THE SEARCH

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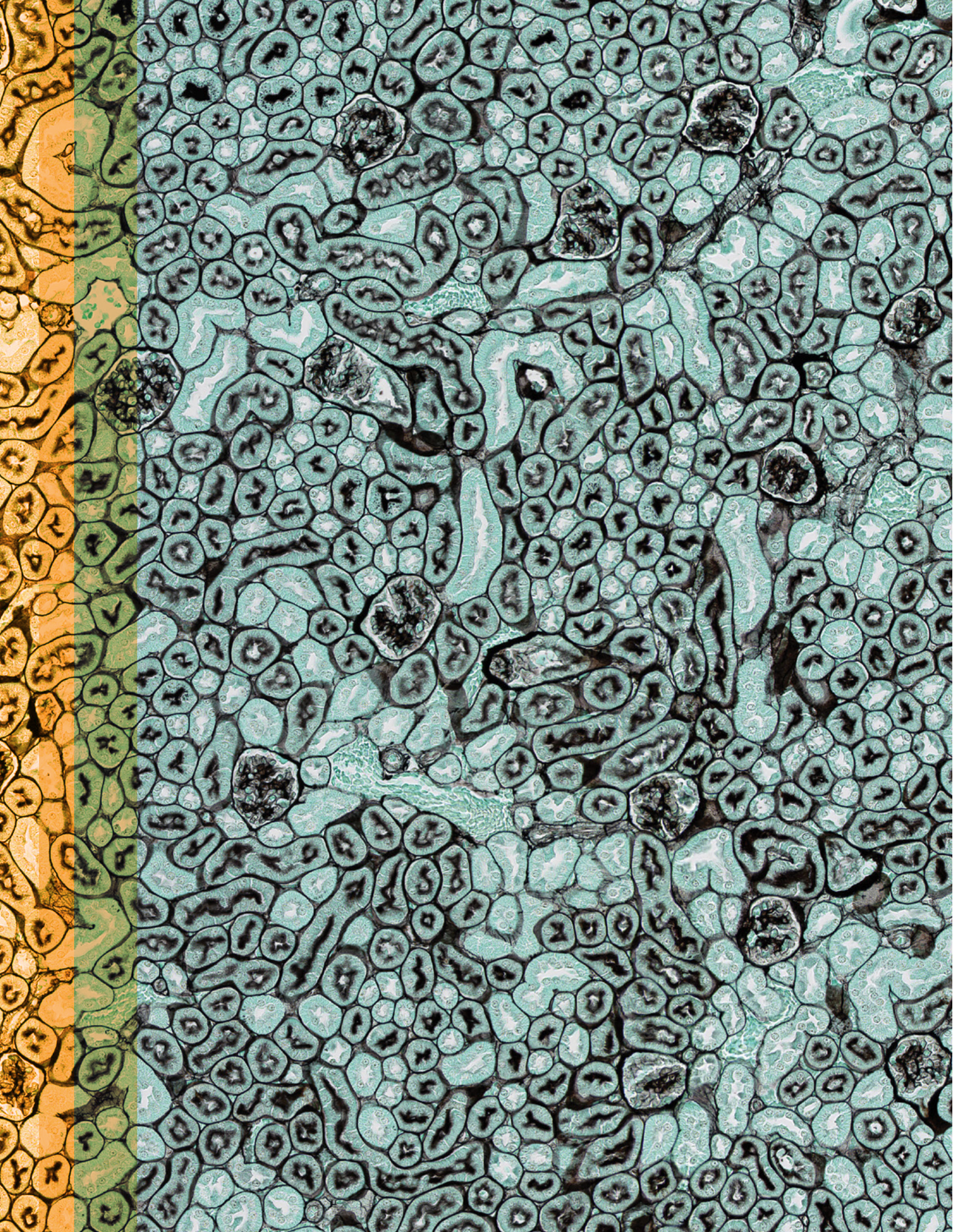

THE SEARCH

A PUBLICATION OF **THE JACKSON LABORATORY**

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Professor George Weinstock, Ph.D., a pioneer in his field, is leading microbial genomics research at The Jackson Laboratory for Genomic Medicine.
Photograph by Marie Chao

LEFT
Histological section of a mouse kidney.
Image by Mark Lessard, Ph.D.

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Mission
We discover precise genomic solutions for disease and empower the global biomedical community in the shared quest to improve human health.

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Sacramento, Calif.

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The Jackson Laboratory
Leading the search for tomorrow's cures

President's message

In October 2014, we celebrated the opening of The Jackson Laboratory for Genomic Medicine in Farmington, Conn. This event marked a pivotal moment in the history of the Laboratory: Built on a foundation created by decades of research in genetics, this new facility will serve as the launching pad for discoveries that will transform the future of medicine and human health.

JAX has now entered a new era — one in which the full potential of genomic science will be realized, not just through scientific advances but also through new, more collaborative approaches in the lab and the clinic. Thus, it's fitting that in this issue of *The Search*, we look back on JAX's history, as well as at current JAX research and other developments that are blazing our path to a great future. The work of George Weinstock and his lab, and that of Ron Korstanje, both profiled here, embodies the creativity and multidisciplinary teamwork that define the future of JAX science.

Just a few weeks after the opening of JAX Genomic Medicine, the Laboratory announced the largest philanthropic gift in its history: an initial $5 million donation from David and Barbara Roux, matched by an additional $5 million in their honor for a total gift of $10 million, that will endow three faculty chairs and establish the Roux Family Center for Genomics and Computational Biology. This endowment gift will enhance our ability to recruit and retain world-leading scientists to our faculty and to support their groundbreaking research. Just as important, the philanthropic leadership and vision it represents will inspire others to rise to new heights in support of our mission.

The Laboratory got more good news in November, when Maine voters overwhelmingly approved a $10 million bond to support a biomedical research facility devoted to genetics and cancer research. While JAX is not specifically named in the proposal, we are confident that we will prevail in the application process and be able to move forward with our plans for a new Center for Biometric Analysis, a state-of-the-art phenotyping facility.

We are building momentum toward a great future for The Jackson Laboratory — and for that, we thank all of JAX's friends and supporters. Your confidence in our mission makes this bright future possible.

Edison T. Liu, M.D.

President and CEO, The Jackson Laboratory

news&notes

JAX, Beth Israel Deaconess enter multi-faceted affiliation

The Laboratory and Beth Israel Deaconess Medical Center (BIDMC) have established a new academic, research and service relationship to advance cancer research and patient care, and accelerate personalized genomic medicine.

A recently signed agreement calls for JAX and the BIDMC Cancer Center to establish a comprehensive relationship in research and medical education as well as in the creation of new diagnostic and therapeutic services that could greatly improve patient care.

"Our new affiliation with JAX will enhance our ability to improve our patients' lives by accelerating the application of genomics to cancer care," says Kevin Tabb, M.D., president and CEO of BIDMC, a patient care, teaching and research affiliate of Harvard Medical School.

Says JAX President and CEO Edison Liu, M.D.: "As an independent biomedical research institute with a focus on genetics and genomics, JAX is in a unique position to partner with healthcare systems that can connect genetic and genomic research to the clinical setting. This affiliation will enable both organizations to accelerate the pace at which research progress can be translated into new treatments and cures."

The affiliation brings together two of the world's most sophisticated mouse model platforms used in genomic cancer research.

The pioneering JAX mouse model PDX (patient-derived xenograft) provides a platform for studying the genomic profiles of individual cancers through molecular diagnostic testing. BIDMC's "Mouse Hospital," developed by BIDMC Cancer Center Director Pier Paolo Pandolfi, M.D., Ph.D., uses genetically altered mice to replicate human cancers and enables investigators to conduct human clinical trials in parallel with animal studies.

Additional collaborative activities expected to take place under the agreement include:

- the creation of new genomics-based training programs that will disseminate knowledge about innovative diagnostics beyond academic medical centers to community-based physicians;
- joint faculty appointments;
- clinical genomics applications, including a state-of-the-art diagnostics platform to analyze patient samples and help guide personalized therapies;
- development of diagnostic reports to help treating physicians use genomic data in patient care, and to access appropriate clinical trials; and
- development of mouse-based approaches to prospectively identify optimal individualized anti-cancer drug regimens.

Historic gift from David, Barbara Roux will advance genomic medicine research

Technology investor and Laboratory Trustee David Roux and his wife, Barbara, have given JAX $10 million to support research and find cures for genetic diseases.

The gift will be used to create the Roux Family Center for Genomics and Computational Biology. This center, to be based at the Laboratory's Maine and Connecticut campuses, will be endowed with three new faculty chair positions and a permanent fund for recruiting expert staff and driving research and discovery. The center will enable scientists to harness the full power of innovative genomic technologies and computational strategies to analyze the human genome, and discover new and better ways of preventing and treating disease.

The Rouxs' initial gift of $5 million — the largest in the Laboratory's 85-year history — will trigger a matching gift in their honor by JAX for a total fund of $10 million.

"At a time when public funding for disease research continues to dwindle, David and Barbara Roux have stepped forward to make a truly inspirational statement about the importance of supporting the future of genomic medicine in the shared quest to improve human health," says Edison Liu, M.D., president and CEO of the Laboratory. "Their gift provides incredibly important leadership in this cause, and we are enormously grateful for their generosity."

"Barbara and I are tremendously excited by the work that The Jackson Laboratory is doing in the area of genomic medicine," says David Roux, co-founder and senior director of Silver Lake, one of the world's leading private-equity firms. "This remarkable research is transforming the world's understanding of disease and the search for personalized and precise cures. We are privileged to help support these efforts."

See a profile of David and Barbara Roux on page 28.

CBIF FUNDS YALE-JAX PROJECT TO DEVELOP NEW MOUSE MODELS FOR CANCERS

Connecticut Innovations' Connecticut Bioscience Innovation Fund (CBIF) has made a $500,000 grant to support a new collaboration between Yale University and JAX scientists to develop humanized mouse models that more accurately represent human responses to cancer and cancer therapies.

JAX Professors Jacques Banchereau, Ph.D., and Karolina Palucka, M.D., Ph.D. — director of immunological sciences and associate director for cancer immunology, respectively — will work with Richard A. Flavell, Ph.D., FRS, chair and professor of immunobiology at the Yale School of Medicine and a Howard Hughes Medical Institute investigator.

JAX and Yale have each developed special, humanized mouse models that can host human cancers and other diseases. These models have provided a valuable new way to carry out preclinical studies assessing novel therapies as well as develop more specific and personalized approaches to treatments.

"This project aims to develop a next-generation humanized mouse model that could revolutionize how research is conducted and how drugs are developed and tested," Flavell says.

"Connecticut is fortunate to have some of the world's leading experts in immunology and the development of new mouse models to understand cancer and other diseases," says Margaret Cartiera, Ph.D., director of bioscience initiatives at Connecticut Innovations, a state-funded organization that invests in high-tech job creation. "We look forward to seeing the results from this new collaboration and the advances in human health it will lead to in the future."

SUCCESSFUL BOND VOTE POSITIONS JAX TO BUILD BIOMETRIC ANALYSIS CENTER

Maine voters in November approved a $10 million state bond that will likely help fund construction of a new Center for Biometric Analysis on the Laboratory's Bar Harbor campus.

The Laboratory will apply to the state for the funding and is considered uniquely qualified because it has the required scientific and technical expertise and is also prepared to contribute $11 million of its own money toward the research center's construction and equipment costs.

"We are pleased and humbled by the support of the people of Maine for our new research facility," says Michael Hyde, JAX's vice president for external affairs and strategic partnerships. "We take our responsibility to Maine very seriously, and we will make you proud."

Using high-powered imaging and analytical devices, scientists at the center would measure in mice the precise biological changes that accompany disease and that predict response to medical interventions. These analyses, coupled with gene sequencing and computational biology techniques, would help pinpoint the genetic roots of disease, contributing to better diagnosis, prevention and treatment of cancers, neurodegenerative diseases such as Alzheimer's and other afflictions in humans.

Plans call for a four-story, 16,000-square-foot facility that becomes the world's most sophisticated biometric analysis center for precisely measuring cholesterol, triglycerides, glucose, blood pressure, body mass and many other biological indicators of health and disease.

DIVERSITY OUTBRED MICE BETTER PREDICT POTENTIAL HUMAN RESPONSES TO CHEMICAL EXPOSURES

A genetically diverse mouse model developed at the Laboratory is able to predict the range of response to chemical exposures that might be observed in human populations, JAX researchers and colleagues report.

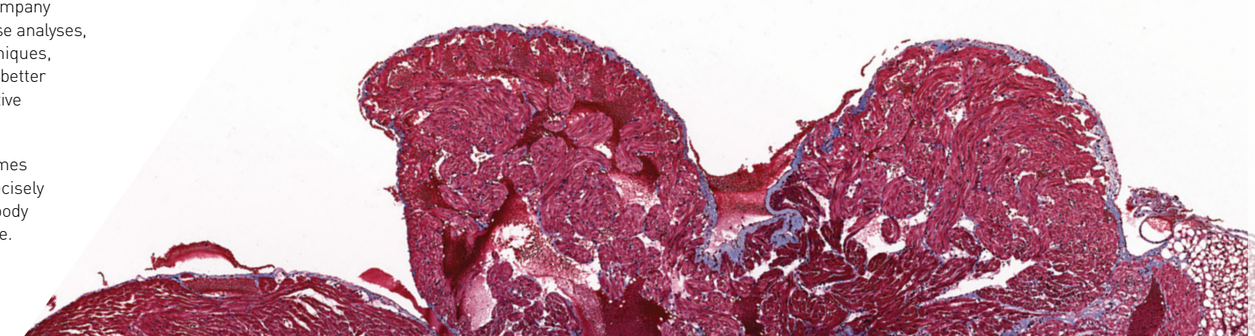
Like humans, each Diversity Outbred (DO) mouse is genetically unique, and the extent of genetic variability among these mice is similar to the genetic variation seen among humans. Using these mice, researchers from the National Toxicology Program of the National Institute of Environmental Health Sciences (NIEHS) were able to identify specific genes or chromosomal regions that make some mice more susceptible, and others more resistant, to the toxic effects of benzene. Benzene is a common air pollutant and human carcinogen found in crude oil, gasoline and cigarette smoke, and naturally produced by wildfires and volcanoes.

The scientists found that each Diversity Outbred (DO) mouse responded to the effects of the chemical exposure differently.

"This is a critical and exciting study for us to be able to demonstrate that the DO mice have a highly variable response to a common environmental toxin," says JAX Professor Gary Churchill, Ph.D., study co-author. "The implications of the study are that humans are also likely to show a wide range of sensitivity, and this suggests that regulators should take individual variation into account when establishing safe exposure guidelines."

Because the researchers knew the genetic makeup of each mouse, they could pinpoint the genetic regions involved in susceptibility or resistance to the chemical exposure, and then look for related regions in human chromosomes.

The research is published in *Environmental Health Perspectives*, the journal of the NIEHS.



JAX RESEARCH TEAM IDENTIFIES NEW MECHANISM FOR MISFOLDED PROTEINS IN HEART DISEASE

A Jackson Laboratory research team has found that the misfolded proteins implicated in several cardiac diseases could be the result not of a mutated gene, but of mistranslations during the "editing" process of protein synthesis.

In 2006 the laboratory of JAX Professor and Howard Hughes Medical Institute Investigator Susan Ackerman, Ph.D., showed that the movement disorders in a mouse model with a mutation called sti (for "sticky," referring to the appearance of the animal's fur) were due to malformed proteins resulting from the incorporation of the wrong amino acids into proteins as they are being produced.

"We know that in certain heart diseases... cardiomyocytes can accumulate malformed proteins."

— **Susan Ackerman, Ph.D.**, JAX faculty

In new research published in the *Proceedings of the National Academy of Sciences*, performed in collaboration with Paul Schimmel, Ph.D., and colleagues of The Scripps Institute, Ackerman and colleagues demonstrate that the same mechanism leads to misfolded proteins and cell death in the heart.

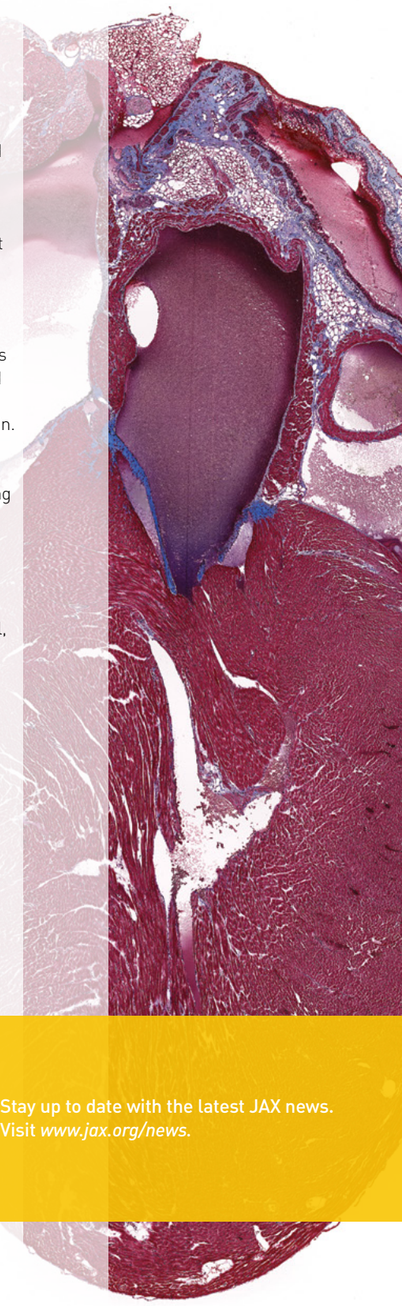
"We now have the second description of mistranslation causing pathology, this time in the heart," Ackerman says. "We know that in certain heart diseases, such as desmin-related cardiomyopathy and systemic amyloidosis, cardiomyocytes can accumulate malformed proteins. This is analogous to the toxic sludge of misfolded proteins that, in neurodegenerative diseases like Huntington's, kills neurons."

To understand the effects of mistranslation, the researchers tinkered with the ability of alanyl-tRNA synthetase, an enzyme involved in protein synthesis, to fix its mistakes. Alanyl-tRNA synthetase is supposed to load the amino acid alanine onto specific transfer RNAs (tRNAs), which then transport the alanine to ribosomes, where it is added to proteins under construction.

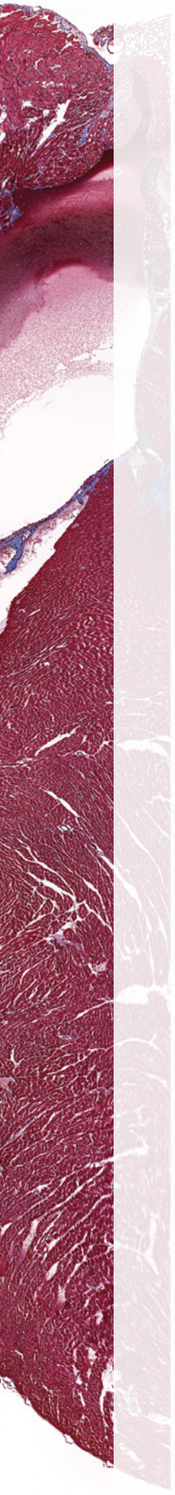
However, on occasion this enzyme puts the wrong amino acid on these tRNAs. When this occurs, the enzyme recognizes the error and removes the amino acid, preventing it from being included at the wrong site in the protein. A severe reduction in this process, called editing, led to early embryonic lethality, suggesting that editing is important in multiple cell types, not just neurons.

"Then we asked, what if we take sticky mutation, which still has some editing potential, and lower the amount of the enzyme by half?" Ackerman says. "And we found that, indeed, this loss of editing activity did have an effect on the heart, leading to the death of cardiomyocytes and affecting the function of the heart."

The results suggest that genetic factors that disrupt the accuracy of translation may contribute to defects of the heart and possibly other tissues, as well as the brain, Ackerman notes.



Stay up to date with the latest JAX news. Visit *www.jax.org/news*.



MAINE CANCER FOUNDATION FUNDS FOUR JAX RESEARCHERS

Four Laboratory scientists will receive grants for their cancer-related research from Maine Cancer Foundation (MCF).

The recipients include Julie Wells, Ph.D., a research scientist, who will receive $50,000 to study how lung cancer spreads and forms tumors in other sites in the body, and Archana Gopalan, Ph.D., a postdoctoral associate, who will receive $50,000 to study how brain cancer tumors contain many types of cells and how this impacts the success of treatment.

Two other awards will go to JAX researchers studying different aspects of leukemia: Assistant Professor Jennifer Trowbridge, Ph.D., whose $50,000 grant will support her studies of how leukemia progresses from a benign form to a lethal form, and Professor Leonard Shultz, Ph.D., who will receive $168,834 to develop a genetically modified mouse that can be used to understand the cellular and molecular changes in leukemia.

To date MCF has awarded more than $1.8 million in research grants to JAX. The Laboratory recognized MCF in July with the JAX Champion Award in recognition of its role as research partner and advocate.

JAX expands faculty

IMMUNOLOGIST, HIV EXPERT DERYA UNUTMAZ, M.D.

Derya Unutmaz, M.D., an immunologist who studies the molecular mechanisms of T cells and their involvement in HIV infection and other chronic inflammatory diseases in humans, has been named a professor at The Jackson Laboratory for Genomic Medicine in Farmington, Conn.

Unutmaz joins JAX from the New York University School of Medicine in Manhattan, where he was professor of microbiology, pathology and medicine.

HIV, the virus that causes AIDS, "is finely adapted to infect and destroy CD4+ T cells," a category of human immune cells, Unutmaz explains. "My research has focused on understanding what HIV 'knows' about the immune system and how HIV infection leads to disease. We are now using the knowledge we acquired from studying HIV to other chronic inflammatory disorders and to understand the aging of the immune system. JAX will be an ideal institution to continue our studies at the genomics level and translate them for clinical use."

His laboratory's discoveries include the role of cytokines (proteins produced by immune cells) in making CD4+ T cells more vulnerable to HIV infection; and how HIV preferentially infects and perturbs human T cell subsets, including NKT, regulatory T (Tregs) and IL-17-secreting (Th17) cells.

The Turkish-born Unutmaz earned his M.D. at Marmara University Medical School in Istanbul. He completed postdoctoral appointments in the immunology department of Novartis in Basel, Switzerland; the Immunobiology Research Institute of Novartis and Chiron Corp. in Siena, Italy; and the Skirball Institute of New York University.

He joined the Vanderbilt University School of Medicine faculty in 1999 as assistant professor of microbiology and immunology, rising to associate professor. In 2006 he moved to the New York University School of Medicine as an associate professor of microbiology, later adding appointments to the departments of medicine and pathology.

The author of 81 research papers, Unutmaz has contributed to seven awarded and pending patents.

ADDICTION RESEARCHER VIVEK KUMAR, PH.D.

Vivek Kumar, Ph.D., a neuroscientist who studies neuronal circuits that regulate addiction, attention deficit and hyperactivity disorder, depression and other behaviors, has joined the Laboratory faculty in Bar Harbor as an assistant professor.

Since 2009 Kumar has been in the department of neuroscience at the University of Texas Southwestern Medical Center in Dallas, first as a postdoctoral fellow in the laboratory of Joseph S. Takahashi, Ph.D., and since 2011 as an instructor. He holds an A.B. in biology from the University of Chicago and earned his Ph.D. at the University of California, San Diego, in the laboratory of Michael G. Rosenfeld, Ph.D. Kumar studies reward behaviors such as addiction using mouse models, applying functional genomics, high-throughput behavioral screening, biochemistry, molecular biology and imaging techniques.

He has already established collaborative relationships with several Laboratory faculty members. Last year he co-authored a paper in *Science* with JAX Professor Gary Churchill, Ph.D., Takahashi and other researchers, establishing that responses to cocaine and methamphetamine differ between two substrains of C57BL/6, or "Black 6," laboratory mice. In that paper, Kumar and colleagues identified Cyfip2 as a gene that regulates cocaine response through control of structural plasticity in the brain.

In other work, using an approach known as forward genetics (observing physiological traits and then determining the genetic sequence responsible for them), Kumar has screened more than 30,000 mice for behavioral deficits, identifying several new mouse models.

Kumar's wife, Neha, has also joined the Laboratory as a senior financial analyst.

DEVELOPMENTAL GENETICIST BASILE TARCHINI, PH.D.

Basile Tarchini, Ph.D., a geneticist who studies the early developmental mechanisms organizing the inner ear in mammals, has joined The Jackson Laboratory research faculty as an assistant professor.

Tarchini, a Swiss citizen, earned his undergraduate degree and Ph.D. at the University of Geneva in the laboratory of Professor Denis Duboule. He moved to Montréal, Canada, for a postdoctoral fellowship at the Institut de Recherches Cliniques de Montréal, where he was first a postdoc and then a research associate in the laboratory of Michel Cayouette, Ph.D.

"Fundamental to our interaction with the world," Tarchini says, "hearing and balance rely on both the proper layout of movement detectors at the surface of hair cells — the stereocilia — and the uniform orientation of the bundles they form across neighboring cells. While deafness is the most common sensory impairment in humans and hair cell damage a leading cause, the molecular machinery imparting and connecting these two levels of planar polarity is still largely unknown."

Last year Tarchini was the first author in a study, published in *Developmental Cell*, showing a previously unknown role in the auditory system for a group of proteins known to control cell division. "We showed that these proteins occupy a specific region at the cell surface to define the exact placement of stereocilia and outline the V-shaped bundle," he explains.

REPRODUCTIVE GENETICIST EWELINA BOLCUN-FILAS, PH.D.

Ewelina Bolcun-Filas, Ph.D., who studies the genes and processes involved in the development of healthy eggs and sperm, has joined The Jackson Laboratory faculty as an assistant professor.

"Many genetic and environmental factors have been linked to reproductive disorders such as infertility, birth defects or premature ovarian failure," Bolcun-Filas says. "The overall goal of my research is to understand the molecular mechanisms controlling the development of healthy gametes — egg and sperm cells — and how misregulation of these mechanisms can lead to reproductive disorders."

The Polish-born Bolcun-Filas earned her M.Sc. in biology/genetics from Jagiellonian University in Krakow, Poland. After completing her Ph.D. in developmental biology from the Georg-August-Universität, Institut für Humangenetik in Göttingen, Germany, she held a postdoctoral fellowship at the MRC Human Genetics Unit in Edinburgh, U.K. She comes to JAX from Cornell University, where she has been a postdoctoral associate and research scientist in the laboratory of Professor John Schimenti, Ph.D. (himself a JAX adjunct faculty member).

"The long history of reproductive biology research, world-renowned specialists and great genetic and genomic resources make JAX an ideal institution to start my independent career," Bolcun-Filas says.

Genomics icon lands at JAX

STORY BY NICOLE DAVIS
PHOTOGRAPHY BY MARIE CHAO
& JENNIFER TORRANCE

George Weinstock, a world expert in all things genomic, builds a new research program to apply his deep knowledge of genomes and microbes to human health.

> *"I never met a genome I didn't like,"*

George Weinstock, Ph.D., tells me, chuckling, as we talk one afternoon in Boston. A superstar in the field of genomics, Weinstock joined The Jackson Laboratory for Genomic Medicine in 2013, bringing a trove of knowledge and experience to the organization and to his new role as professor and associate director of microbial genomics.

His career spans several fundamental revolutions in biomedical science, from the first experiments to stitch together or "recombine" DNA from multiple sources (known as recombinant DNA technology), to the development of methods for decoding or "sequencing" DNA, to the emergence of genomics as a formal scientific discipline. Weinstock has played varied roles in those scientific transformations: student, teacher, enthusiast, leader and, of course, pioneer.

Charles Lee, Ph.D., professor and scientific director of JAX Genomic Medicine, calls him "a legend in the field of genomics who passionately devotes himself every day to understanding the biological impact of each DNA sequence variant obtained, on human biology and pathology."

At this moment in our interview, though, I ask Weinstock something decidedly less weighty: Does he have a favorite genome?

Just a glimpse of his genomic scorecard reveals a menagerie of organisms whose genomes he has helped lay bare: *Treponema pallidum*, the bacterium that causes syphilis, as well as countless other microbes; the rodent kings of the laboratory — rat and mouse; the geneticist's darling, the fruit fly Drosophila melanogaster, and its insect cousin, the honeybee; and the sea urchin, a model organism beloved for its photogenic chromosomes.

But let us not overlook the genome that catapulted genomics into the limelight — our own. Weinstock was a leader of the Human Genome Project, an international effort to sequence the complete genetic code contained in our cells. Launched in 1990 and lasting just over a decade, it spurred a new generation of discoveries fueled by genome-based knowledge.

Those include so-called "personal" genome projects that reveal the genetic blueprint of a single person, such as Dr. James Watson, the legendary co-discoverer of the double helical structure of DNA. Weinstock led the team that sequenced Watson's genome in 2007.

And entirely new fields have been born, such as metagenomics, the study of whole communities of organisms through the sequencing of their combined genetic material. This approach has opened the floodgates on studies of microbial ecosystems, particularly our own — the human microbiome. A diverse world of microbes, including viruses, bacteria and fungi, resides in and on our bodies. Some of these passengers summon health, while others inflict disease. Weinstock has been at the forefront of this work, too, revealing the genomic underpinnings that distinguish microbial friend from foe, and, more recently, applying that knowledge to real-life medical problems.

With such a wide-ranging view of the genomic universe, spanning the DNA of organisms both great and small, it is perhaps understandable that Weinstock struggles to name a favorite genome. "They all have their own personalities," he says. "They are all great."

FROM THE BEGINNING

A giant, a legend, a pioneer — all are words used by others to describe Weinstock and his contributions to genomics.

Indeed, the arc of his career knits together a string of remarkable accomplishments. It also mirrors some of the seminal moments in the last few decades of biological research — tracing the birth and rise of genomics.

"George Weinstock has been one of the leaders in genomics since the beginning of the Human Genome Project," says David Botstein, Ph.D., the Anthony B. Evnin Professor of Genomics at Princeton University, who was Weinstock's graduate adviser at the Massachusetts Institute of Technology (MIT). "I know nobody who has a broader or deeper command of all the elements of genomics, from nucleic acid biochemistry to computational analysis."

Weinstock discusses latest findings with his wife and research partner, Erica Sodergren, Ph.D.

To see a related video clip and photo gallery of George Weinstock, visit *www.jax.org/thesearch/weinstock*.

Although the field of genomics is relatively young by science's standards, Weinstock has devoted his entire career to its pursuit, basically doing "genomic-y" things before there even was a word to describe the application of large-scale, systems-level approaches to biological problems.

"It's basically, if you think about it, what I've been doing ever since [my career began]. It's just that the technology has become more and more advanced," he says.

Perhaps it is not surprising, then, that his path in science — and in life — begins with the story of another remarkable era in science.

BIG SCIENCE: A FAMILY AFFAIR

Weinstock's parents met at the Los Alamos National Laboratory in New Mexico while working on the Manhattan Project, which produced the first atomic bombs during World War II. His father was a physical chemist and his mother a toxicologist. Although their work at Los Alamos lasted only a few years, the experience was transformative — for them and for their future son.

"There were lots of stories about all of the amazing people who were there and the things that were done. So, I was exposed to that," Weinstock says. Nevertheless, science was not a calling he initially embraced. "I was growing up. I was rebellious. I didn't necessarily want to be a scientist."

Despite the rebellion of his youth, Weinstock unearthed a deeply rooted interest in science while an undergraduate at the University of Michigan. A talented chemistry teacher helped ignite his passion for science, and he decided to major in chemistry, then physics and ultimately, biophysics.

Although he didn't follow in his father's footsteps scientifically, Weinstock credits his father with kindling his own passion for big, transformative science. "My father always had some sense that it's good to pick something really important to work on, not just something incremental."

In 1970, Weinstock left for Cambridge, Mass., to pursue a graduate degree at MIT.

It was a formative time, not just in his career, but also in molecular biology and genetics. Several seminal discoveries were made as the fields bloomed, many by Weinstock's MIT colleagues, and even himself.

He also met his future wife and scientific colleague, Erica Sodergren, Ph.D., then a fellow MIT graduate student. The couple married in 1974, and later headed west to Stanford University for their postdoctoral training. Eventually, they landed in Texas, where Weinstock became an associate professor at the University of Texas at Houston.

Although the couple often worked together as colleagues, it was usually at a distance. "She waited 20 years before working in my lab," Weinstock says.

Sodergren hesitated because she worried deeply about disrupting the dynamics of their family and of Weinstock's lab. "I had seen other husbands and wives working together, and there could be heightened friction," she says. "They had their home life together and they had their scientific life together and it was like there was no separation."

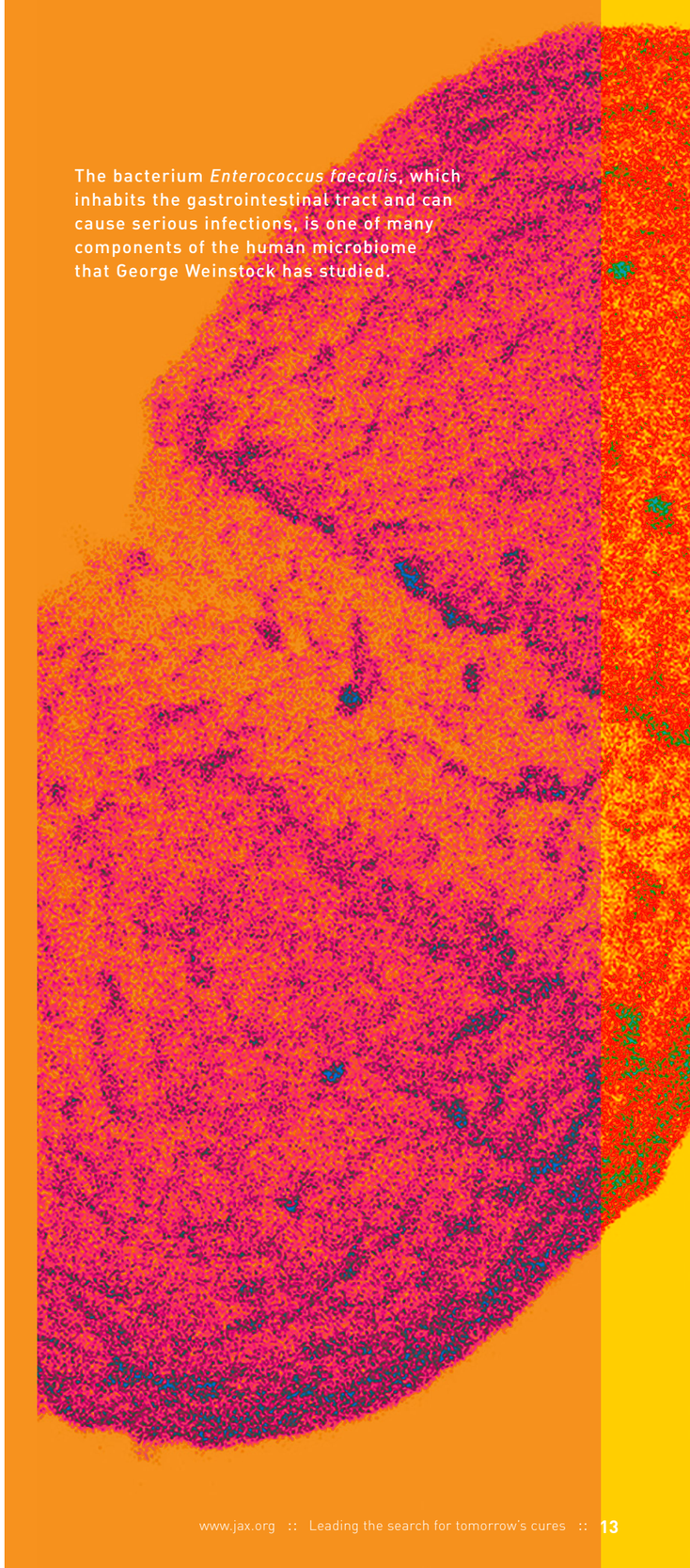
Ultimately, her concerns proved unwarranted — the couple has worked together in the same lab, harmoniously, for some 30 years.

THE GENOME GUY

Weinstock cut his teeth on sequencing genomes long before the approach was mainstream. He and a University of Texas colleague were awarded a National Institutes of Health (NIH) grant to sequence *Treponema pallidum*, the bacterium that causes syphilis. The grant was Weinstock's first to sequence a genome.

And while he didn't have to set up a large genome center to sequence that microbe, he worked for one several years later. In 1999, he joined the Human Genome Sequencing Center (HGSC) at Baylor College of Medicine, also in Houston, where he co-directed the HGSC and served as professor of molecular and human genetics. Sodergren joined him in his new role, helping to set up the genome center and boost its efforts around the Human Genome Project.

Baylor's HGSC was one of the five major centers to contribute to the Human Genome Project, working on the sequences for human chromosomes 3, 12 and X, and made many other important scientific contributions under Weinstock's leadership.



The bacterium *Enterococcus faecalis*, which inhabits the gastrointestinal tract and can cause serious infections, is one of many components of the human microbiome that George Weinstock has studied.

It was an exhilarating time for him, his wife and many others throughout the scientific community. "There would be one point where we would have 10 or 15 of these different projects, where you are working with whole communities of hundreds of scientists to sequence 'their' genome, and then you do some analysis and turn out a transformative paper for the whole field," says Weinstock.

As Baylor's genome center and others cranked through various genome projects, a number of leading scientists, including Weinstock, began to push for something new — to tackle an unexplored frontier. One of the most intriguing areas was the human microbiome, sometimes called the second human genome.

In some ways, it was a daunting prospect. The number and diversity of microbes that call the human body home are staggering. As Weinstock recently told a crowd at the grand opening symposium for the new campus of JAX Genomic Medicine in Farmington, Conn., "There are more bacteria in your mouth than there are people on Earth."

"You get through some ceilings and you are suddenly in a new realm of being able to see things. That's what pulls us forward, and that trip is not over yet."

— George Weinstock, Ph.D.

But such microbial exploration was indeed feasible, enabled by dramatic advances in the technologies for decoding DNA. These so-called "next-generation" methods, lower in cost and higher in throughput than earlier versions, made it possible to sequence not just one species of bacteria, but whole communities of them — with hundreds, even thousands of different species — all at once.

With the backing of the NIH, the Human Microbiome Project was launched in 2007. The initial five-year effort culminated with a flurry of scientific papers that offered a first glimpse of the types and diversity of microbes associated with the healthy human body. The basis for this work was a vast collection of samples from nearly 250 healthy volunteers, drawn from as many as 18 different body sites across five major anatomical areas, including the airwas, skin, mouth, gut and vagina.

Now, in the project's second phase, researchers across the country, including Weinstock, are extending these findings by probing the microbiome in various states of health and disease, such as pregnancy, type 2 diabetes and inflammatory bowel disease.

Weinstock and his lab members share a light moment.

A LIFELONG COLLEAGUE

Working so closely with Weinstock over many years, Sodergren has a unique perspective on his life's work. One of his lesser-known gifts, she notes, is teaching.

"He's taught undergraduates, pre-med students, graduate students in research and medical students. And he's been very successful in all of these approaches," she says. "That is a really impressive talent that many people don't have."

She also highlights his ability to bridge disciplines.

"I see him as a Renaissance thinker," says Sodergren. "Many scientists make the choice to really channel their focus and they don't go outside their area of expertise very much. So now they have to form these consortiums where they can bring in a lot of different expertise to address complex problems.

"But George has always done consortia-type work; he is always collaborating with people with broad backgrounds. That is a really powerful scientist to have as your colleague."

THIRD ACT

After spending nearly a decade at Baylor and its HGSC, Weinstock and Sodergren moved in 2008 to another prestigious genome center at Washington University in St. Louis. He became associate director of The Genome Institute and pursued his pioneering work on the microbiome as well as countless other projects. As self-professed "genome center people," the Weinstocks had little inclination to leave.

Then he stumbled across the Laboratory's plans for expansion in Connecticut and its bold new vision for genomic medicine. He knew JAX President and CEO Edison Liu as well as many others at JAX. "I felt I had to take a look at this, even though we weren't looking to move because, boy, it would just be a perfect place to finish up."

Now Weinstock brims with enthusiasm for what lies ahead. He plans to extend his foundational research on the microbiome, advancing both its basic and clinical applications. He is also working hand-in-hand with physicians to translate next-generation sequencing into clinical use. That includes forging collaborations across the Connecticut medical community, including the University of Connecticut Health Center, Hartford Hospital and the Connecticut Children's Medical Center.

As just one example of his latest research, Weinstock and his colleagues are using DNA sequencing to analyze stool samples from newborns in the neonatal intensive care unit. These infants are supremely vulnerable to infection, and sequencing can provide a window on which patients are likely to develop a viral or bacterial illness — sometimes days before it emerges clinically.

Given his impressive reputation, it is not at all surprising that Weinstock is pushing the envelope of genomics and technology in this way. No one knows precisely where things will go from here, but it is certain to be a remarkable journey.

"You get through some ceilings and you are suddenly in a new realm of being able to see things," Weinstock says. "That's what pulls us forward, and that trip is not over yet."

Nicole Davis, Ph.D., is a freelance writer and communications consultant specializing in biomedicine and biotechnology. She has worked as a science communications professional for nearly a decade and earned her Ph.D. studying genetics at Harvard University.

DISCOVERY

STORY BY MURIEL TRASK DAVISSON, PH.D.

THE FOUNDING

The Jackson Laboratory was founded in 1929 in Bar Harbor, Maine, by Clarence Cook ("C.C.") Little. Dr. Little was educated at Harvard, where he did genetics research using laboratory mice with Dr. William Ernest Castle at the Bussey Institute. Dr. Castle might be seen as the father of mouse genetics, as the Bussey was the source of most early mouse genetic researchers, including Dr. Little and 17 other Jackson Laboratory scientists.

Convinced that genetically defined mice would be key to understanding cancer, while at the Bussey Dr. Little began developing the first inbred mouse strain, called DBA (for its coat color, dilute brown non-agouti). After receiving his D.Sc. in 1914, Little worked at Harvard and at Cold Spring Harbor Laboratory, N.Y., where he began developing the now famous C57BL inbred strain, commonly called "black 6" and today the most commonly used mouse in global biomedical research. He became president of the University of Maine in 1922, and three years later moved to the presidency of the University of Michigan at Ann Arbor, where he remained until 1929, when he resigned to establish The Jackson Laboratory. A more detailed account of his career and the early years of mouse genetics may be found in the book *Making Mice* by Karen A. Rader, Ph.D.

While in Michigan Dr. Little continued his research on cancer with his genetically defined strains of mice and connected with Michigan businessmen who would provide the funds for establishing the Laboratory. They may have become interested in his research from talks he gave to the summer community on Mount Desert Island while leading biology programs from the University of Maine in 1924 and 1925.

Roscoe B. Jackson, head of the Hudson Motor Car Co., and his brother-in-law Richard Webber, head of the J. L. Hudson Department Stores, were already partially funding Little's research in Michigan. Land for the Laboratory's Bar Harbor campus was donated by George B. Dorr, who was instrumental

Muriel Davisson is a seventh-generation resident of Mount Desert Island, Maine, and the only MDI native so far to serve on the Laboratory's research faculty. She earned an A.B. cum laude in zoology from Mount Holyoke College in 1963 and a Ph.D. in genetics from Pennsylvania State University in 1969. She was a college summer student at JAX in 1962, working with Drs. Paul Sawin and Richard Fox, and a research assistant from 1963 to 1964. She returned as a research associate in 1971 and retired as professor emeritus in 2012. She has been an eyewitness to more than half of JAX's 85-year history. Here, from her own unique perspective, are milestones of the Laboratory's first eight decades of genetics research, discovery and medical contributions. Look for a second installment from Muriel in the next edition of The Search, *highlighting the achievements of JAX faculty.*

Background design adapted from:
Payson, Meg Brown. *Shimmersea: 4 triptych.* The Jackson Laboratory for Genomic Medicine, Farmington, Conn. 2014. By eo art lab. Sublimated metal print.

in establishing Acadia National Park. Funding for construction of a modest laboratory building and the first five years of operation was provided by Jackson, and Edsel Ford, of Ford Motor Co. When Jackson died suddenly while traveling in Europe in March 1929, the Laboratory was named for him and remained The Roscoe B. Jackson Memorial Laboratory until 1963 when it was renamed The Jackson Laboratory, or JAX.

Dr. Little's philosophy in founding JAX was that good research would come from a small group of scientists in an independent research environment with the freedom to follow their creative ideas, interact easily with colleagues and use genetically defined mice as research tools. Because of his conviction of the power of genetically defined mice to understand cancer, the subsequent emphasis on genetic research at JAX and the genetically defined mouse strains developed here, JAX has always been a center for mouse genetics and a mecca for mouse geneticists.

THE EARLY YEARS

The fledgling Laboratory barely survived its first full year of operation following the stock market crash of 1929. As funds tightened, the original staff of 15 pulled together to conserve resources. The research staff included two brothers from Maine who had been Dr. Little's students. To feed the staff, Dr. Joseph Murray provided vegetables from his family farm in Hampden, and Dr. William Murray led fishing expeditions. These difficult times established the Laboratory's long tradition of cooperation and sharing.

Several important firsts occurred during JAX's initial decade. In 1933 the entire staff published a paper on the maternal transmission of mammary tumors in mice, followed by co-author Dr. John Bittner's paper identifying an agent transmitted in milk, later identified as mammary tumor virus. This work led to the entire field of study on how cancers are initiated by oncogenes in mammalian cells.

Also in 1933, JAX began selling mice from its inbred strains. The distribution of mice not only formalized the sharing of JAX mouse resources with other scientists, but also became a source of revenue for research and mouse breeding. In 1938 JAX received the first grant awarded by the newly established National Cancer Institute (NCI) at the National Institutes of Health (NIH). In 1941 JAX staff published the first book on mouse genetics and biology, *Biology of the Laboratory Mouse*, which became the "Bible" for researchers using mice as a research tool. Also in 1941 Dr. George Snell initiated and edited *Mouse Genetic News*, issued by the Laboratory and containing the original mouse genetic nomenclature guidelines, lists of inbred and mutant mouse strains, and laboratories with their mouse stocks. This newsletter became the predecessor of *Mouse News Letter* in 1949 through which JAX scientists shared pre-publication research data and information on mouse strains for most of the Laboratory's first 50 years.

In 1947 JAX suffered a literal trial by fire. During the October 1947 Bar Harbor fire, which burned much of the northern and eastern side of Mount Desert Island, JAX was destroyed, including most of its mouse strains. (A few strains survived at Hamilton Station, an outpost in nearby Salisbury Cove.)

Financial and moral support flowed in swiftly after the fire, affirming the importance of JAX to basic biomedical researchers worldwide. A total of $483,000 was provided by the NCI, the American Cancer Society, the Maine Cancer Society and the Damon Runyan Foundation, including $123,000 from the Jackson and Webber families. The Ladies Auxiliary of Veterans of Foreign Wars provided support for a new library, beginning a long-standing association between the organization and JAX. Equally important, researchers returned breeding pairs of strains of mice they had obtained from JAX, and all but one of the pre-fire strains were re-established.

The spirit of surviving the Great Depression years probably helped Dr. Little and his staff face the aftermath of the '47 fire. He is quoted as saying, as he stood looking over the devastated Laboratory site, "Now at least we can see the ocean."

The '47 fire had many positive aftereffects. The scientific community recognized the Laboratory's importance to basic biomedical research and mouse genetic resources. The original Laboratory building was replaced with a better, more secure building. In the early 1950s an off-campus Foundation Stocks of Inbred Strains was established at JAX's Highseas facility nearby. And finally, rustic, wooden buildings were built around the quadrangle just south of the main research building to replace the tents in which summer students had lived.

Although mice have always been the primary model organism at JAX, it should be noted that several other mammalian species have also had cameo appearances. Drs. Paul Sawin and Richard Fox did research using rabbits at Hamilton Station, and Drs. Paul Scott and John Fuller carried out behavioral research with dogs there. Deer mice, rats and hamsters all had brief tenures at JAX. Even axolotls, a type of salamander, lived on campus during Dr. Richmond Prehn's tenure as director.

MILESTONES IN THE MODERN AGE

In 1956 Dr. Little retired and Dr. Earl L. Green became JAX's second director. In 1958 the Morrell family donated land on the southern boundary where a production facility was built to enable expansion of the mouse-distribution program. The juxtaposition of large production colonies and strain inbreeding with genetic researchers generated increasing numbers of spontaneous-mutation mice, and in 1959 the first formal funding for a mouse models program was obtained when Drs. Earl and Margaret Green were awarded a grant by the National Science Foundation (NSF) to support the Mouse Mutant Stocks Center.

Donation by the Morris/Hawkes estate of the Highseas summer "cottage" in 1951 enabled JAX to establish a precollege Summer Student Program to complement its college program. The first JAX/Johns Hopkins Short Course on Medical and Experimental Mammalian Genetics was held in the summer of 1960, co-directed by JAX's Dr. John Fuller and Dr. Victor McKusick of Johns Hopkins.

When I joined JAX in 1971 as a research associate in Dr. Thomas Roderick's laboratory, it was an exciting time in mouse genetics. Technology for visually identifying

individual mouse chromosomes had just been developed, whereas previously only clusters of linked genes, called linkage groups, had been identified. Now these linkage groups were rapidly assigned to the physical chromosomes. Polymorphic biochemical markers had been identified in the 1960s and were being exploited to expand the genetic map of the mouse, and rapidly map genes and new spontaneous mutations to chromosomes. Perhaps most exciting was the discovery of extensive genetic conservation between the human and mouse genomes. Dr. Roderick and I joined the Comparative Mapping Committee of the Human Gene Mapping Workshops in 1977 and remained members or chairpersons until these workshops ceased in the mid 1990s.

The 1980s saw the beginnings of JAX's lead role in mouse bioinformatics. Having collected and published mouse genetic information since the 1950s, Margaret Green in 1981 published a seminal and comprehensive book with descriptions of mouse genes and mutations, strain information, a map of the mouse genome and the genetic mapping data that she used to create it. Later in this decade databases and analysis programs initiated by Drs. Roderick, Janan Eppig, Joseph Nadeau and me coalesced to form the predecessor of Mouse Genome Database, which grew into Mouse Genome Informatics and is still the world's single most comprehensive database on mouse genomics, attracting millions of visits each year.

In 1989 JAX faced yet another trial by fire, when the production facility was destroyed by a blaze that started in a mouse room being renovated by an outside contractor. After hearing a loud explosion, we stood at our windows in the research building watching in disbelief as a large column of black smoke and flames grew. Many of us rushed to the site and rescued boxes of mice from some of the breeding rooms in a "bucket brigade" until firemen refused us entry for our own safety. A few geneticists helped triage which surviving pups would be fostered to get the production strains up and breeding again as quickly as possible. True to the Laboratory's tradition of cooperating and sharing, JAX researchers provided foster dams from their own colonies and assumed responsibility for providing resources to the worldwide research community.

In the fire's aftermath, financial support poured in from around the world, including a large monetary gift sent by Japanese colleagues. Dr. Ken Paigen became the next JAX director six months earlier than planned. Called when he was about to board a plane back to California from Maine, he returned to Bar Harbor and took charge of the Laboratory's recovery. Later Ken and I flew to Washington, D.C., and met with Dr. Judith Vaitukaitus, director of National Center for Research Resources at the NIH, to make the case for rebuilding the production facility because of JAX's critical role in providing resources for biomedical research. The NIH later awarded JAX two grants totaling $18.2 million for mouse facility construction. The outpouring of support reaffirmed how critical JAX was to the biomedical research community.

In the 16 years following the fire and rebuilding, research capacity was expanded by the addition of the Snell research wing in 1989, the north research wing in 1993 and the east research wing in 2006. In 2000 the Genetic Resources wing was built to consolidate resource programs — cryopreservation, genetic resource science, importation — and to provide space for large-scale projects.

The 21st century began the era of large-scale science, programs involving many scientists. Between 2000 and 2006, JAX scientists obtained funding for four such programs — a center to develop mouse models of neurological diseases; a center for new models of heart, lung, blood and sleep disorders; a Shock Center grant to expand studies on aging; and a genome dynamics center to study systems biology.

In the last two decades JAX has expanded beyond the Bar Harbor campus. A breeding facility at the University of California at Davis gave JAX a West Coast presence, providing space to expand contract breeding and to breed commonly used strains, while also enabling shorter shipping distances and times. Moving to a larger facility in West Sacramento, scientists at this campus began to provide contract research support to researchers at pharmaceutical and biotech companies, as well as universities, by helping with experimental design, doing the experiments (e.g., drug dosing and results assessment) and providing space for breeding mice.

In 2011 The Jackson Laboratory for Genomic Medicine was born when Connecticut approved a bond to bring JAX to its medical school campus in Farmington. The genome center, formally dedicated Oct. 7, 2014, will provide state-of-the-art genomic sequencing and analysis, giving JAX a much more direct connection to clinical research and human health.

When I joined JAX in 1971 it had only the Bar Harbor campus and about 350 employees. Now in 2015 JAX has more than 1,600 employees on campuses in Maine, California and Connecticut.

THE FUTURE

A revolution in science, computation and engineering has radically increased the speed and affordability of unlocking each person's unique genetic code, or genome, opening a powerful new realm of personalized medicine. Under the leadership of Dr. Edison Liu, who became president and CEO in 2012, JAX is accelerating its research in genomic-based personalized medicine. The Jackson Laboratory for Genomic Medicine's human genomics research and JAX's traditional research in mouse genetics together are helping us to better understand disease and to bring precise genomic solutions to physicians and their patients.

JAX is already making advances in personalized medicine for cancer. A strain of mice developed by JAX's Dr. Leonard Shultz can be implanted with patient tumor tissues to test the efficacy and safety of anti-cancer drugs. This allows JAX to provide a "virtuous loop" of discovery — developing and testing new therapies by working from human to mouse to human, with ever-greater precision. A collaborative breast cancer study in Maine between JAX and the Maine Cancer Initiative is developing "avatars" — mouse surrogates for individual human patients —so alternative drug therapies can be tested while the patients are undergoing initial standard treatment.

By working along the whole continuum of the research spectrum, from mouse genetics to human genomics, and from bench to bedside, JAX will create precise, personalized treatments and cures whose potential impact is nothing less than life-changing.

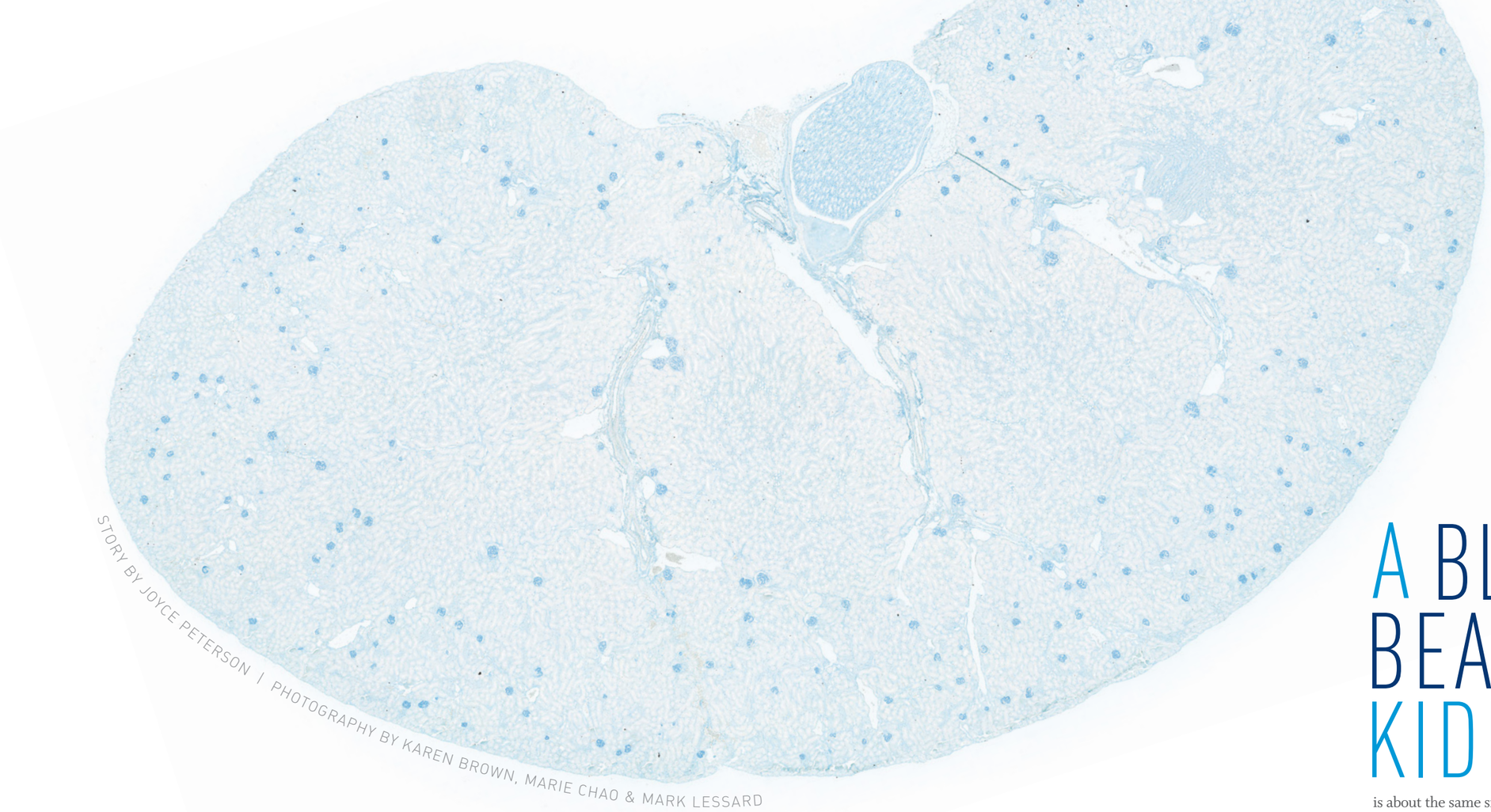


Image of a mouse kidney from Ron Korstanje's research

STORY BY JOYCE PETERSON | PHOTOGRAPHY BY KAREN BROWN, MARIE CHAO & MARK LESSARD

BEARING DOWN ON KIDNEY DISEASE

A BLACK BEAR'S KIDNEY

is about the same size as a human's, even though the average black bear is about twice the size of the average human. But that's where the similarities end.

The kidney of the American black bear (Ursus americanus) is a conglomeration of marble-size spheres, unlike the smooth, uniform-looking human kidney. And the bear kidney has a neat trick that the human version can't match.

"Black bears go into hibernation in the fall with healthy kidneys," explains Jackson Laboratory Assistant Professor Ron Korstanje, Ph.D., contemplating a bear kidney floating in a glass jar on his office desk in Bar Harbor, Maine. "They don't urinate during hibernation, and by the time spring arrives, their kidneys are damaged and have lost most of their function."

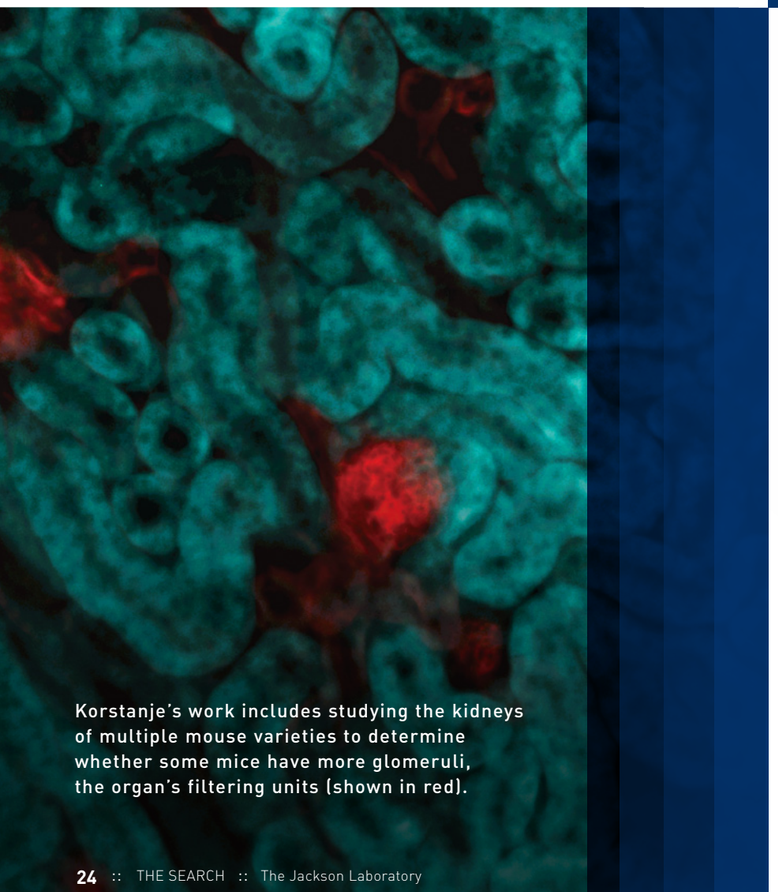
Yet, intriguingly, the bears' kidneys appear to regenerate themselves back to normal function during the spring and summer. "How does that happen?" Korstanje asks. "And if we figure that out, can we come up with treatments that can prevent or reverse kidney damage?"

The Korstanje lab focuses on the genetics of age-related kidney disease — kidney function naturally deteriorates with age. Combine the aging of the huge baby boom population cohort and the steep increase in people with type 2 diabetes, and the nation faces a rapid and costly increase in people with kidney disease and impaired renal function. It is estimated that 20 million Americans have chronic kidney disease, accounting for more than $42 billion a year, almost a quarter of the Medicare budget.

When patients lose more than 85 percent of kidney function, they must undergo dialysis treatments to remove waste and excess water, maintain proper levels of chemicals including potassium and sodium, and control blood pressure. The most common treatment is hemodialysis, in which a patient's bloodstream is connected to a machine by a catheter or fistula. It's a time-consuming and often uncomfortable process.

"Patients in the early stage of kidney disease," Korstanje notes, "when treatment would be most effective, typically don't have any symptoms. And by the time disease symptoms appear, irreversible damage to the kidneys has likely already occurred. So, finding a way to diagnose patients before this damage occurs would significantly improve treatment options."

The Dutch-born Korstanje came to The Jackson Laboratory as a postdoctoral associate in 2001 in the laboratory of Professor Beverly Paigen, Ph.D. Korstanje's work earned him the notice of colleagues at the University of Groningen in the Netherlands, and he was recruited "back home" in 2004, as a research associate in the medical biology division to study nephrology. Within two years, Korstanje advanced to the rank of assistant professor. But he returned to JAX in 2007 as a research scientist in Paigen's laboratory, and was promoted to assistant professor in 2013.



Korstanje's work includes studying the kidneys of multiple mouse varieties to determine whether some mice have more glomeruli, the organ's filtering units (shown in red).

If Korstanje looks healthy and athletic, that's because he is. He's a familiar figure running on the carriage roads of Acadia National Park, and his office is papered with race numbers from the many marathons and "Tough Mudder" events he has run.

Korstanje's lab has investigated the genes that are associated with kidney disease in mice, with the aim of determining genetic variations that might make patients more susceptible to kidney disease. To date his lab has identified more than 30 relevant genes in the mouse. Determining the function of each of those genes would take many years of research, but a shortcut solution was just eight miles from The Jackson Laboratory along Route 3, past the town of Bar Harbor and along the rocky, scenic coast of Mount Desert Island.

At the Mount Desert Island Biological Laboratory (MDIBL), Hermann Haller, M.D., and Mario Schiffer, M.D., visiting faculty from Hannover Medical School in Germany, study zebrafish to identify genes that could be involved in kidney disease. They are focusing on four of the genes Korstanje identified in mice, those that appear to have the strongest influence on kidney disease susceptibility.

Zebrafish (*Danio rerio*), freshwater fish that are related to minnows, are small and pretty, with sporty blue and gold racing stripes along their sides and fins. But the MDIBL fish are especially dazzling: the researchers have introduced fluorescent proteins into zebrafish larvae, and under ultraviolet light they emit a bright green glow. The technique enables researchers to easily examine the zebrafish's two nephrons, the basic filtering structures that are also found in the kidneys of mammals (including mice, humans and black bears).

MDIBL Director Kevin Strange, Ph.D., says, "By utilizing this combined mouse-zebrafish approach, what would have taken several years and cost millions of dollars in the mouse alone was accomplished in less than a year and for less than $10,000 using zebrafish."

The JAX and MDIBL researchers have joined forces with clinicians at the Maine Medical Center in Scarborough, Maine, to build a statewide research collaboration known as ReMAINE.

"WE CAN LEARN A LOT FROM OTHER SPECIES AND HOW THEY DEAL WITH CHALLENGES TO KIDNEYS."

— Ron Korstanje, Ph.D.

"Now we can begin to look for these genes in the patient population," Strange says, "and determine which ones are indicators of early kidney disease. If we're successful, not only will there be the potential for improved quality of life, but also for a significant reduction in the health care costs associated with treating patients with chronic kidney disease."

To see a video clip and a photo gallery of Ron Korstanje, visit *www.jax.org/thesearch/korstanje.*

Back at The Jackson Laboratory, Korstanje has received a special delivery: a beat-up cardboard box marked "Bear Kit." "We developed a small collection kit — containing a vial of fixative, a vial of buffer, forceps, an instruction sheet and a data sheet — and had them distributed to spring bear hunters," he says. "We expected to get maybe a dozen kits back and we've received about 40 samples, which also include some basic information from the hunters about the bears such as gender and approximate weight and age."

Gary Striker, Ph.D., a professor of nephrology at Mount Sinai Hospital in New York, N.Y., and an expert renal pathologist, examines and scores the samples. "This will allow us to establish a rough timeline for kidney recovery and some estimation on the impact of age and sex," Korstanje says.

The JAX researchers collaborate with Rita Seger, M.D., Ph.D., of the University of Maine (UMaine's mascot: the black bear), who studies bone and kidney metabolism of hibernating bears. Seger's team has provided liver samples from a bear, from which the Korstanje lab will extract DNA and ultimately assemble the world's first complete black bear genome.

Then, to see which genes are expressed at the various seasons of the black bear's year, the Korstanje lab will examine RNA samples taken from bear kidneys in the first weeks after hibernation, others taken at the point when regeneration appears to begin, and still others taken before fall hibernation.

He says that if his lab can identify black bear genes that have higher expression during the kidney regeneration process, they can go back to their mouse models, look at what happens to these genes after kidney damage, "and see if we can alter this process when we make the expression of these genes more 'bear-like,'" with the ultimate goal of identifying potential drug targets for human kidney patients.

Black bears' kidneys may be unique as far as land animals go, but it turns out that the kidneys of marine mammals — seals, porpoises and whales — are very similar in structure, Korstanje says. Living in the ocean, "they obviously take in a great deal of salt, which would be very damaging to a human kidney, and in fact increased human consumption of salt by humans is contributing to hypertension and kidney damage. How do these animals deal with such high salt concentrations?"

At the College of the Atlantic in Bar Harbor, Allied Whale Marine Mammal Stranding Coordinator Rosemary Seaton and students collect any marine mammals that wash up on the shores of Frenchman Bay and conduct necropsies on them. Korstanje's research lab manager, Sue Sheehan, collects kidney tissue samples from the Allied Whale team for study.

Besides mice, zebrafish, bears and marine mammals, Korstanje's lab can now collect vital data about kidney function and disease from clinical collaborators who care for human patients with chronic kidney disease. "We can test the candidate genes we find that appear to be associated with kidney disease," Korstanje says, "and then we can make and study mouse models with the same genetic profiles as the patients'."

Earlier this year Korstanje and his lab published a paper on the genetics of a human disease known as Alport syndrome. Patients with the disease, which is caused by a mutation in a single gene, die relatively young of kidney failure, but the age of onset and severity of the disease vary widely. In a mouse model of Alport syndrome, the team showed that other genes influence the amount of kidney damage, and the lab is now mapping these "modifier" genes.

Chronic kidney disease in humans is also associated with certain medications. About one percent of Americans take lithium, which is widely prescribed for bipolar disorder and schizophrenia. About 20 percent of patients develop diabetes insipidus, a condition in which patients experience extreme thirst and excrete large amounts of urine, and others develop kidney disease.

Korstanje's lab tested the effects of adding lithium to the diet of mice from 30 different strains of mice (leaving half the mice from each strain untreated). Some of the treated mice produced much more urine than normal — as much as their own body weight in a day. The lab is now screening for candidate genes for this diabetes insipidus-like condition.

"We can learn a lot from other species and how they deal with challenges to kidneys," Korstanje says. "If we understand which genes are involved in the process of kidney damage and renal function decline, we might be able to slow down this process and postpone the need for dialysis, or even better, prevent it altogether."

THE ULTIMATE GOAL IS TO IDENTIFY POTENTIAL DRUG TARGETS FOR HUMAN KIDNEY PATIENTS.

Rita L. Seger, M.D., Ph.D., of the University of Maine, Ron Korstanje's collaborator on the physiology and ecology of the American black bear, poses with cubs on a research expedition in the Maine woods. *Photo by Karen Brown.*

Envisioner, investor

STORY BY BARRY TEATER
PHOTOGRAPHY BY MARIE CHAO

David Roux believes genomic medicine will transform health care even more than people realize, and he's placing his bet on The Jackson Laboratory.

While growing up in Lewiston, Maine, in the 1960s and 70s, David Roux was aware of The Jackson Laboratory in Bar Harbor but had no inkling he would ever be involved with it. He was planning a career in business, not science.

But a half century later, Roux is not only a trustee of the Laboratory but also its top benefactor and a valued visionary who is helping shape its future in genomic medicine.

Roux and his wife, Barbara, recently gave $5 million to the Laboratory, triggering a $5 million match in their honor by JAX. Theirs is the largest philanthropic gift in the Laboratory's 85-year history.

So just who is David Roux?

At 58, he is a successful technology investor whose 30-year career as an entrepreneur, corporate executive and financier helped usher in the digital age. And he is an active philanthropist whose experience, wisdom and critical thinking are as valued as his financial gifts by the nonprofit organizations he supports.

"I don't know anyone else like him," says David Yarnold, president and CEO of the National Audubon Society, one of Roux's philanthropic causes. "He's thoughtful and analytical, and all of his life experience has gone through some kind of special 'Dave blender' that results in enormous wisdom about life and organizational excellence, about management, about communication. He has this real gravitas."

*"I'm very proud of the fact that dozens of people who have worked for me have gone on to be CEOs and lead their own companies. I get a big kick out of **their** success."*

— David Roux

FAST TRACK

Roux made his mark early, only a year out of Harvard Business School, when he co-founded and was CEO of the first commercial CD-ROM publishing company, Datext, later sold to Lotus. That initial success led him to increasingly senior executive positions in the technology industry, first at Lotus, and later at software giant Oracle, where he was one of Chairman Larry Ellison's top lieutenants as head of corporate development and then as chairman and CEO of Liberate Technologies, an Oracle subsidiary.

But it was a highly calculated gamble in his early 40s that paid the greatest career dividends for Roux, not only boosting his family's wealth but scaling up his impact on the global technology industry. He and three trusted associates believed the general market had underestimated the scope, impact and durability of the Internet and related new technologies, so they left their corporate jobs in 1999 and co-founded a firm called Silver Lake to invest in private technology companies.

Today, Silver Lake is the world's largest technology private equity firm with $23 billion in assets under management. It has invested in, bought, shaped and sold some of the most recognized technology brands including Skype, Dell, Alibaba, Ameritrade, Go Daddy, Groupon and Avaya. The companies in its investment portfolio generate more than $80 billion of revenue annually and employ more than 160,000 people internationally.

Asked in an interview what gave him the Midas touch at Silver Lake, Roux pauses and speaks deliberately, true to his self-described plodding, methodical nature.

"I have really only three skills," he says. "I'm very comfortable forming an opinion about how complex technologies and markets will evolve.

"The second thing is I have an ability to pick out from complexity and chaos a few things that are important … and to concentrate on those.

"The third thing — and it may be the most important — is that I have a good eye for talent, and I enjoy working with developing, motivating, incenting young talent. I like the mentoring relationship. I've always liked building teams. I'm very proud of the fact that dozens of people who have worked for me have gone on to be CEOs and lead their own companies. I get a big kick out of their success."

'FEROCIOUS INTENSITY'

Friends and associates of Roux agree with his self-assessment but add other distinguishing traits including insatiable curiosity and extraordinary drive.

"He's obsessive about everything," says Yarnold. "He decided to become a golfer, and before you knew it he was a single handicapper."

Jim Davidson, a co-founder of Silver Lake who has known Roux for two decades, says his business partner is "intellectually curious at a level that's just not commonly encountered in the world. He's constantly challenging himself, learning more, going deeper. And I think that intellectual curiosity is just part of him and his DNA, and drives him a lot."

Roux is "a very impressive guy, and I'm not easily impressed," says Richard Morrissey, an attorney who leads the London office of the New York law firm Sullivan and Cromwell, which as represented Silver Lake on certain deals. Morrissey has known Roux since their freshman year at Harvard, where they served on the humor magazine *The Harvard Lampoon* together.

"Dave's a deeply amusing and quick-witted character," he says. "The quirkiness and humor of the *Lampoon*, he still carries with him and uses to great effect in his daily personal and business life … which is important because it masks a ferocious intensity that he has brought to really every stage of his life. And that intensity has allowed him to be extremely successful.

"If you had that intensity without it being covered by the humor and deep human compassion he has, it would be very scary," Morrissey says with a laugh.

FOCUSED ON PHILANTHROPY

Today, most of Roux's business hours are devoted not to earning money but to helping various nonprofit causes, "and Barbara is very much my partner in all of this," he says.

"Dave has chosen to step back and leave a lot of money on the table, arguably, in order to devote his substantial resources, intellect and very valuable time to a variety of charities, including Jackson," says Morrissey. "And what's most valuable about Dave is not his financial resources but his time and judgment. To have someone who has taken the kind of significant resources he has and devote them — both the money and the intellect — to a cause like Jackson is quite remarkable.

"Most guys like him just work forever to make more and more money, but the basic humanity in him has forced that intensity away from a business track onto a track that is much more productive for society."

A FAMILY TRADITION

Roux's philanthropic ambition is rooted in his upbringing in southern Maine.

His mother, Connie Longley Roux, was a computer programmer with New England Telephone who helped maintain the company's first generation of digital switches. After raising six children, she went back to college to earn her degree, all while volunteering for various church and civic activities "and generally spending lots of time helping other people live more complete lives," Roux says. Her brother was James Longley, Maine's 69th governor in the late 1970s, and she ran for the state Senate, losing by only 146 votes to Olympia Snowe, the eventual U.S. senator.

Roux's father, Donald, was a banker who coached high school sports and was chairman of the Lewiston school board, a member of the local Rotary Club and head of the region's United Way for many years.

The Rouxs instilled in their children "relentlessly positive attitudes" and "worked to make the communities where they lived better places," Roux says.

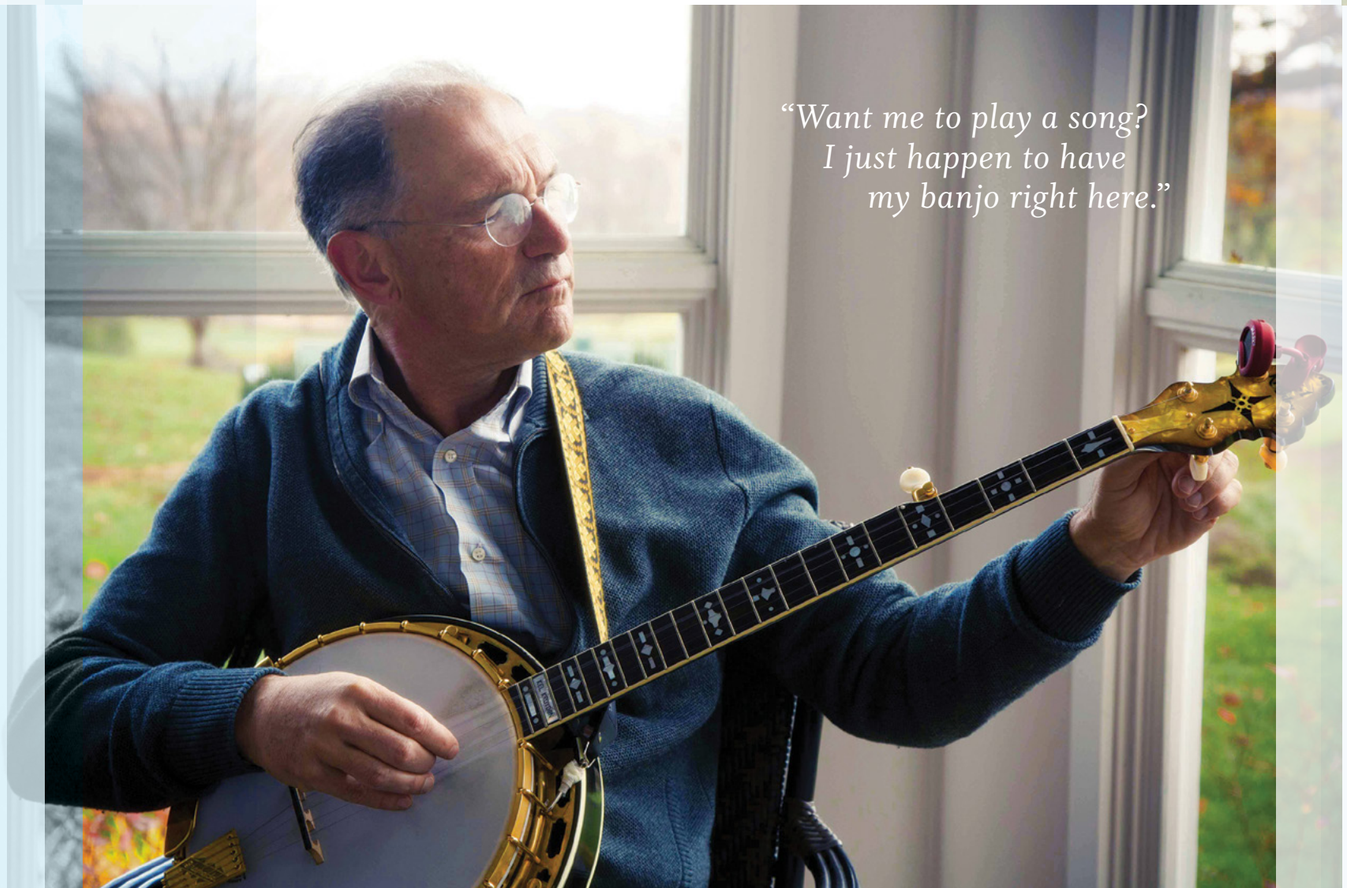
LEAVING SILICON VALLEY

In recent years, Roux has reduced his day-to-day involvement in Silver Lake, stepping down as co-CEO but remaining a senior director at the firm. He and his wife returned East from the San Francisco Bay Area to be closer to family, including their three adult children, Jocelyn, Alex and Margot. They have a summer home in Harpswell, Maine, but live primarily on St. Bride's Farm, a 350-acre horse farm in northern Virginia, where Barbara is an accomplished equestrian who breeds, trains and shows world-class show jumpers.

Roux enjoys having more time for his many recreational passions — golf, fly fishing, sailing, mountain biking, watching sports and playing the banjo.

"Want me to play a song?" Roux asks an interviewer on the phone. "I just happen to have my banjo right here."

He launches into a medley of classic bluegrass tunes — "Banjo in the Hollow," "Cumberland Gap," "Cripple Creek" and "Foggy Mountain Breakdown" — and continues to strum the instrument playfully throughout the rest of the call.



"I think that Dave was profoundly influenced by his parents, both of whom were extraordinary people," says Morrissey. "Each had great dignity and the thought that you had an obligation to give something back to the society that you operated in. I think they transferred that sense of obligation, rather than a sense of entitlement, to Dave."

Echoes Jim Davidson, Roux's Silver Lake partner: "He was raised well by his family in Maine. He understands how fortunate he has been, so I think giving back is important (to him)."

STRATEGIC GIVING

The Rouxs practice their philanthropy in three realms — education, environmental conservation and global health — and are strategic in their commitments.

"There's no shortage of worthy causes in the world," Roux says. "What it comes down to is we pick the ones that matter most. For me, it needs to be meaningful, it needs to be fundamental, and it needs to be something that I can do something about. I like for there

to be a serious victory attached to the effort. How is it exactly that we can make the world a better place as opposed to whining and winching about it?"

Roux's many commitments over the years have included Audubon, the Environmental Defense Fund, Bowdoin College, Harvard, the Positive Coaching Alliance, which promotes character-building through youth sports, and the Institute for Health Metrics and Evaluation, which tracks global health trends, at the University of Washington.

BULLISH ON JAX, GENOMICS

Today, "JAX is at the top of my list," Roux says. "I think it's just brimming over with potential, and I can play a small part in helping to realize it. What's exciting to me and to Barbara about JAX is this organization has both the willingness to tackle big problems and the talent and associated execution skills to have a meaningful chance of actually solving them."

The Rouxs' recent major gift to the Laboratory will be used to create the Roux Family Center for Genomics and Computational Biology, with three new endowed faculty chair positions and a permanent fund for recruiting expert staff and driving research and discovery at JAX's research campuses in Bar Harbor and Farmington, Conn.

"We think about this as philanthropic risk capital," Roux says. "Not everything we try will work. Not every research path will pan out. But enough of them will. And each time something doesn't work, we learn something and it contributes to the tree of knowledge. We get better and better and better — the processes, the people and hopefully the collaborations with people around world who are doing the same thing — and together we can solve some serious problems. We can cure some diseases, we can find new treatments, we can invent new therapies, we can do better diagnostics. There is lots of exciting stuff to come.

"It is absolutely clear to me that the technology around genomic medicine and computational biology is going to have a bigger and more profound impact than people realize," Roux says. "It's going to roll in like waves on a beach. It's just going to keep breaking. That's what I find interesting, exciting, provocative and so promising.

"I think about it as being an extraordinarily good investment — like investing in semiconductors in 1960 or personal computers in 1970 or software in 1980 or the Internet in 1990 or social networking in 2000. We both think that this suite of related (genomic) technologies has the potential to transform medicine and human health, and you don't often get the chance to make investments like that."

5 questions

PHOTOGRAPH BY MARIE CHAO

Jeremy Racine, Ph.D.

Postdoctoral Associate

The Jackson Laboratory

To see a video clip and a photo gallery of Jeremy Racine, visit *www.jax.org/thesearch/racine.*

What is your academic background?

I did my undergraduate work at Cornell University where I majored in biochemistry, and spent much of my free time as a member of the Cornell University Emergency Medical Service. My first taste of research was the two summers I spent as an intern in a nephrology laboratory at Yale School of Medicine. After graduating from Cornell, I decided to test the waters of a career in research. I spent three years at Harvard Partners Center for Genetics and Genomics/Brigham and Women's Hospital as a research technician in a Drosophila genetics laboratory, while continuing to take night classes at Harvard Extension School. It was here that I first delved into immunology. After leaving Boston, I attended the Irell & Manella Graduate School of Biological Sciences at City of Hope National Medical Center in Duarte, Calif. I anticipated continuing work as a biochemist but instead joined the laboratory of Dr. Defu Zeng, studying type 1 diabetes and hematopoietic stem cell transplantation.

Why did you apply to the Laboratory's Postdoctoral Scholars Program?

The Jackson Laboratory offers a unique opportunity to learn and make use of powerful mammalian genetic tools. Prior to joining JAX, my research was limited to using currently available mouse models. I was intrigued by the idea of joining an institution where I would have access to the latest, or help generate the newest, mouse models for studying and treating type 1 diabetes. Additionally, I was attracted to the attention JAX paid to training postdocs beyond the bench work.The attention to detail in training a "whole scientist" appealed to me.

What have you gained from the program so far?

I have only been at JAX a few months, but my decision to train here has already started to pay off. Soon after arriving I had an opportunity to attend the annual Short Course on Medical and Experimental Mammalian Genetics and rapidly was exposed to the newest knowledge in mouse and human genetics. It was an excellent primer for someone like me who had not been heavily exposed to genetics in some time. Some of my early experiments in the lab have already led to the decision to generate a new mouse model for me to work with, and because of the expertise here at JAX, I should soon be receiving some founder mice to start establishing this new model. I had considered myself fortunate as a graduate student to have some exposure in handling a mouse colony, but I have already learned a lot more since coming to JAX. This early exposure will be indispensable to having and maintaining my own mouse colony at some point in the future.

What are you researching?

I am currently working in the laboratory of Dr. David Serreze and studying treatments to prevent type 1 diabetes in "humanized" NOD mice that harbor the human-diabetes-relevant allele HLA-A2.1. While traditional mouse models have served us well in understanding how autoimmune diseases develop, it will be this next generation of humanized mice that will help scientists expand the number of useful therapies for autoimmune diseases from the mouse to the clinic.

What do you plan to do after completing the program?

It is my hope that at the end of the program I can obtain a position at an academic institute where I have both research and teaching responsibilities. I have been fortunate in my career to have some excellent mentors who have instilled in me a love of research, and I hope to pass that love of science on to the next generations in both the classroom and laboratory. Additionally, with my exposure to humanized NOD mouse models here at JAX, I hope to expand my work into humanized mouse models of other autoimmune diseases.

beyond the news

EYEING THE EYE

A JAX-led team reveals the unique biology of Schlemm's canal, a key eye structure implicated in glaucoma

STORY BY NICOLE DAVIS, Ph.D.

Nearly 200 years ago, a gifted German anatomist stumbled upon a rather macabre discovery. While examining a man who died at his own hand, by hanging, the anatomist unearthed a thin-walled canal, forming a delicate ring around the whites of the eyes. Ordinarily, such a structure might have escaped notice, but in this corpse, it was engorged with blood.

SIMON W. M. JOHN, Ph.D.

Although no drawings were made to document this seminal observation, the canal bears the name of its discoverer, Friedrich Schlemm, and is now known to play important roles in normal eye physiology and disease. It is also the focus of an important paper, published this past summer in the journal *PLOS Biology* and led by Jackson Laboratory Professor and Howard Hughes Medical Institute Investigator Simon W. M. John, Ph.D.

"Although researchers have learned much about the effects of pharmacologic agents on Schlemm's canal as well as its local ultrastructure through electron microscopy, we know remarkably little about its formation, functional architecture and specialized molecular features," says John.

It has been well established that Schlemm's canal is a critical gatekeeper in maintaining the proper flow of fluid from the eye. Disturbances in the flow of this fluid, known as aqueous humor, can raise pressure within the eye — a major risk factor for glaucoma, a condition that eventually leads to blindness.

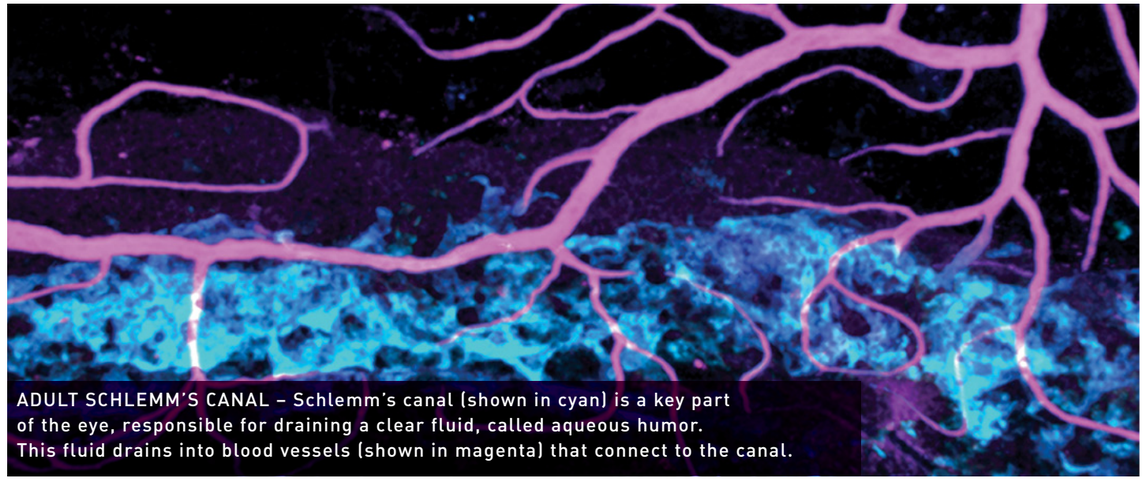
However, some fundamental questions remain about the canal's form and function. Surprisingly, until now, no one has studied the structure with such a powerful combination of tools, including high-resolution, three-dimensional analyses, and modern molecular and genetic approaches. To help answer the lingering questions about Schlemm's canal, John's team harnessed these methods and developed new ones, which can now be used by others across the scientific community.

Krishnakumar Kizhatil, Ph.D., an associate research scientist in John's laboratory, sought to understand how Schlemm's canal forms, both at a gross anatomical level and at a molecular level. "Ultimately, we would like to understand the molecular mechanisms involved in controlling fluid flow into Schlemm's anal and consequently eye pressure," says Kizhatil. "This will allow us to better understand what goes wrong in glaucoma, and also give us information that can be exploited to develop new therapies."

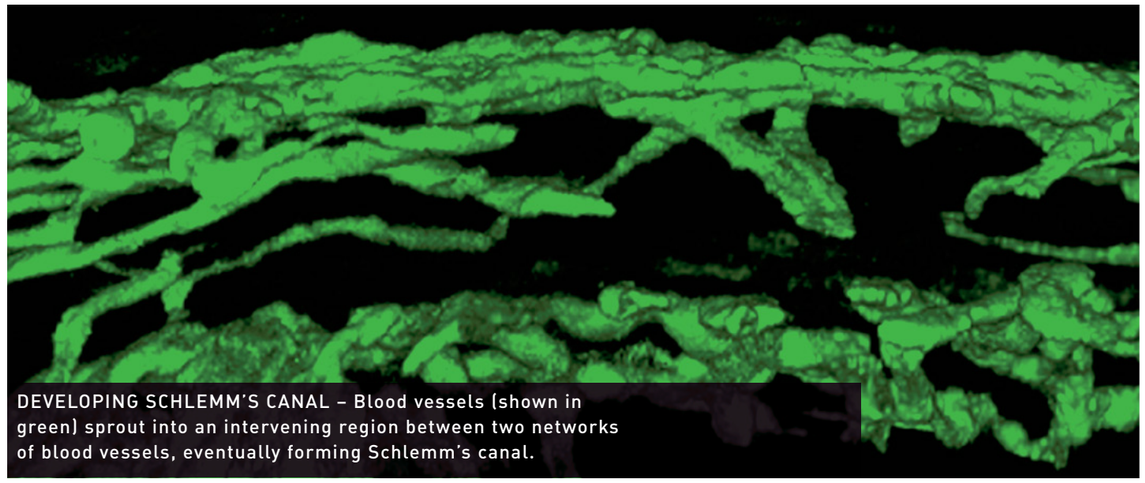
Using the mouse as a model, Kizhatil and his colleagues at JAX and Tufts University School of Medicine in Boston developed a new so-called "whole-mount" approach to visualize the canal in three-dimensions during its various stages of development.

Fluid-carrying vessels in the body, such as blood and lymphatic vessels, generally emerge through one of several distinct processes. Using a series of molecular markers to characterize the emergence of Schlemm's canal, the scientists discovered that it arises from blood vessels through a previously unknown mode of vascular development, which they call "canalogenesis." This developmental program shares some similarities with other modes of vessel development, but also exhibits distinct differences.

In addition, Kizhatil and his colleagues uncovered a key role for a protein called KDR. This protein, previously known for its role in forming blood vessels, is also required for early development of the canal.



ADULT SCHLEMM'S CANAL – Schlemm's canal (shown in cyan) is a key part of the eye, responsible for draining a clear fluid, called aqueous humor. This fluid drains into blood vessels (shown in magenta) that connect to the canal.



DEVELOPING SCHLEMM'S CANAL – Blood vessels (shown in green) sprout into an intervening region between two networks of blood vessels, eventually forming Schlemm's canal.

Another key advance is the researchers' discovery that a previously unknown class of endothelial cells lines Schlemm's canal. This cell type blends together features of cells lining both blood and lymphatic vessels. Importantly, this mix of molecular attributes is not known to exist in any other cell type in the body and is likely to be a critical specialization for determining fluid flow into the canal.

Taken together, these molecular explorations provide a critical window on the formation of this delicate eye structure. Furthermore, they provide essential new information about the nature of Schlemm's canal that may lead to a new paradigm of treatment aimed at features previously thought to be unique to lymphatic vessels.

John believes the discoveries and new tools provided by the paper will have a lasting impact on our understanding of Schlemm's canal and its roles in ocular health and disease.

Nicole Davis, Ph.D., is a freelance writer and communications consultant specializing in biomedicine and biotechnology. She has worked as a science communications professional for nearly a decade and earned her Ph.D. studying genetics at Harvard University.

The Jackson Laboratory

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Guests mingle in the atrium of The Jackson Laboratory for Genomic Medicine in Farmington, Conn. The 183,500-square-foot research center was formally dedicated on Oct. 7, 2014.

Photograph by Jennifer Torrance