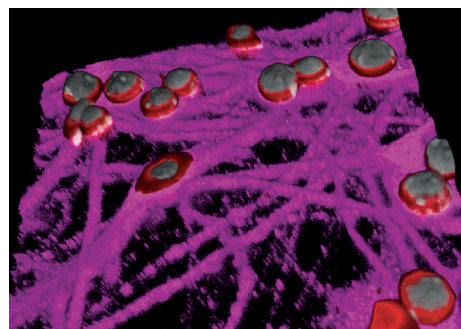
A project in the Andersen lab puts the Buck squarely in that mix as researchers seek new avenues to prevent and treat Alzheimer's disease.

This research focuses on the possibility that cellular senescence—a process whereby mitotic cells stop dividing under stress and secrete factors that cause inflammation and lead to tissue degradation—occurs in neurons. This phenomenon was thought to be impossible under the old “neurons-don't-divide” dogma.

this cell fate. Interestingly, older studies in post-mortem brain samples from Alzheimer's patients have demonstrated the upregulation of an important marker of senescence, p16.

To address this central question, the Andersen lab is studying neuronal senescence in human, rather than mouse neurons. The project raises the tantalizing possibility that senolytic drugs that target and kill senescent cells may serve as a novel therapy for Alzheimer's.

However, because neurons do not naturally replace themselves via cell division, the possibility exists that eliminating senescent neurons may have catastrophic consequences. In this case, it might be more efficacious to target events downstream of senescence induction, specifically the noxious agents released from senescent cells that can damage neighboring cells and drive the spread of disease.



Confocal image 3D reconstruction of primary human neurons at 49 days in vitro after fluorescence immunocytochemistry for MAP2 (violet), HMGB1 (red) and DAPI (grey).

Recent studies in mouse models report contradictory results in this regard. One suggests that neurons undergo senescence and the other that it is non-neuronal glial cell types that undergo

“When I first came here, I thought, ‘Oh, Chris Benz, he works on breast cancer, that’s nice,’ then when you realize you’re looking at some of the same mechanisms of aging, it gets interesting. The Buck’s collaborative environment is really special.”



Julie Andersen, PhD
Professor

BENZ LAB

The Benz lab undertakes bench-to-bedside and community-to-bench efforts to reduce the incidence of breast cancer and to improve patient outcomes.

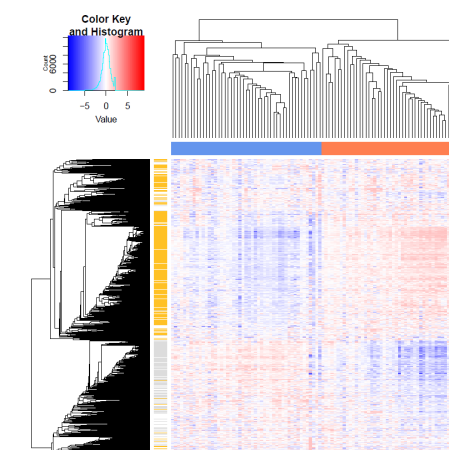
Normal breast tissue at risk for cancer development: a surprising role for fat

Normal breast tissue is 80 percent fat, produced by adipocytes. Only 5 percent is breast glandular epithelium that might or might not ever turn into breast cancer.

Most researchers are focused on the breast epithelium when studying either a newly diagnosed breast tumor or a healthy woman's risk and predisposition to developing breast cancer. They ignore new evidence that breast adipose tissue, when metabolically altered, becomes a key nutrient source and growth stimulus driving established breast cancers.

A new project in the Benz lab pushes well beyond even that cutting edge concept of “cancer-fat cell crosstalk” by demonstrating that the metabolically altered type of fat driving breast cancer growth can also be commonly found in the otherwise normal breasts of many healthy and non-obese (BMI <30) women, conferring them with an unsuspected excess risk of developing breast cancer.

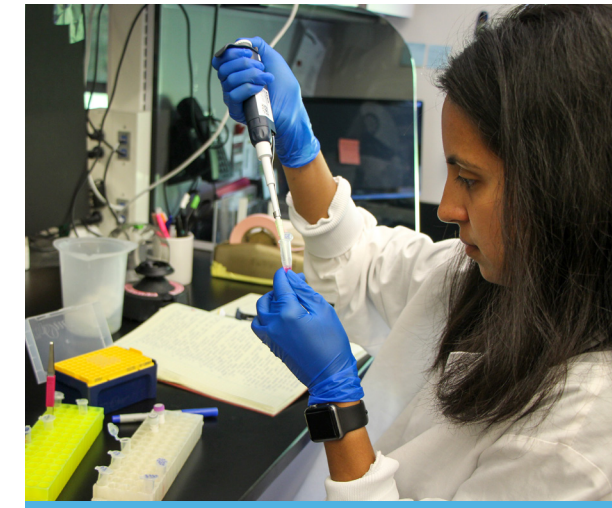
Utilizing RNA sequencing on 151 normal breast tissue biopsy samples from healthy donor women, the Benz team found that about half exhibited an unsuspected “high-risk” transcriptome phenotype characterized by abundant metabolically altered fat cells, ie., tumor-promoting adipocytes. Since these donor breast samples contained only normal appearing breast epithelium amidst the metabolically altered fat, Benz now believes that these tumor-promoting adipocytes not only provide a fertile “soil” for future growth of breast cancers, but over years likely transform some of the normal epithelial cells into a new breast cancer.



Study of normal breast samples yields new clues about future breast cancer risk. Risk of developing breast cancer is due in part to the cancer-promoting effect of actively metabolizing breast fat (high risk adipocyte transcriptome, right side of heat map).

While their current findings may soon help personalize breast cancer risk assessment for women of all ages, the Benz lab is also trying to design new breast cancer prevention strategies based on reverting a woman's “high-risk” breast transcriptome to a more normal phenotype by deactivating the metabolically altered breast adipocytes.

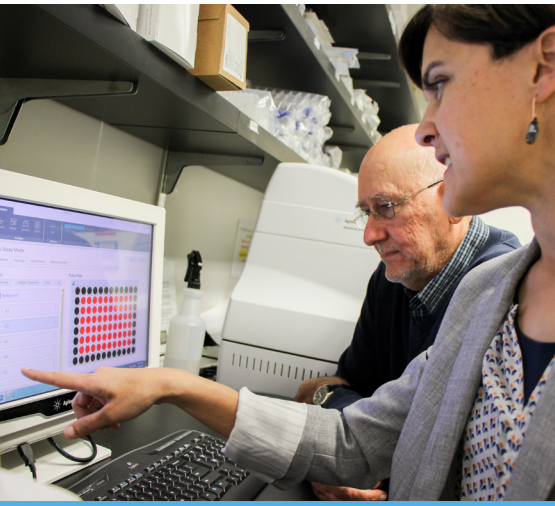
This new area of research evolved out of the Marin Women's Study, which Dr. Benz helped initiate in 2006. The study also involved technology and built upon results from The Cancer Genome Atlas (TCGA), a landmark cancer genomics program, which molecularly characterized over 20,000 primary cancers spanning 33 cancer types.



“Even though the common mantra of research mentors continues to be ‘focus, focus, focus’, I find the emphasis on interdisciplinary research at the Buck actually broadens the scope of an investigator’s scientific interests and helps foster more transformative and disruptive breakthroughs.”



Christopher Benz, MD
Elizabeth M. A. Stevens Professor of Cancer and Developmental Therapeutics



BRAND LAB

The Brand lab is focused on biological energy flows and the role of mitochondria in health, disease, and aging. The lab aims to suppress excessive mitochondrial formation of free radicals to delay or prevent age-related diseases.

Mitochondria: stopping free radicals at their source

Mitochondria are subcellular structures in which nutrients are oxidized to extract their energy content in the process of oxidative phosphorylation. This energy is then distributed to the rest of the cell to drive the essential machinery of life.

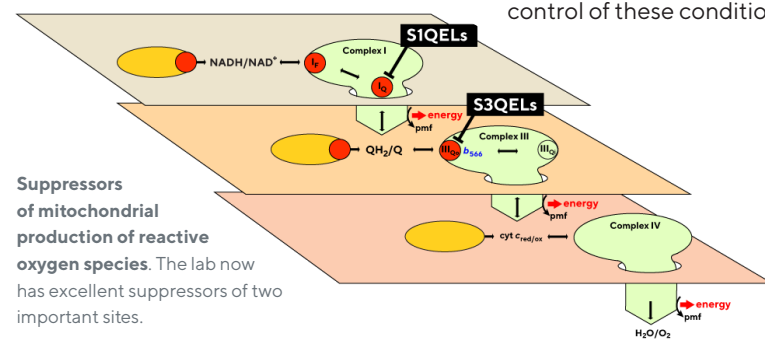
However, in addition to releasing energy, nutrient oxidation also produces free radicals and other reactive oxygen species. Impaired energy distribution and excessive free-radical production are thought to be among the primary drivers of aging and age-related disease.

The lab has pioneered new approaches to better understand mitochondrial function and dysfunction within cells and have applied these approaches to investigate the role of mitochondrial energy metabolism in aging and disease.

To investigate free-radical production, researchers have characterized the specific sites and regulation of mitochondrial superoxide and hydrogen peroxide generation, and are studying how these sites contribute to cellular oxidative stress and damage.

Using high-throughput screening, we have identified novel suppressors of superoxide formation that do not inhibit energy metabolism, and we are using these exciting new molecules to probe and modulate mitochondrial superoxide production in cell and animal models of aging and disease. We envision treatments that would minimize the production of superoxide and hydrogen peroxide by mitochondria without inhibiting energy metabolism.

The lab is collaborating with others, both inside and outside the Buck, to evaluate and mitigate the role of dysfunctional mitochondria in aging and the diseases of aging, including: diabetes; cancer; loss of hearing, vision, and mobility; osteoporosis; heart and kidney diseases; stroke; cognitive decline; and Parkinson's, Alzheimer's, and Huntington's diseases. Our research has already opened up new possibilities for the control of these conditions.



“We aim to cut through the guesswork and establish how the free radicals that impact aging and disease are generated, and how they can be decreased.”



Martin Brand, PhD
Professor

BREM LAB

The Brem lab is focused on understanding how and why traits differ between individuals, and discovering genetic changes that impact aging behaviors.

Using the secrets of evolution to solve problems in aging and disease

Over the four billion years that life has evolved on this planet, organisms have acquired amazing traits. Some, like lion manes and butterfly wings, capture our attention by their sheer beauty. Others get us excited in a very different way—by their relevance to biomedicine.

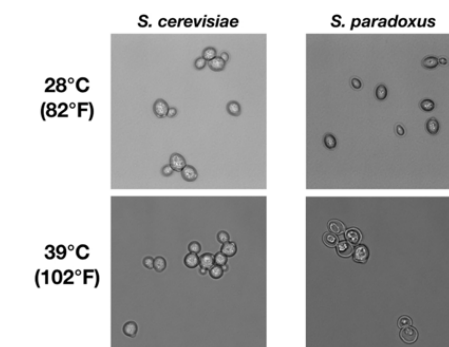
Ecologists have catalogued remarkable cases of disease and stress resistance in the plant and animal worlds, which have arisen to solve problems similar to those in human patients. Think about extreme longevity in naked mole rats, for example, or limb regeneration in amphibians. The central goal of the Brem lab is to figure out the molecular basis of natural resistance abilities like these—ultimately leading to the design of drugs that mimic them in the clinic.

With this motivation, the Brem lab has developed a new approach to pinpoint DNA sequence differences that govern trait variation between wild organisms, even if they are millions of years diverged.

The new technique involves: mating two genetically distinct parents to form a hybrid; disrupting one of the two parents' copies of a given gene with an artificial mutation with only the other parent's copy remaining intact; and measuring the trait of interest as a readout of the function of the intact copy of the gene.

Massively parallel experiments of this type enable a survey across the genome of divergent sites that impact the trait. The first application of this new tool, published last fall, used heat tolerance in single-celled yeasts as a model system. Ongoing work in the Brem lab is applying the same

new method to longevity in nematode worms and cellular senescence in mice.



***S. paradoxus* cells are predominantly large-budded dyads at high temperature.** Each panel reports results from microscopy experiments of *S. cerevisiae* DBVPG1373 and *S. paradoxus* Z1 after 24 hours of liquid growth at the indicated temperature; at 28°C, both species were approaching stationary phase. (Images by Carly Weiss, courtesy of the Brem Lab)

Since Darwin, evolutionary genetics has had one ideal: to pick a species off a tree or out of a lake and find out how and why, long ago, it acquired longevity, regeneration, disease resistance, or any other phenotype. With this new approach, the Brem lab is working to make this dream a reality. Evolution has solved biomedical problems again and again in far-flung species, and efforts in the Brem lab will put the genetic mechanisms of these natural resistance states within reach.



“We want to know how evolution works and use its secrets to solve problems in aging and disease.”



Rachel Brem, PhD
Associate Professor



CAMPISI LAB

The Campisi lab is focused on taming cellular senescence, the source of chronic inflammation linked to many chronic age-related diseases.

Creating a new mouse model to study cellular senescence

While senescence prevents cancer early in life, the cells are not necessarily benign; they secrete numerous molecules, some of which promote inflammation.

Cellular senescence is an evolutionarily selected state whereby stressed cells cease to proliferate. As they accumulate with age, senescent cells eventually cause chronic inflammation, tissue degeneration and many age-related diseases, including, ironically, late life cancer.

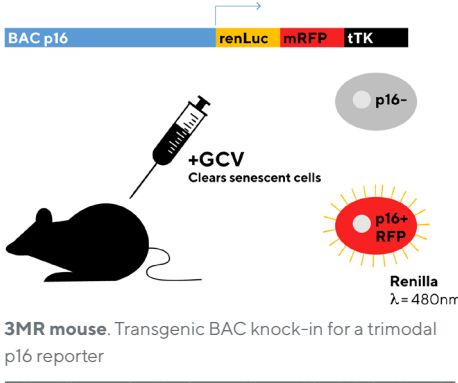
The current mouse model has been a crucial tool for linking cellular senescence to the manifestations of aging. This year, everyone in the Campisi lab provided input on creating two new transgenic mouse models to study cellular senescence.

While the current mouse model, created by the lab in 2011 and published in 2014, has contributed to significant progress in the field (it's been shared with dozens of academic centers around the world and used to link senescence with numerous and diverse diseases of aging), the new mice will have distinct advantages over the current model.

The current model depends on the ability of senescent cells to express p16INK4a, a tumor suppressor protein, to track and clear senescent cells. While many senescent cells express p16, some don't—which means some senescent cells get missed.

The new and improved mice will depend on the ability of senescent cells to express either of two senescence-associated markers, p16 and p15. In addition, the new mice will be engineered (utilizing modified

CRISPR technology) to allow researchers to eliminate senescent cells in a tissue-specific manner, as opposed to clearing these cells from the entire mouse body, as is now the case.



3MR mouse. Transgenic BAC knock-in for a trimodal p16 reporter

Current research suggests that senescent cells produce systemic factors that can affect distal tissues; the new mice will enable scientists to study senescence-related pathology both inside and outside the tissue. For example, the new mice will enable an understanding of how senescence in the gut might advance Alzheimer's disease, or how senescent cells in the brain might contribute to melanoma.

Finally, the new mice will allow a more robust detection of senescent cells in living animals, more efficient isolation of senescent cells from tissues (so they can be more precisely studied), and the application of new methods to understand how senescent cells can drive so many age-related diseases.

ELLERBY LAB

The Ellerby lab is focused on understanding the pathways that lead to nerve cell death in Huntington's and Alzheimer's diseases.

Exploiting a gene that protects against Alzheimer's disease

The ApoE4 gene, present in approximately 10 to 15 percent of people, increases the risk for Alzheimer's and lowers the age of onset. Having two copies of the allele increases an individual's risk of developing Alzheimer's by 12 times. But having another one of the ApoE variants, ApoE2, appears to be protective for the memory-robbing disease and enhances longevity.

ApoE2 tends to get short shrift in research. A project in the Ellerby lab is aimed at changing that. Researchers are exploring how ApoE2, which is present in only seven percent of the population, can be exploited to support healthspan and protect against Alzheimer's.

The ApoE gene provides instructions for making a protein called apolipoprotein E, which combines with fats in the body to form lipoproteins which are responsible for packaging cholesterol and other fats and carrying them through the bloodstream.

Previous research indicates that E4 alters lipid metabolism in a way that negatively impacts brain plasticity. Those who carry the E2 allele are likely to be exceptionally long-lived and there is evidence that E2 directly impacts brain health, although there is no real understanding of what E2 does in the body.

Ellerby's team is reprogramming skin cells from individuals (both male and female) with genetic backgrounds involving each of the ApoE alleles (E2/E3/E4).

Researchers are looking at the resulting induced pluripotent stem cells and characterizing their cellular and functional differences. Researchers are also growing human brain cells and brain organoids—neurons, astrocytes, microglial cells, and cerebral organoids—from the stem cells in order to determine whether ApoE2 enhances stress response and cell survival with the goal of identifying the molecular pathways relevant to the protection.

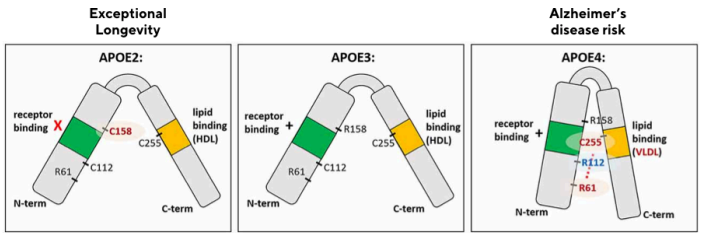
And finally, researchers plan on moving the research into aging mice to test whether an overexpression of ApoE2, or a treatment with factors produced by E2, increases healthspan in the animals.



"It's an exciting time. We are focused more and more on translating our discoveries into therapeutics. As one of the original faculty, it's rewarding to see this progression. I'm really hopeful for the future."



Lisa Ellerby, PhD
Professor

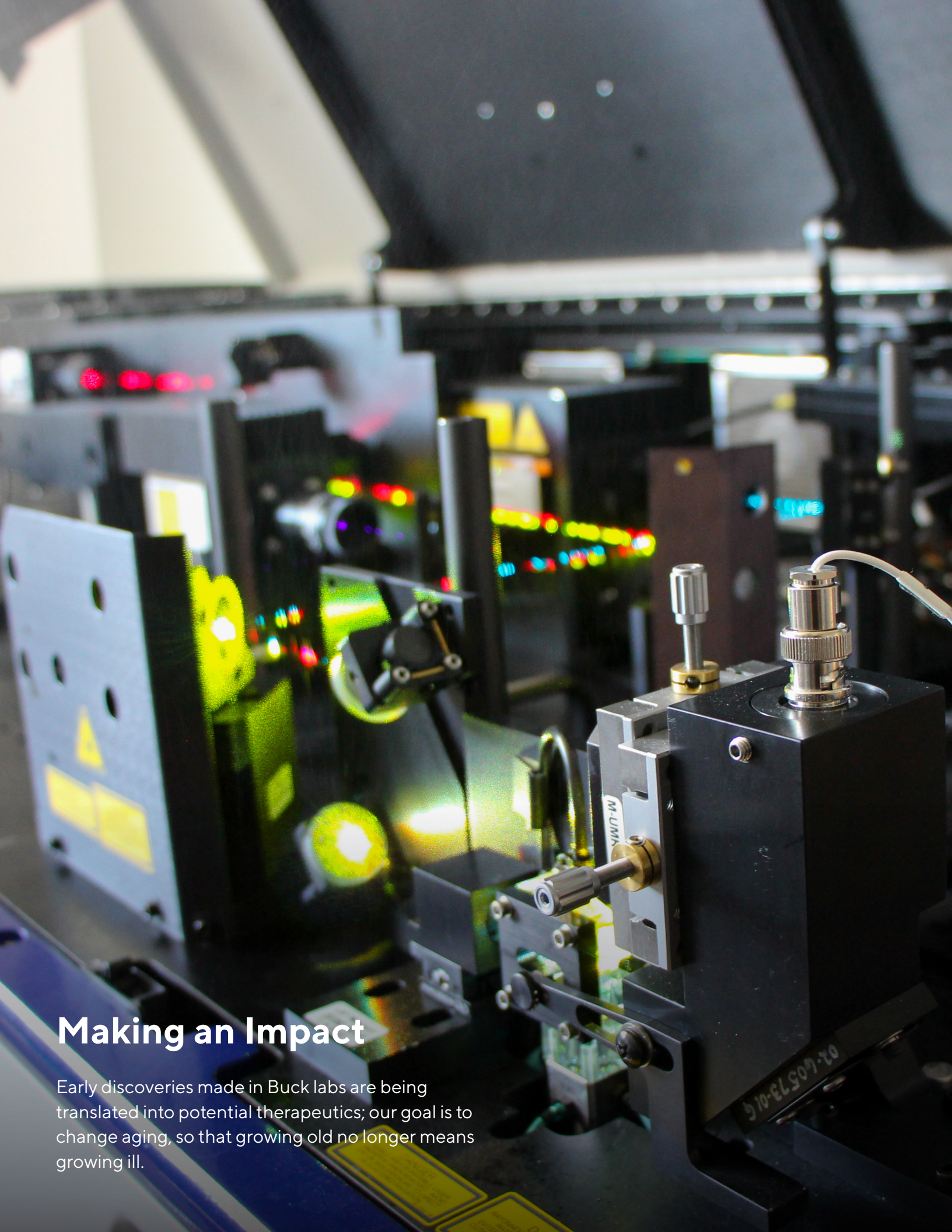


The alleles of the ApoE gene. ApoE2 is associated with exceptional longevity; ApoE4 is linked to an increased risk of developing Alzheimer's disease; ApoE3 is neutral.

"I enjoy my colleagues at the Buck. There is so much rivalry at big universities. It's so different at the Buck. We can focus on being successful together."



Judith Campisi, PhD
Professor



Making an Impact

Early discoveries made in Buck labs are being translated into potential therapeutics; our goal is to change aging, so that growing old no longer means growing ill.

GARRISON LAB

The Garrison lab aims to understand how changes in the brain circuits that control homeostasis lead to systemic aging.

Breakdown of homeostasis in the aging brain

Communication between the brain and the rest of the body allows an animal to regulate its internal state; with age this homeostatic capacity declines.

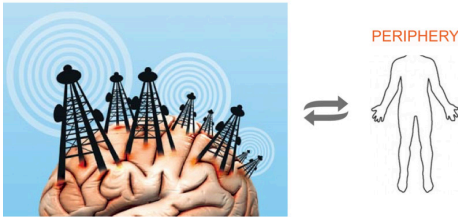
In mammals, homeostasis is controlled by a small structure at the base of the brain called the hypothalamus. It's where the key neurons that control all aspects of organismal homeostasis are located, including reproductive function, energy and fluid homeostasis, body temperature regulation, and circadian rhythms and their associated behaviors (eating, drinking, sleeping, etc.).

The majority of physiological functions that decline with age are broadly governed by the hypothalamus—a shift in energy homeostasis, for example, is one of the hallmarks of changes that occur during aging. And a precipitous decline in female reproduction is one of the earliest signs of aging in many animals.

There is an age-related increase in inflammation specifically in the hypothalamus, and corresponding dysregulation of the homeostatic systems that this brain region controls. Thus, the hypothalamus is a primary regulator of the process of aging in the whole body; mechanisms operating there are potential targets for anti-aging interventions.

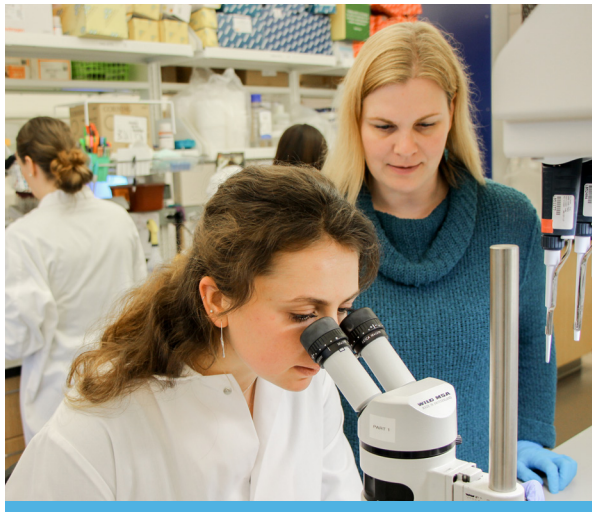
The hypothalamus is the most neuro-chemically diverse region of the brain and contains hundreds of intermingled cell types, which use signaling molecules called neuropeptides to communicate with the rest of the body.

The Garrison lab is working to understand how these long-range secreted signals influence aging. Researchers are developing new methods to monitor and manipulate neuropeptide signaling in living animals, and are also identifying the fundamental enzymes that regulate neuropeptide communication.



Neuropeptides: the brain's WiFi.
The hypothalamus controls long distance communication between the brain and other tissues using neuropeptides.

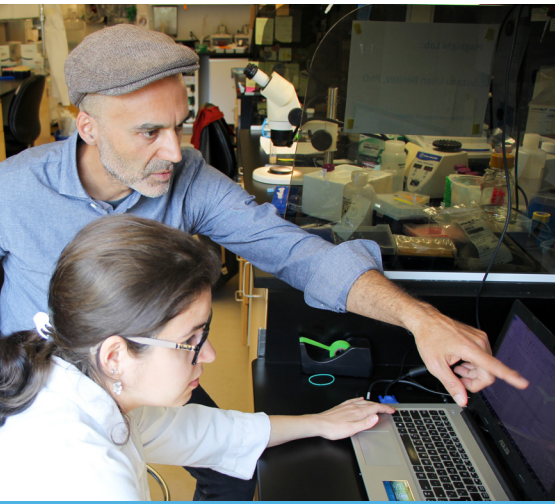
Their goal is to discover how age-related changes in neuropeptide signaling systems in the brain can influence whole organism healthspan and longevity, and to discover strategies to preserve neuropeptidergic signaling with age.



"I am incredibly excited to be part of the newly established Center for Reproductive Longevity and Equality at the Buck. This will be the first facility anywhere in the world focused solely on reproductive equality and longevity as it relates to aging, and is truly visionary."



Jennifer Garrison, PhD
Assistant Professor



HAGHIGHI LAB

The Haghighi lab focuses on understanding the molecular mechanisms that govern communication between the central nervous system (CNS) and the peripheral organs and tissues.

Aging, disease, and the blood-brain barrier

The presence of a barrier that separates the CNS from the circulatory system is a unique and highly evolutionarily conserved feature found from fruit flies to humans.

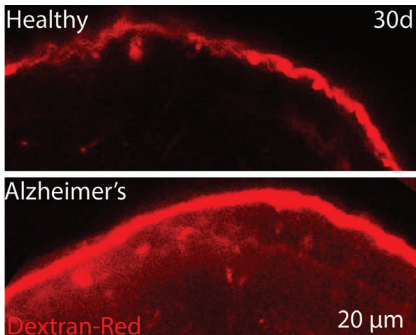
This anatomical separation, which is referred to as the blood-brain barrier, has the crucial role of establishing a protective, nutrient-rich and ionically balanced environment for nerve cells to function optimally. Accumulating experimental evidence indicates that the blood-brain barrier may become less robust with age and particularly weakened under disease conditions such as Alzheimer’s and Parkinson’s diseases.

The Haghighi lab has been developing assays and novel approaches to study the molecular mechanisms that lead to changes in the blood-brain barrier integrity under normal aging, as well as in Alzheimer’s.

One of the intriguing observations that the Haghighi lab has recently made indicates that the blood-brain barrier, as the first line of defense, responds strongly to systemic inflammation. Experimental results, using the fruit fly model, show that inflammatory signals produced by the intestine or the musculature can trigger receptors in the blood-brain barrier.

The lab, as part of an NIH-funded project, has been conducting a number of genetic experiments aimed at understanding the nature of these inflammatory signals originating from the periphery (gut and muscle), and the way these signals are processed by the blood-brain barrier cells, and their ultimate effect on neuronal function and survival.

Preliminary experiments in the lab suggest that limiting the generation of inflammatory signals from the gut, or inhibiting the processing of these inflammatory signals in the blood-brain barrier, can both improve age-dependent decline in different aspects of CNS function and the overall health of the organism.



Representative images of a disrupted blood brain barrier in aged Alzheimer’s disease flies as compared to control healthy flies. Flies were injected with Dextran-red dye in the abdomen.

These intriguing results reveal the important role of peripheral, or systemic inflammation, on the health of the CNS, and point to the blood-brain barrier as a novel therapeutic target. By understanding the details of molecular steps involved in the cross communication between peripheral inflammatory signals and the blood-brain barrier, we could generate the opportunity to protect the CNS more efficiently as we age, and perhaps nip degeneration in the bud!

JASPER LAB

The Jasper lab works to enhance stem cell function to promote longevity through tissue repair.

Exploring MANF as a rejuvenating factor in parabiosis and aging

Older mice who are surgically joined with young mice—in order to share a common bloodstream—get stronger and healthier, making parabiosis one of the hottest topics in age research.

The Jasper lab has identified mesencephalic astrocyte-derived neurotrophic factor (MANF) as one of the factors responsible for rejuvenating the transfused older mice. This major project led to publication in *Nature Metabolism*.

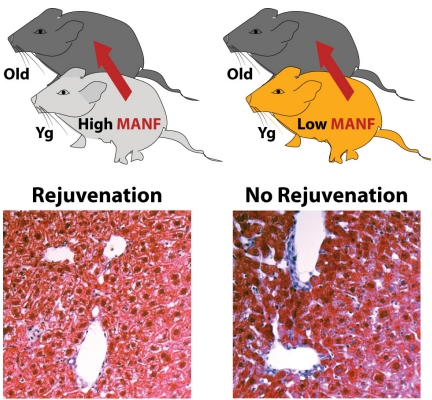
MANF, a naturally occurring, evolutionarily conserved repair mechanism, which regulates metabolism and immune response in flies, mice, and humans, declines with age—which highlights the promise of replenishing it as an anti-aging treatment.

Scientists are building on identified hallmarks of MANF-deficiency: flies genetically engineered to express less MANF suffer from increased inflammation and shorter lifespans; MANF-deficient mice have increased inflammation in many tissues, as well as progressive liver damage and fatty liver disease; older mice who share blood with MANF-deficient younger mice did not benefit from the transfusion of young blood.

MANF appears to regulate inflammatory pathways that are common to many age-related diseases; researchers found that liver rejuvenation spurred by parabiosis was dependent on MANF.

In addition, they showed that supplementing MANF in aging mice slowed liver aging, prevented fatty liver disease in animals on a high fat diet, and improved age-related metabolic

dysfunction. Researchers are studying the larger implications of MANF’s therapeutic uses.



Research in young and old mice that surgically shared a common blood stream showed that MANF was essential for liver rejuvenation in the older animals.

The Jasper lab continues to explore mechanisms that promote tissue repair in aging organisms. The lab is also pursuing an NIH-funded project to understand the link between neuronal metabolism and changes in protein turnover rates in the aging brain.



“Enhancing natural repair mechanisms to extend healthspan is an exciting proposition, and the Buck is a great place to do the work. Our collaborative environment can really help speed the process.”



Heinrich Jasper, PhD
Professor



KAPAHI LAB

The Kapahi lab seeks to understand the role of nutrition and energy metabolism in lifespan and disease utilizing worms, flies, and mice as model systems.

Advanced glycation end products explain why glucose accelerates aging, Alzheimer’s disease, and Parkinson’s disease

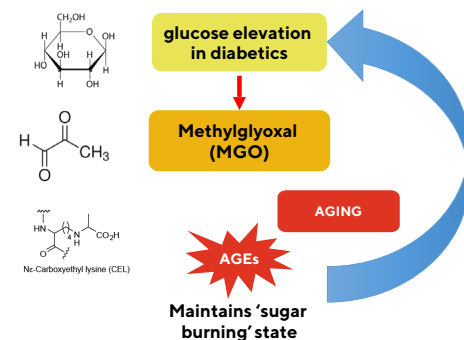
More than 100 million U.S. citizens are living with type 2 diabetes or prediabetes.

While having diabetes doubles the overall risk of developing Alzheimer’s disease and Parkinson’s disease, it also accelerates aging and can lead to vision loss, heart disease, kidney failure, and painful nerve damage. Some with prediabetes develop complications before their disease becomes full-blown.

One of the projects in the Kapahi lab aims to develop therapies that would treat or prevent the toxic effects of glucose that accelerate aging and neurodegenerative diseases.

The Kapahi lab studies a compound called Methylglyoxal (MGO) which is formed as an unwanted byproduct during glucose metabolism in the body. MGO is extremely toxic and reacts with essential proteins, DNA, and lipids to form advanced glycation end products (AGEs), which have been implicated as the cause of many diabetic complications and linked to Alzheimer’s disease and Parkinson’s disease.

While AGEs are a natural byproduct of metabolism (and are usually cleared in healthy, younger individuals), they can also be ingested via the diet. The browning of meat is an example of the AGEs-related cross-linking that occurs in proteins.



Formation of advanced glycation end products (AGEs). An inevitable by-product of metabolism, advanced glycation end products (AGEs) are toxic molecules formed when proteins, DNA and fats become bound after exposure to sugar. Our bodies have inherent defense mechanisms that can clear them. But the production of AGEs really ramps up when blood sugar is high, and eating a typical high-carbohydrate, highly processed Western diet can overwhelm those natural defenses.

The Kapahi lab has elegantly used *C. elegans*, a nematode worm, and mammalian cells to identify novel genes and compounds that enhance our natural defenses against the formation of AGEs. Researchers in the lab are studying the effects of these genes and compounds in slowing aging, Alzheimer’s disease, and Parkinson’s disease using worms, mice, and patient-derived induced pluripotent stem cells.

KENNEDY LAB

The Kennedy lab is focused on moving research on aging from simple organisms to mammals to improve human health.

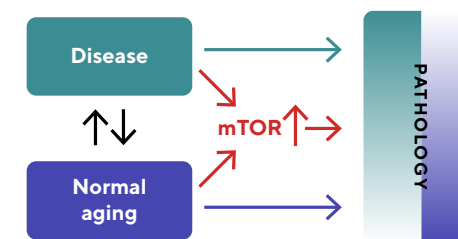
Reducing activity of the mTOR pathway to extend healthspan and lifespan in mammals

The Kennedy lab continues to work on the identification and characterization of small molecules with the potential to extend human lifespan, and more importantly, healthspan.

These studies primarily use either normal mice or mutants that display accelerated aging pathology. Of these, we have focused for some time on a mouse model of Hutchinson–Gilford progeria syndrome, a rare human disease associated with rapid aging of the cardiovascular and other systems in the body. We have found that targeting aging pathways with small molecules can delay pathology in this mouse model. These small molecules may impact normal aging as well.

Increasingly, it is becoming clear that reducing activity of the mTOR pathway can lead to increased lifespan and healthspan in mammals. This makes it critical to understand how mTOR regulates aging and to identify strategies for intervention. We are continuing to exploit mouse models to understand links between mTOR and aging, and to determine the mechanisms by which reduced mTOR signaling prevents the onset of specific diseases, including Alzheimer’s disease.

Finally, the Kennedy lab is using a simple model organism, yeast, to attempt to understand aging holistically, not only identifying individual pathways, but understanding how all of the aging determinants integrate to control the link between the rate of aging and environmental influences.

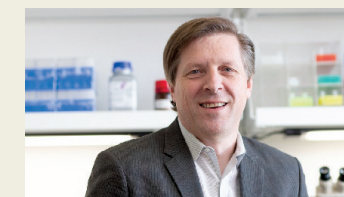


The nutrient signaling pathway mTOR (mammalian Target of Rapamycin) is a key regulator of aging and age-related disease. Reducing activity of the pathway can lead to increased lifespan and healthspan in mammals.

In summary, the lab continues to pursue aging from multiple angles in multiple organisms in an attempt to better understand this near universal process, and to use that knowledge to extend human healthspan.



“Our work in multiple animal models shows that the processes driving aging are conserved among species. Studying these common pathways are enabling the development of therapies that would slow the aging process—forestalling chronic disease.”



Brian Kennedy, PhD
Professor



LITHGOW LAB

The Lithgow lab focuses on understanding the mechanisms of aging and how aging causes age-related diseases, in particular neurodegenerative diseases.

Protein quality and aging

The Lithgow lab was founded on the early discoveries of gene mutations that extended the lifespan of simple animals (the nematode *C. elegans*).

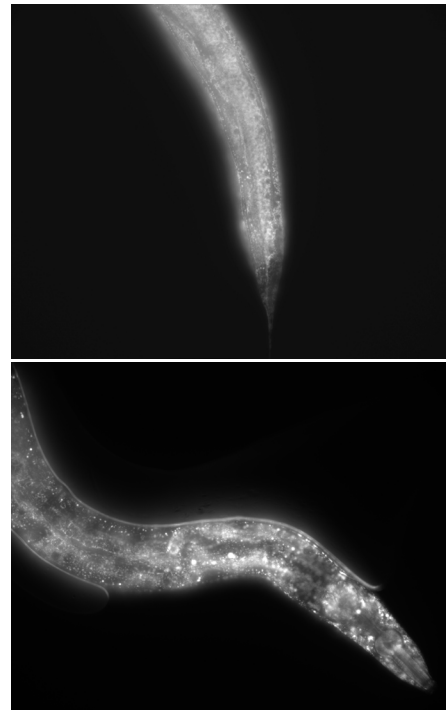
The lab initially investigated the relationship between stress resistance and longevity, and was successful in showing that key components of the stress response mechanisms, including molecular chaperones, not only protected against stress but also determined normal lifespan.

Upon moving to the Buck, the Lithgow lab discovered the first drug-like molecule that extended an animal's lifespan. This chemical biology approach became a major new direction for the lab. Subsequently, the lab has discovered many chemical interventions in aging, including some nutrients and naturally occurring metabolites.

One major connection between stress and normal aging is the age-related deterioration of protein quality. Protein conformation (three-dimensional shape) is vital to protein quality, but aging degrades the cellular systems that maintain protein conformation.

The lab has identified at least a thousand proteins that become insoluble during aging—almost half of them contribute to aging. Using drug-like compounds, we are able to slow down the accumulation of aggregated proteins resulting in healthy lifespan extension.

Researchers combine this approach with genetics to uncover novel mechanisms of drug action and aging. Such studies were initiated in the *C. elegans* model but are now being undertaken in mouse models, including models of Alzheimer's disease.



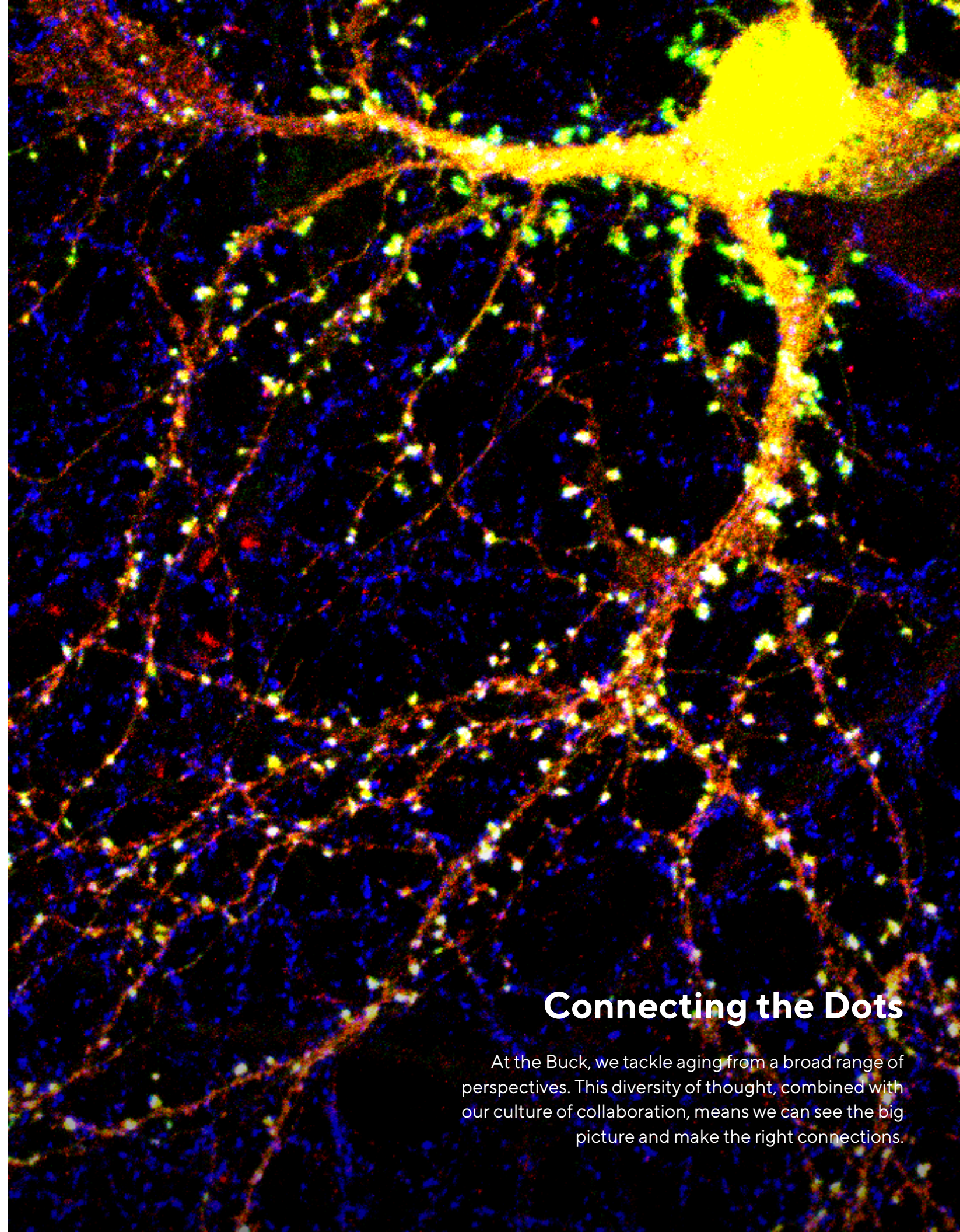
One-day-old *C. elegans* nematode (top) compared to a middle aged (seven-day-old) animal (bottom). The mitochondria in the older animal are beginning to deteriorate, giving rise to mislocalized proteins collecting in small granules. The Lithgow lab uses this strain of worms to identify compounds that prevent the protein aggregation.

The Lithgow lab is also one of three nodes for the Caenorhabditis Intervention Testing Program. This NIA-funded program aims at finding robust and reproducible interventions in aging by testing for the effects of compounds on healthspan and lifespan at three research sites and across genetically diverse strains.

“The realization that scientists working in diverse diseases—say Alzheimer’s and cancer—were really working on the same thing was stunning, and led to the development of geroscience.”



Gordon J. Lithgow, PhD
Professor
Vice President, Academic Affairs



Connecting the Dots

At the Buck, we tackle aging from a broad range of perspectives. This diversity of thought, combined with our culture of collaboration, means we can see the big picture and make the right connections.



MELOV LAB

The Melov lab seeks to identify molecular hallmarks of aging to guide the development of anti-aging therapeutics. The lab’s multidisciplinary geroscience approach includes a heavy reliance on multiple model systems, and state-of-the-art genomic technologies that use advanced computational methods.

Getting to the genetic roots of sarcopenia

Sarcopenia, the loss of muscle tissue that occurs during aging, is a major driver of frailty and disability in older adults.

One of the projects in the Melov lab aims to get at the root cause of sarcopenia by utilizing new, real-time genomic sequencing technology to analyze and compare samples of human muscle tissue taken from three groups: young; old; and those with sarcopenia.

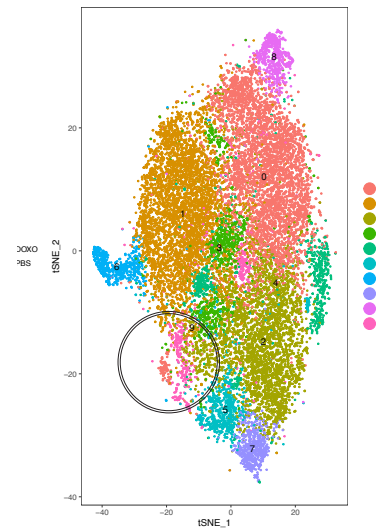
The technology will focus on exons, a coding region of a gene (or messenger RNA) that contains the information required to encode a protein. The technology will involve long-read sequencing to identify novel transcripts and alternative splicing events when exons get rearranged.

This is no small feat considering that exons can be 10,000 or 100,000 bases long (involving the nucleic acids A, T, G, and C, which make up our genetic code).

Scientists have long thought that inappropriate splicing of exons, which damages proteins, is involved in the aging process, but the means of examining this phenomenon has been lacking.

Advanced computational methods will be utilized to compare sequencing results with extensive physiological information from the 80 individuals who donated biopsies for the research at McMaster University in Hamilton, Ontario. Information about walking speed, strength, daily living habits, and results from a variety of functional tests

will be crunched with genomic data to map variations in individual gene expression in the samples.



Single cell RNA sequencing of skeletal tissue from mice treated with a senescence-inducing drug. Each dot in the sample is a single cell. The bioinformatics analysis technique clusters cells that have similar gene expressions. The cells within the circle are senescent.

Researchers expect that young individuals will have comparatively fewer variations with what is known about gene expression in muscle, with older individuals having some, and those with sarcopenia having substantial variations in gene expression. The research could point to specific genes as probable in sarcopenia, providing therapeutic insights and opportunities to correct mutations in muscle organoids grown in a lab dish.

NEWMAN LAB

The Newman lab works to harness metabolic signals to treat geriatric symptoms of aging.

Learning how ketone bodies and other metabolic molecules act as signals, and harnessing those signals to treat the aging body and brain

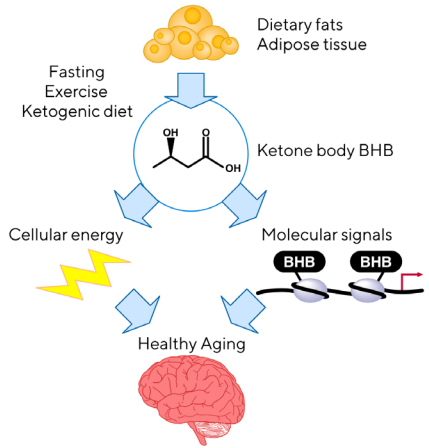
The Newman lab studies ketone bodies and other signaling metabolites that link nutrition, metabolism, and aging.

Ketone bodies are small molecules made by the body as a way of using fat for energy when we fast, exercise, or eat a low-carbohydrate, ketogenic diet. Ketone bodies are a fuel that is burned in the cells of our brains, hearts, and other organs to keep life moving. But we are learning they are more than fuel—they are signals, too.

They bind to proteins, inhibit enzymes, and activate receptors—acting much like drugs. Through these signaling activities, ketone bodies help control: gene expression; inflammation; metabolism; and senescence, all of which affect aging.

Newman is studying how ketone bodies work to slow the effects of aging on the brain, and how they might be useful in normal aging, Alzheimer’s disease, and delirium.

This work is grounded in studies Newman carried out with his mentor, Eric Verdin, showing that a ketogenic diet can extend healthy lifespan in laboratory mice, including maintaining memory as they age. Ketogenic diets also help to calm abnormal epilepsy-like activity in brains of those with Alzheimer’s disease, which could lead to new therapies to help an aging brain cope with neurodegeneration.



The Newman lab studies ketone bodies, small molecules that allow us to use fat for energy when we fast, exercise or eat a low-carbohydrate diet. Ketone bodies act much like drugs, helping to control: gene expression; inflammation; metabolism; and senescence.

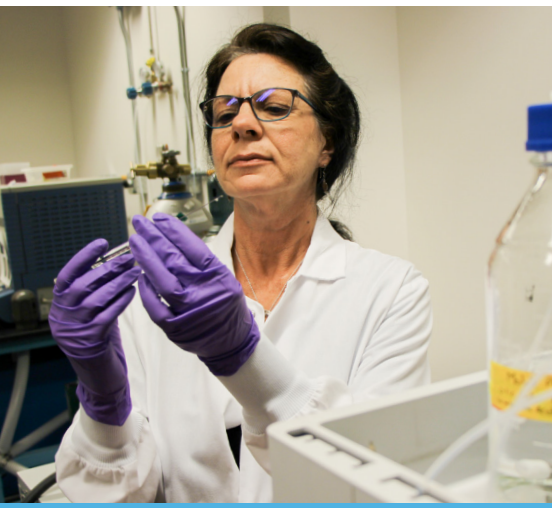
As a geriatrician physician/scientist, Newman is especially interested in applying new therapies emerging from geroscience to complex geriatric syndromes like delirium, frailty, and functional decline—conditions that rob so many older adults of their independence. He works with collaborators around the San Francisco Bay Area and across the country to accelerate the translation of geroscience into clinical trials, and to train geriatricians and geroscientists to carry out studies that will transform the care of older adults.



“Geriatrics and geroscience are a perfect fit. Aging is beautiful, but we all want to stay strong, sharp, and independent, and I really think we’re going to have entirely new ways of doing that soon.”



John Newman, MD, PhD
Assistant Professor



RAMANATHAN LAB

The Ramanathan lab is focused on understanding the molecular physiology of skeletal muscle regeneration in aging.

Using mass spectrometry-based metabolomics to map pathways for reversing age-related muscle loss

It is gratifying to work on something everyone understands from their daily lives—that healthy and strong muscles can be the foundation of a healthy metabolism, a sharp mind, and a fulfilling life.

The Ramanathan lab is developing cutting edge technologies that will help us uncover how to keep skeletal muscle strong for life, and reverse age-related muscle degeneration, also known as sarcopenia. The lab is excited to be one of the first to build a functional, human skeletal 3D organoid to test interventions that can promote muscle mass and strength. The lab will extend this platform to develop a model of human sarcopenia in vitro, and screen for biologics and small molecules that can reverse this aging-related phenomenon.

In parallel, researchers believe that cellular metabolism is a central axis that is dysregulated in sarcopenia. Cellular metabolism is integrated into critical cellular pathways, including: glucose signaling; nutrient sensing; and cell cycle and stem cell mediated tissue repair. Therefore, it is not surprising that metabolic dysfunction is an underlying driver of skeletal muscle differentiation, and underlies several diseases.

It is recognized that metabolic signals from molecules, including lipids, are critical regulators of tissue homeostasis. But little is known about the molecular identities, and temporal and spatial dynamics of lipids/metabolites during fundamental cellular processes, such as differentiation, immunological responses or senescence. Therefore, the central question of the lab's

research program is *How do metabolic signals control muscle differentiation, repair, and senescence?* This central biological question will interface with a parallel development of technology that will enable the comprehensive profiling of cellular metabolites in tissues and biofluids, known as metabolomics.

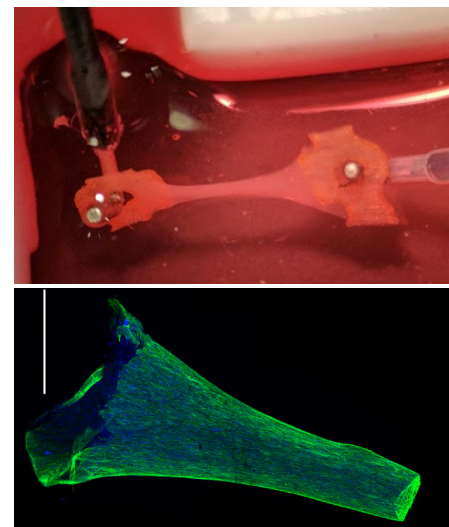


Image on top is living muscle fiber grown from a human biopsy. On the bottom, researchers use a force sensor to do strength tests on muscle fiber after the fiber has been treated with a compound that shows promise in improving strength and function.

By pursuing these two approaches the lab will map how skeletal muscles lose their metabolic homeostasis during aging and how researchers could target specific pathways to ameliorate this degeneration.

SCHILLING LAB

The Schilling lab aims to uncover how protein pathways are implicated in aging and disease.

Using high-end technology in mass spectrometry to gain insights into underlying mechanisms of aging and diseases at the molecular level

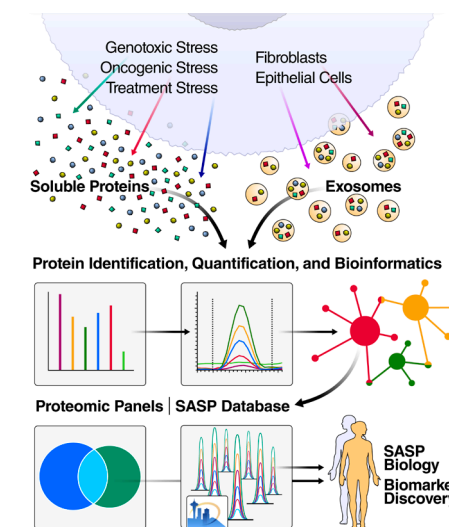
Cells are complex machines comprised of proteins and enzymes that form protein networks that ensure the appropriate function of healthy tissues.

The Schilling lab uses analytical chemistry methodologies, such as mass spectrometry, to investigate what may change or get disrupted at the molecular level during aging and disease. Lab members can measure thousands of proteins at the same time, and the acquisition approach that we are using is truly unbiased.

Researchers collaborate with experts in specialized fields of research on aging both at the Buck and outside institutions. Results on projects comprising cellular senescence, Alzheimer's disease, age-related muscle loss (sarcopenia), and cancer have often led to unexpected findings, generating new research directions involving molecular pathways that were previously unknown. Scientists also generate new hypotheses based on protein changes that are identified in existing models of disease.

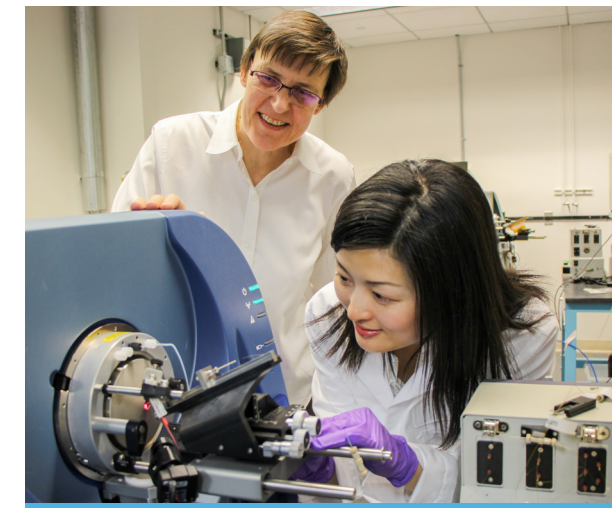
Researchers apply our multiplexing assays for high-throughput screening of protein-drug interactions in order to better understand drug targets and mechanisms of action of therapeutics that may be candidates for future aging interventions. The lab is very excited about a project aimed at developing biomarkers of aging, which would be used to identify early molecular signs and markers of aging that can also be used to monitor outcomes of potential treatments.

Recent efforts have been targeted at finding biomarkers for cancer in a large international study with collaborator Thea Tlsty, PhD, at the University of California, San Francisco. This project involves measuring protein profiles of the extracellular matrix (a tissue scaffold that holds cells together) from cancerous and neighboring normal tissues removed during surgeries on patients with esophageal, gastric, colon, and lung cancer.



The process utilized in the Schilling lab to develop senescence-derived biomarkers of aging.

Overall, the lab aims to provide excellence in both technology and the application of tools to address biological questions to provide new ideas and research directions that could revolutionize how we think about aging and related diseases.



“The Buck is a one of a kind place that enables an incredible diversity of scientists from all over the world to focus on the biology of aging. This is the future of science and the biology of aging.”



Arvind Ramanathan, PhD
Assistant Professor

“Establishing the field of geroscience was groundbreaking. My group would like to provide the necessary analytical technology methods to move geroscience to the next level.”



Birgit Schilling, PhD
Assistant Professor



TRACY LAB

The Tracy lab uses mouse models and cultured human neurons to examine the mechanisms that trigger synaptic and neuronal dysfunction during the development of Alzheimer’s disease and other dementias.

Using electrophysiological techniques to develop Alzheimer’s disease therapeutics

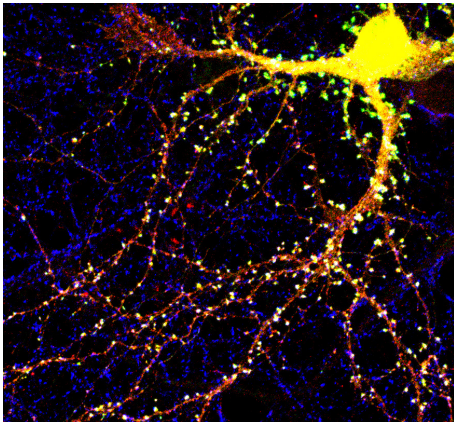
Neurons are electrically excitable cells that typically fire five to 50 times every second as they process and transmit information by electro-chemical signaling.

The Tracy lab is studying the signaling components at the synapse, the tiny gaps across which neurons relay electro-chemical messages. The average human brain has about 100 billion neurons; and each neuron may be connected to up to 10,000 other neurons, passing signals to each other via well over 100 trillion synaptic connections.

Synapses are plastic—remodeling and modulating themselves in order to encode memories or reorganize information throughout a lifetime.

a change in electrical strength is defective in Alzheimer’s disease leading to memory loss; researchers are using electrophysiological techniques to measure and track this dysregulation as the disease progresses. The ultimate goal is to develop the means to boost electrical strength or to prevent the dysregulation from increasing early in the disease process.

Collaborating with the Schilling lab, researchers are also looking at the hundreds of proteins that are affected during synaptic signaling, seeking to understand how they change throughout the disease process. In particular, researchers are altering cultured human neurons by adding tau, a microtubule-associated protein, which accumulates in the brain and becomes toxic to neurons in Alzheimer’s disease. The goal is to mimic what happens in the development of sporadic Alzheimer’s disease, which accounts for 95 percent of all cases.



This is an image of a neuron captured by confocal microscopy. It has many synapses that form on the small spine structures protruding from its branches. These synapses are critical for encoding memory in the brain.

Researchers in the Tracy lab believe the ability of the synapse to undergo

“As a neuroscientist, I appreciate the opportunity to learn about the aging process and the mechanisms that are at play throughout the entire organism. We can’t separate what goes on in the brain from the rest of the body.”



Tara Tracy, PhD
Assistant Professor

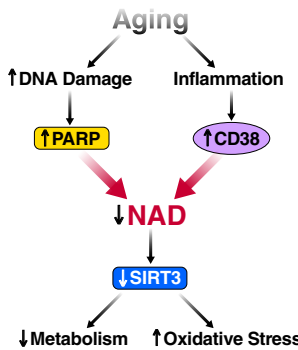
VERDIN LAB

The Verdin lab studies the relationship between aging and the immune system, and how immune aging is regulated by nutrition.

Energy metabolism and aging: a key relationship

Energy metabolism is central to aging. All living organisms maintain organ and cellular integrity using monitoring and repair systems.

These processes are energetically demanding and require a constant supply of energy. Much of this energy is generated in the mitochondria from food during feeding or from energy stores during fasting. Remarkably, energy metabolic efficiency decreases during aging. This limitation in energy supply slowly degrades all cellular activities and allows damage to go unchecked. The Verdin lab is focused on understanding the complex relationship between energy metabolism and aging. The lab seeks answers in four different areas:



1. NAD metabolism: This key metabolite shuttles energy within cells and is critical for the activity of many enzymes. Cellular NAD+ levels decrease in multiple organs during aging, thereby decreasing metabolic efficiency. Three broad classes of enzymes use NAD+ and compete for a limited pool of NAD+: sirtuins have broad anti-aging activities; PARPs help repair DNA damage; and CD38 is involved in immune activation. The lab’s working hypothesis is that increased PARP and CD38 activities during aging decrease the pool of NAD+ available for sirtuins

and therefore limits their anti-aging activities. Researchers have recently shown that senescent cells can induce CD38 expression, and they are currently focused on identifying the mechanism of activation.

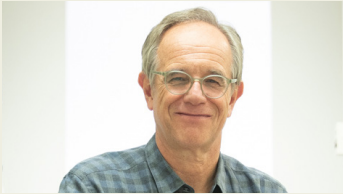
2. Mitochondrial sirtuins: There are 7 sirtuins proteins, three of which are present in mitochondria: SIRT3; SIRT4; and SIRT5. SIRT3 expression is enhanced by fasting and caloric restriction, and decreased during aging. SIRT3 is necessary for the protective effect of caloric restriction against aging in several models; and mice lacking SIRT3 show accelerated aging and chronic inflammation.

3. Chronic inflammation and aging: Degradation of mitochondrial function during aging leads to decreased energy as well as distress signals from the mitochondria. These signals are adaptive under normal conditions, but can become toxic during aging because of their intensity, which can lead to chronic inflammation. Excess inflammation is a hallmark of aging and further contributes to the development of chronic diseases.

4. Ketogenic Diet: During fasting or under a ketogenic diet the liver transforms energy from fat into a unique energy carrier called beta-hydroxybutyrate or BHB. Scientists have found that BHB has unique anti-inflammatory properties that suppress aging. The lab is studying how BHB suppresses inflammation, and is developing novel BHB precursors as potential anti-aging drugs.



“I’m most proud of the fact that we’re tackling aging—a huge problem—head on. We’re saying ‘hell no’ to the status quo. Age-related illness does not have to be a fact of life.”



Eric Verdin, MD
CEO



ZHOU LAB

The Zhou lab is focused on understanding the plasticity and homeostasis of the cellular proteome under stress and aging.

New high-throughput screening technology for discovering novel longevity pathways in aging and age-related diseases

Being in the right complex at the right time is important, especially for proteins.

The survival and health of each cell in our body relies on the proper protein homeostasis and function within the cell, yet researchers have yet to determine how aging affects protein functions.

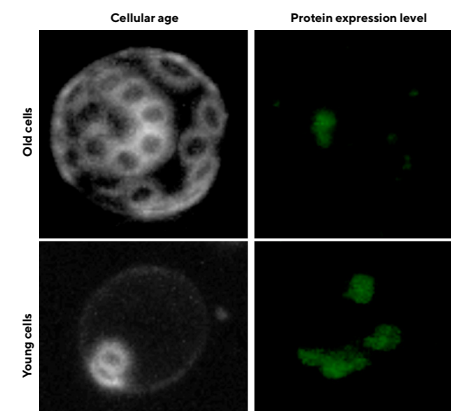
The Zhou lab aims to change that, with a goal of discovering if and how protein dysfunction contributes to age-related conditions such as Alzheimer's and Parkinson's diseases, and whether correcting abnormal functions can ameliorate or block the progression of age-related pathology.

The Zhou lab works in budding yeast, a classical model organism for research in aging. The lab has invented a new screening technology to look for specific proteins that fail to execute their function in aged budding yeast cells.

"I think there will be lots of information about aging that will become available once we crack this domain open. I am really excited to pursue this inquiry."



Kai Zhou, PhD
Buck Fellow



Research in yeast shows a reduction in a mitochondrial protein in older cells.

Enriching for older cells is no simple matter. They cannot be identified in aggregate; and yeast cells cannot be forced to divide quicker than nature allows—yeast cells usually die after 20 to 24 divisions. Using fluidic technology and marker tags, the lab has devised a means of retrieving older cells from a pool of thousands of cells. New technology will also enable the lab to image individual cells to determine the timing of protein dysfunction.

The lab will use the same screening system to test how the protein functions are affected in different conditions, starting with caloric restriction. Given that caloric restriction has been shown to extend healthspan in several species, researchers in the Zhou lab are keen to understand how a Spartan diet affects organisms at the cellular level, hypothesizing that it fixes some problems that occur with natural aging.

BUSINESS DEVELOPMENT

Business-building at the Buck: The right place at the right time

Groundbreaking discoveries into the underlying biology of aging have led to much excitement around the possibility of extending both lifespan, and more importantly, healthspan—the healthy years of life.

As these discoveries are readied for translation into the clinic, the development of therapeutics and interventions designed to impede aging and tackle the chronic diseases that typically accompany it is now a question of not if, but when. The need could not be more acute. According to the United States Census Bureau, by 2035 older people will outnumber those under 18 for the first time in American history.

It is not surprising that venture capitalists and entrepreneurs, seeing the potential of treating people with new and novel medicines and a market that would dwarf all previous blockbusters, have poured into this space. **As the world's first independent scientific institute with a sole focus of research on aging, the Buck is in a unique position in this burgeoning field.** Thanks to our singular focus and our highly collaborative environment, the Buck has an impressive track record of identifying and co-founding companies that address this exciting and unprecedented opportunity.

Propelled by an unparalleled IM Pei campus specifically designed to promote collaboration, world-class technology, and a flexible licensing program, the Buck has founded seven companies that have been successfully launched and now interrogate novel mechanisms of aging. These companies collectively have raised

over \$400M from venture and public markets, and either have delivered or are progressing well in bringing new drug candidates into human clinical trials.

The past two years have been a period of unprecedented progress in business development at the Buck.

During this time alone, three new companies have launched (BHB Therapeutics, Napa Therapeutics, and GeroState Alpha). Using the science behind ketone bodies (packets of energy stored in the body), BHB Therapeutics spun out from the Newman and Verdin labs, and is creating novel and nutritional consumer products to reverse aging, including cognitive impairment and cardiovascular disease. Napa Therapeutics, based on work from the Verdin lab, is focused on how the cofactor NAD may rescue or replenish energy decline; while GeroState Alpha, spun out from the Melov and Lithgow labs, aims to be the first company to create interventions to improve maximum, rather than average, lifespan.

Perhaps our most famous offspring, Unity Biotechnology, of which Buck professor Judith Campisi is a scientific co-founder, has its lead compound in clinical trials and

several promising candidates in pre-clinical stages. Unity, whose market cap has been as high as \$700M, is developing drugs that focus on eliminating accumulated senescent cells, which are a fundamental mechanism of aging and a driver of many common age-related diseases.

In addition to new company formation and technology development in startups, the Buck has multiple collaborations to further research on aging and develop therapeutics that might arise from the research. Prominent collaborators include Calico, the pioneering Google-backed company with a goal of changing aging as we know it, and the multinational biopharmaceutical giant, Astellas.

The success of our collaborators and our spinoffs will put the Buck in the enviable position of doing well by doing good. With equity positions in all of our spinoffs, including milestone and percentage of sales payments on drugs we help develop, the Buck is positioned to receive a steady revenue stream as discoveries are developed and potentially moved into the clinic and onto the market. These revenues will of course be plowed back into supporting Buck science. In the ultimate virtuous circle, these revenues, and the resultant science financed by them, will propel our work to help us all live better, longer.

Nicole Shanahan brings women and reproduction into the aging equation

By the time she visited the Buck, Nicole Shanahan, through many conversations with prominent scientists, had learned that research into the field she most cared about was sorely lacking.

On her first visit, while walking around the buildings and chatting with scientists, she couldn't help but be struck by the energy that seemed to permeate the campus. She felt comfortable bringing up the subject that was weighing on her mind.

While Buck scientists focus on the process of aging, Nicole was concentrating on the beginnings of life, specifically fertility, and her own recent problems with it. She asked Buck CEO Eric Verdin if it might be fruitful to study aging's relationship to female reproductive longevity.

A few months later, Nicole Shanahan—attorney, entrepreneur, and a CodeX Research Fellow at Stanford Law School—became the founder of the Buck's new Center for Female Reproductive Longevity and Equality. Shanahan's \$6M initial donation, through the Sergey Brin Family Foundation, has sparked a groundswell of excitement in this emerging field. One question she asks is, What took so long?

The area of female reproductive longevity is a scientifically underserved field. In fact, only this year—for the very

first time—did the National Institute on Aging consider the basic biology of aging in reproductive tissue a funding priority. This is especially concerning, because science has shown a strong correlation between ovarian aging and morbidity.

In fact, early menopause is associated with a higher mortality risk for women, and is also linked to a higher risk for age-related diseases, such as dementia, osteoporosis, heart disease, and diabetes.

“A woman’s decisions about child-bearing, and being able to extend the childbearing years, have profound effects on her career, her life choices, and her long-term health.”



Nicole Shanahan speaks to the audience at the official launch of the Center for Female Reproductive Longevity and Equality.



Shanahan, whose past charitable giving has focused primarily on social justice issues, sees a strong link between women's reproductive health and women's rights. She believes, “A woman's decisions about child-bearing, and being able to extend the childbearing years, have profound effects on her career, her life choices, and her long-term health. Once I dug into it, it was pretty astonishing to find out how little attention has been paid to this field of discovery research.”

The time to devote significant attention and resources to women's reproductive longevity is now. Shanahan was delighted to find a kindred spirit in Buck CEO Eric Verdin who immediately saw a natural affinity between this issue and the Buck's mission. “In speaking with Eric and learning more about the Buck's work, it didn't take long to realize this is a great fit,” Shanahan says. “I'm enormously excited to see where this journey takes us.”

IMPACT CIRCLE

The latest Impact Circle award sends bees buzzing to the Buck

The project seeks to understand the mechanisms behind dramatic lifespan differences in genetically identical bees.

Members of the Impact Circle vote annually to support a Dream Big research project after hearing pitches by our faculty. The competition is friendly, fierce, and fun, and it gives these donors an insider's view of our research. Impact Circle members receive early insights into promising new avenues of inquiry and enjoy the satisfaction of propelling significant advancements in our scientific understanding. A \$5,000 donation is the entry point for joining the Impact Circle.

This year the Impact Circle awarded Simon Melov \$100,000 to bring honey bees to the Buck! Donors are supporting his efforts to understand and exploit the mechanisms behind the dramatic lifespan differences between genetically identical insects. Queen bees live five to eight years, whereas worker bees generally live just five weeks. Melov, who helped his cause by dressing up as a bee for his presentation, will use state-of-the-art genetic tools to tweak apart the distinctions.

“Many thanks to the Impact Circle for supporting my project, which is unique in the field of research on aging,” said Melov, who brought an Australian postdoc bee specialist to the Buck. “We think the mechanisms that allow the queen bee to live such an extremely long life will be conserved in higher organisms. Our hope is that we can move the findings into human cell culture and mice.”

Supporting early research is a winning strategy

Started in 2014, the Impact Circle has funded early stage projects that have gone on to win large federal awards and resulted in high-impact publications. Projects have led to a breakthrough understanding of the aging brain, explored the link between gut health and Parkinson's disease, and delved into how a ketogenic diet might protect against the complications of diabetes.

Realizing that certain donors desire an even higher level of impact philanthropy, this year, Impact Circle members Diane and Larry Rosenberger donated \$45,000 to fund a project in the Andersen and Campisi labs aimed at developing a new model to study Alzheimer's disease.



Simon Melov dons a bee costume to pitch his idea to the Impact Circle.

The research, which will happen in cultured human neurons, will focus on cellular senescence and the possibility that associated inflammatory factors drive pathology in early stages of the disease.

“The best thing about being involved in this group is getting to know the people who are driving the research. It's exciting to be personally invested in the science, and it's rewarding to see the progress being made. The comradery in the group is a big plus.”

— Bob Griswold

Alex and Robert Griswold donated \$30,000 to buy specialized equipment to support a project in the lab of Buck fellow Kai Zhou. Zhou wants to see if correcting abnormal protein localization in cells could impede or reverse the effects of aging, thus potentially preventing age-related conditions such as Parkinson's and Alzheimer's diseases. The Griswolds are longtime members of the Impact Circle, and Bob is on the Board of Trustees.

Buck docent Vernon Dwelly lives life as an adventure

With a quick wit and an engaging smile, Vernon Dwelly, fast approaching his 98th birthday, is a poster child for aging done right. When he retired 35 years ago after 31 years in management at American Express he never looked back. He sculpts driftwood, writes poetry and memoirs (he’s currently working on his second book) and travels the world with his wife Elke. Vernon recently retired as a Buck docent after 14 years of leading tours and speaking publicly about our research. He is still on the advisory council of the Dominican University’s Osher Lifelong Learning Institute.

“I’ve always had hobbies and I like to keep busy,” says Vernon, who grew up in Liverpool, England. “Some of my colleagues from American Express literally died from boredom after they retired. In my mind, that was a tragedy. Life at any age can be an adventure if you approach it with the right attitude.”

Vernon’s sense of adventure started early. His studies at the London School of Economics were interrupted by World War II. He served as a Captain with the British Commandos, Special Services, the equivalent of the U.S. Army’s Green Berets. He worked in intelligence and counter-intelligence and first came in contact with Americans while training an advance group of U.S. Rangers prior to the D-Day invasion. “We did the training on steep cliffs in Scotland and Cornwall, around old castles and their walls. We did hand-to-hand combat and practiced night landings from submarines into ‘occupied German territory’. It was tough work.”



Vernon Dwelly, left, led tours at the Buck for 14 years.

Life in the U.S. and beyond

Vernon visited relatives in the U.S. after the war and decided to stay in this country and become a citizen. His affinity for learning languages made him a perfect match for international assignments with American Express. He ran offices for the company in Japan, Germany, Mexico, and Latin America. He speaks German, Dutch, Spanish, and French and loves learning about and interacting with those from different cultures.

After he retired, international travel with his wife became a priority. “We’ve been blessed,” Vernon says, “It’s wonderful to explore the world, even as messy as it is.” Elke and he visited remote Ladakh, nestled geographically and politically between Tibet, Kashmir, India, and Pakistan. They also traveled the Amazon River in South America, hiked to the top of Mount Kenya, and mountaineered to the base camp of Mt. Everest. Physical discomforts and lack of suitcase space on some of those trips turned Vernon into an entrepreneur. He invented an inflatable, easy-to-pack, two-chambered pillow that still brings in some income.

Vernon was recruited as a Buck docent after taking a tour with an architect friend. “In addition to being one of my hobbies, the Buck has always been educational for me,” he said. “The scientists are fabulous. I’m very positive about what’s being achieved for mankind; and my fellow docents have become great friends.” The Dwellys have

arranged for future support of the Buck by including a gift to the Buck in their trust.

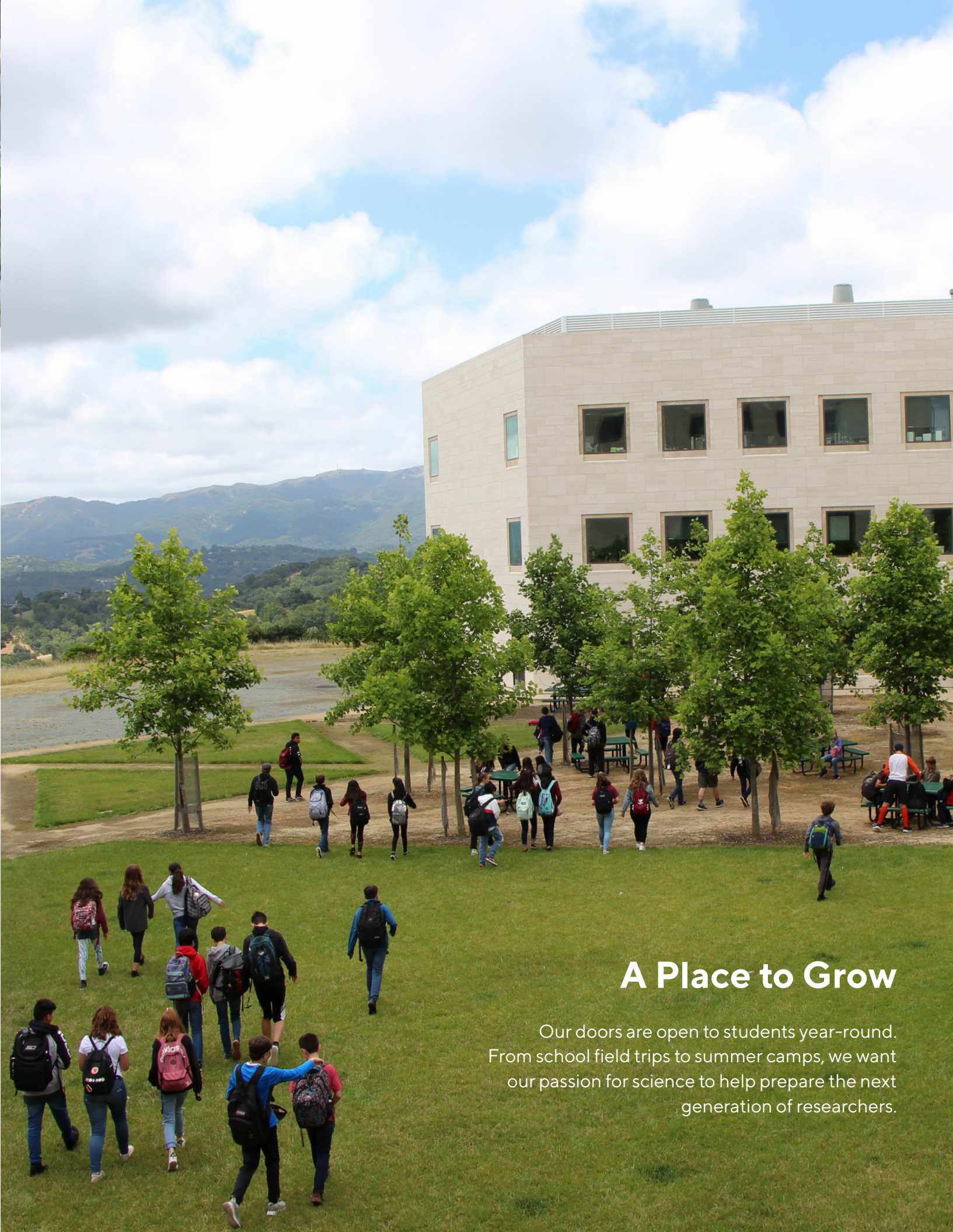
A positive attitude and a life of change

When asked what has changed during his lifetime, Vernon responds with an enthusiastic “everything!” He’s weathered a couple of major surgeries and dealt with family issues. He says he sometimes feels like a cat that has (at least) nine lives. In addition to his curiosity and artistic proclivities, one of his defining characteristics is a remarkably upbeat attitude.

“It’s always been in my nature to be positive and to be interested in the world. I’ve had patience, and most importantly, I can differentiate between things that matter and things that don’t. I think many people encumber themselves with so much stuff that doesn’t matter.”

– Vernon Dwelly

“We’re extremely grateful for Vernon’s support and thrilled that the Buck matters so much to him,” says Lisa Palma, the Buck’s Director of Philanthropy. “I’ve had the privilege of interacting with Vernon for many years and he has become a personal inspiration. Anyone looking for a guide to a rewarding later life need look no further than him.”



A Place to Grow

Our doors are open to students year-round. From school field trips to summer camps, we want our passion for science to help prepare the next generation of researchers.

Our Donors

None of our work would be possible without the generosity of our individual donors, foundations, and governmental agencies. We are extremely proud and grateful to be the recipient of their support.

\$10,000,000 and above

The Buck Trust

California Institute for Regenerative Medicine

National Institutes of Health

\$5,000,000 - \$9,999,999

CHDI Foundation

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FINANCIALS

Comparative Condensed Statements of Net Assets

For years ended June 30 (in thousands)

	2017 Audited	2018 Audited	2019 Audited
Assets			
Cash	\$511	\$972	\$1,037
Accounts, interest and notes receivable	585	282	821
Grants and contributions receivable, net	10,372	12,764	10,544
Investments and investments held in trust	14,604	18,095	19,718
Charitable remainder trusts receivable	1,345	1,514	1,378
Deposit and other assets	2,221	2,154	2,124
Property and equipment, net	93,399	89,519	86,147
Total assets	\$123,037	\$125,300	\$121,769
Liabilities			
Accounts, bond interest and accrued expenses payable	\$4,376	\$3,916	\$3,779
Deferred revenue	3,029	2,704	4,649
Notes payable	5,928	4,926	6,224
Legal settlement payable	4,894	5,035	0
Bonds payable, net	90,412	89,035	87,617
Total liabilities	\$108,639	\$105,616	\$102,269
Total Net Assets	\$14,398	\$19,684	\$19,500
Total Liabilities and Net Assets	\$123,037	\$125,300	\$121,769

Source: Management

Comparative Condensed Statements of Activities and Changes in Net Assets

For years ended June 30 (in thousands)

	2017 Audited	2018 Audited	2019 Audited
Operating revenues, gains, and other support			
Grant revenues	\$17,814	\$23,122	\$24,176
Contributions	9,155	8,706	4,349
Allocation from the Buck Trust	6,167	6,331	6,511
Investment return, net and other income	5,173	4,397	4,795
Total operating revenues, gains and other support	\$38,309	\$42,556	\$39,831
Operating expenses			
Research	\$26,596	\$27,692	\$29,092
General and administrative and fundraising	10,319	11,290	12,671
Pledge write-offs and change in allowance for doubtful accounts	4,210	0	0
Total operating expenses and losses	\$41,125	\$38,982	\$41,763
Change in net assets from operating activities	(\$2,816)	\$3,574	(\$1,932)
Total other changes in net assets	\$664	\$1,712	\$1,748
Change in net assets	(\$2,152)	\$5,286	(\$184)
Net assets beginning of year	\$16,550	\$14,398	\$19,684
Net assets end of year	\$14,398	\$19,684	\$19,500

Source: Management

MESSAGE FROM THE CFO

I am pleased to report that after a period of well documented challenges, the Buck has found its financial footing. This is clearly reflected in our financial statements. As the charts you see on this page illustrate, trend lines are pointing in a positive direction.

During fiscal year 2019, the Institute’s financial results include a strong performance in the receipt of third-party revenues increasing year-over-year and expenses remaining in line with budgets. Revenue is increasing steadily due to the growth of our National Institutes of Health grant portfolio, expansion of our Business Development relationships including Corporate Sponsored Research Agreements and Licensing and Leasing, and our donor engagement programs. We budget conservatively and maintain fiscal discipline throughout the year, allowing us flexibility to pursue both research expansion and hiring opportunities as they arise in our dynamic environment.

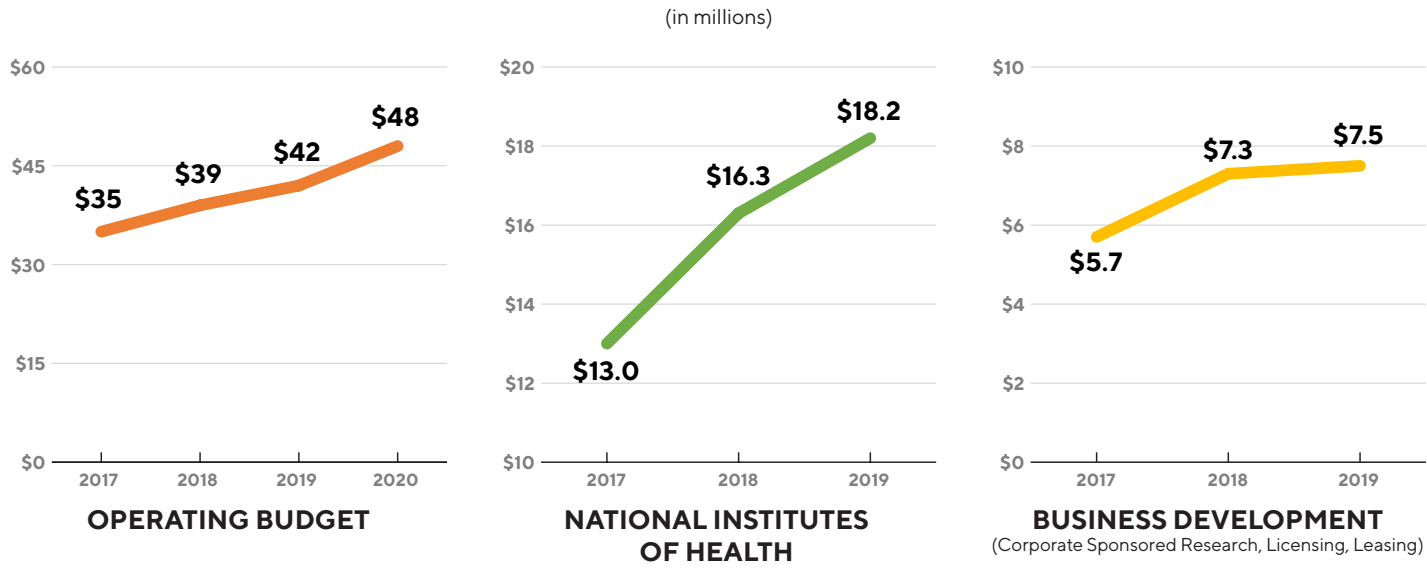
The Buck’s net assets are stable despite the impact of depreciation expense on our property and equipment. Investments and investments held in trust are increasing and are attributable to the receipt of contributions, pledge payments and bequest disbursements. During fiscal year 2019, liabilities decreased as the Buck continued to meet its financial obligations with principal payments on our outstanding tax-exempt revenue bonds and our notes payable to the Buck Trust. Of special note is the elimination of our Legal Settlement Payable during fiscal year 2019.

Along with the Institute’s growth comes an increase in our annual operating budget. We have gone from a \$35 million operating budget in fiscal year 2017 to a \$48 million operating budget in fiscal year 2020. Research expenses are increasing as we invest in our scientific research programs and core technologies. General, Administrative, and Philanthropic expenses are also increasing as we continue to meet the administrative demands of a growing enterprise, ensure that our facilities can accommodate the complex demands of our scientific programs, and provide adequate resources for our philanthropic outreach.



Nancy Derr, CFO

Revenues trending in the right direction



Our audited financial statements together with footnotes and the report of our auditors, PriceWaterhouseCoopers LLP, are available at www.buckinstitute.org/financials.

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