THE SEARCH

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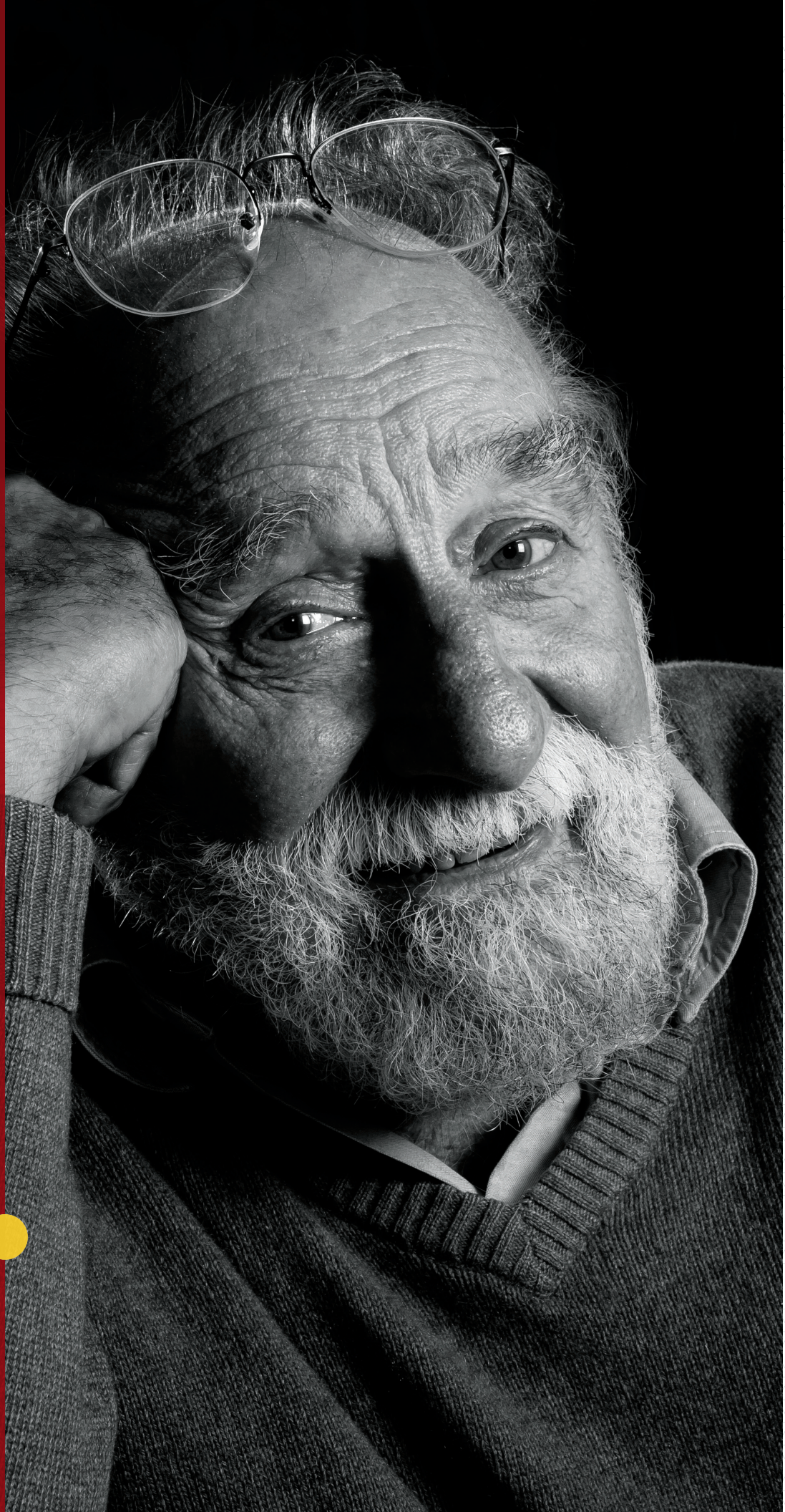

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THE SEARCH
A PUBLICATION OF THE JACKSON LABORATORY

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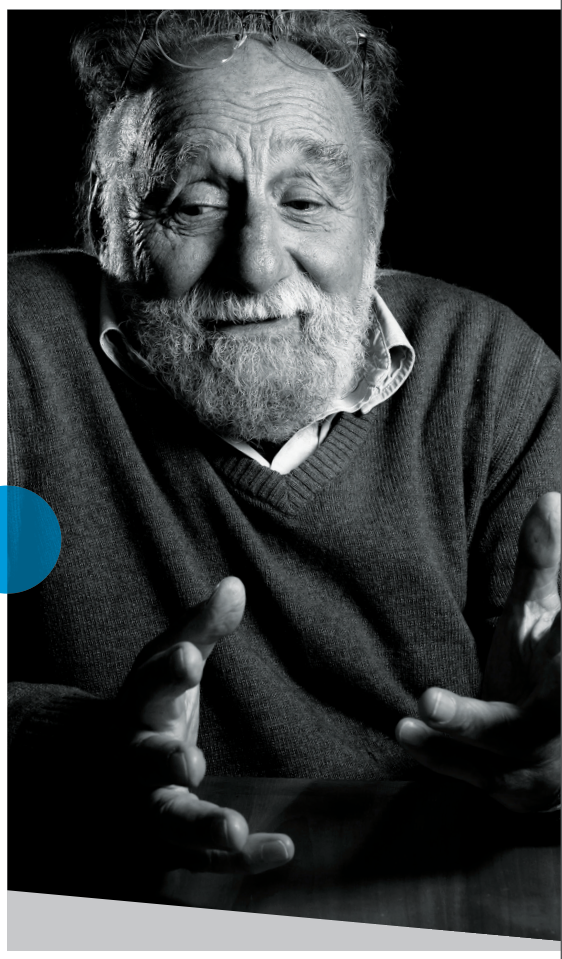

LEFT Construction of The Jackson Laboratory for Genomic Medicine's permanent facility is proceeding at an impressive pace. The new building is scheduled to open in less than a year. *Image courtesy of Mark Wanner.*

Cover photograph by Françoise Gervais

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The Jackson Laboratory
Leading the search for tomorrow's cures

President's message

Hosting the Clinical Genomics in the 21st Century conference over the weekend of October 4 and 5 at The Jackson Laboratory for Genomic Medicine was an exciting experience for me. It was wonderful to spend time with friends and colleagues, many of whom are also among the leading figures in the new field of genomic medicine.

From the formal conference talks to the many side conversations to the wonderful reception and dinner, the time was packed with insight into what is no less than the future of medicine. Genomic data has been accumulating and undergoing analysis for several years without making a large impact on everyday medical practice. But clinical genomics is now arriving, and its implementation is critical to medical progress.

There were several things that resonated with me at the conference, but perhaps the most important was the sense of optimism. Of course, the visiting speakers attended in part because of their optimism. They are experts and forward thinkers who enjoy problem solving. But they—and we—are sure of the viability and scalability of current clinical genomics efforts. The field is moving forward quickly and the roadblocks, while non-trivial, are surmountable.

It was also an event that showcased the ways in which JAX Genomic Medicine is making terrific progress. We've already recruited a truly formidable nucleus of prominent scientists to Connecticut, including Charles Lee, Ph.D., who is directing the scientific effort. (For more about Lee and his vision for JAX Genomic Medicine, see page 8.) And the new building, scheduled to open in less than a year, will provide world-class research facilities.

Many eyes in Connecticut and beyond are on JAX Genomic Medicine. Clinical Genomics in the 21st Century did much to affirm that it's in a good position to fulfill its promise.

Edison Liu
President and CEO, The Jackson Laboratory

news&notes

Energy plant named 'Renewable Energy Project of the Year'

Energy conservation is a high priority at The Jackson Laboratory. Now the Association of Energy Engineers (AEE) for the northeastern United States has named its biomass boiler the "Renewable Energy Project of the Year."

The wood-burning energy plant burns wood pellets instead of fossil fuels and was the largest of its kind in the Western Hemisphere when it began operation in July 2011. Since then it has reduced the Laboratory's fuel oil consumption by 75 percent, with tremendous financial and environmental benefits.

"To date we've displaced over 2.2 million gallons of fuel oil and have saved over $3,000,000," says John Fitzpatrick, senior director, facilities. "And it represents huge savings environmentally. We're removing 13.5 thousand tons of CO_2 a year from our emissions profile."

The AEE awards committee, led by the Region I Vice President David Eberly, recognized The Jackson Laboratory's pellet-burning energy plant as "a significant and innovative renewable energy project, one that has had significant impact on global warming and Maine's wood pellet industry." The committee noted that "although nominations are often limited to more conventional renewable projects such as wind or solar, this project was viewed by the committee as particularly innovative, cost-effective and practical."

Based on advanced technology developed by Swedish energy company Petrokraft, the energy plant generates steam for conversion to electricity by burning wood powder, the product of pulverizing wood pellets into a combustible dust.

Jennifer Trowbridge named Ellison scholar

Assistant Professor Jennifer Trowbridge, Ph.D., has received a four-year, $400,000 grant from The Ellison Medical Foundation as a New Scholar in Aging.

Trowbridge studies hematopoietic (blood) stem cells, cells that give rise to various kinds of blood cells. Her focus has been applicable to cancer as well as aging, as the factors that control self-renewal of the stem cells may also control leukemia stem cells.

"Receiving this prestigious award has sparked a new area of research in my laboratory," says Trowbridge, "studying the epigenetic changes that drive aging of the hematopoietic system. Abnormalities of the blood system, including immune deficiency, anemia and increased chance of developing myeloid leukemia, are major health concerns of our aging population."

The New Scholar awards recognize newly independent investigators, still in their first three years after postdoctoral training, who show outstanding promise in aging research. Trowbridge joined The Jackson Laboratory in September 2012 following a postdoctoral fellowship at Dana-Farber Cancer Institute and Children's Hospital in Boston.

Jennifer Trowbridge

news&notes

MHMC recognizes Chuck Hewett for healthcare leadership

Charles E. Hewett, Ph.D., executive vice president and COO of The Jackson Laboratory, has been named by the Maine Health Management Coalition (MHMC) as among the top 20 Mainers who have worked to improve the value of health care in Maine. The awards, created to celebrate MHMC's 20th anniversary, were presented at the organization's annual symposium in Portland, Maine, on Oct. 10, 2013.

In recent years the Laboratory has provided extensive wellness opportunities for its employees and dependents, which has helped to improve their health outcomes. Between 2008 and 2012, hospital admissions decreased by more than 50 percent, days of care by more than 40 percent, and surgeries and ER visits by nearly 20 percent each. Medical costs have declined 20 percent.

"Being active and healthy is a critical part of a good life," Hewett says. "And an employer has an obligation to encourage employees to eat right and exercise, and make the necessary resources available. It's the right thing to do for people, and it's also good economics for the employer. We're fortunate to have an HR team that delivers great programs and employees who take advantage of them."

For the awards, MHMC assembled a panel of three national judges to evaluate nominations from throughout Maine. The awards are intended "to recognize individuals from around the state that have worked to improve the value of health care in Maine, to teach others about successful efforts that have been/are being carried out, and to inspire others around the state to work collaboratively to improve the quality and lower the cost of health care in Maine."

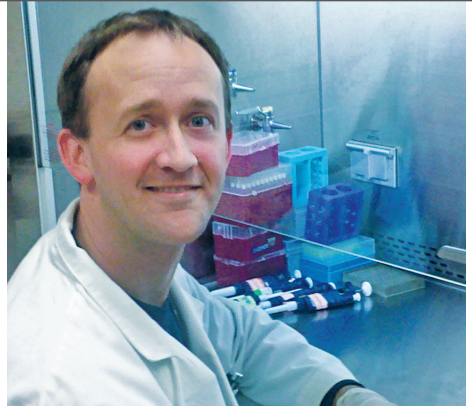
JAX expands health care provider education capabilities

The Jackson Laboratory has **signed an agreement with the National Coalition of Health Professional Education in Genetics (NCHPEG)** to acquire its website, content and other assets. JAX will also hire three of its key employees to expand its efforts in delivering genetics and genomics education to health care professionals.

NCHPEG was scheduled to close when JAX proposed preserving and growing this exceptional national resource. It was founded in 1996 as an "organization of organizations," committed to a national effort to promote health professional education and access to information about advances in human genetics. The organization grew to represent more than 50 health professional organizations, consumer and volunteer groups, government agencies, private industry, managed-care organizations and genetics professional societies.

"The established NCHPEG platform will serve as the foundation for JAX's goals to become producers of continuing medical education materials for health care providers, including physicians, genetic counselors, medical students, nurses and social workers," says Tom Litwin, Ph.D., vice president for education. "This team and platform will also serve as the foundation for the creation and online distribution of genetic and genomic literacy curricula and programs."

Joining the Laboratory are Kate Reed, M.P.H., Sc.M., C.G.C., Emily Edelman, M.S., C.G.C. and Therese Ingram Nissen, M.A. At NCHPEG Reed and Edelman were director and associate director, respectively, of Clinical and Continuing Education, while Nissen was senior instructional designer.



Michael Stitzel

Michael Stitzel joins JAX Genomic Medicine

Michael Stitzel, Ph.D., a researcher focusing on the genetics and epigenetics associated with type 2 diabetes, joined the faculty of The Jackson Laboratory for Genomic Medicine as an assistant professor in August 2013. Stitzel comes from a postdoctoral appointment at the National Human Genome Research Institute in the laboratory of Francis Collins, M.D., Ph.D., the current director of the National Institutes of Health.

"I am very pleased with the recruitment of Dr. Stitzel to JAX Genomic Medicine." says Charles Lee, Ph.D., scientific director of JAX Genomic Medicine. "His work on epigenetic profiling of islet cells is revolutionary for the field of diabetes research."

Pancreatic islet cells produce insulin, and changes to the cells can contribute to diabetes. Stitzel's research explores how genetics and epigenetics—chemical modifications of DNA—and regulation of gene expression in the cells affect susceptibility to type 2 diabetes.

"I was drawn to this position because I share an interest in using genomic approaches to advance precision medicine and investigate the genetic basis of human health and disease," Stitzel says. "Moreover, I'm excited about the potential to initiate new collaborations with JAX faculty and other universities and medical centers in the state. I'm driven to interpret the molecular consequences of genetic variants associated with islet dysfunction and type 2 diabetes, to investigate the functions of the genes they affect, and to apply this knowledge to develop therapeutics."

JAX Genomic Medicine obtains CLIA certification

The Jackson Laboratory for Genomic Medicine is now a **Connecticut-licensed and CLIA-registered clinical laboratory** qualified to accept and process clinical samples of human cells and tissues for DNA testing.

Licensing by the Connecticut State Department of Health and registration under CLIA (Clinical Laboratory Improvement Amendments), which is granted through the Center for Medicare and Medicaid Services of the U.S. Department of Health and Human Services, demonstrates that the JAX facility meets rigorous standards to ensure quality laboratory testing.

"Obtaining these approvals to accept patient samples is a vital step into clinical research for us, as we build a new institution that will break new ground in genomic medicine," says Jackson Laboratory President and CEO Edison Liu, M.D.

The state and federal approvals cover the Laboratory's processes, procedures and current facilities. The testing laboratory in the new facility will undergo further review when construction is complete.

George Weinstock

George Weinstock joins The Jackson Laboratory

George M. Weinstock, Ph.D., a pioneer in the sequencing and analysis of human, model organism and microbial genomes, is joining the faculty of The Jackson Laboratory.

Weinstock is a leader of the Human Microbiome Project, an international effort to apply and develop the latest technological tools to comprehensively characterize the human microbiome. The microbiome is the large and genetically varied population of microorganisms that inhabit the human body and that may be a significant factor in health and disease.

"George Weinstock is a giant in the field of human metagenomics," says Jackson Laboratory Vice President for Research Robert Braun, Ph.D. "He fills a strategic goal for JAX to contribute to the understanding of how the human microbiota influences normal human health and disease. His contributions have and will continue to transform our view of human biology."

"It is an honor for me to join The Jackson Laboratory, one of the venerable institutions in the field of genetics," says Weinstock, who will be the associate director for microbial genomics at JAX. "Genomic medicine is at the leading edge of the current era of biomedical science, and I am extremely excited to be a part of The Jackson Laboratory's vision for this area."


SMEDLEY AERIAL LIFTS
JLG

Charles Lee visits JAX Genomic Medicine's construction site. The new building will be ready for occupancy in October 2014.

A NEW NORMAL

by Mark Wanner
Photography by Jim Graham & Al Fereirra

CHARLES LEE'S VISION FOR GENOMIC MEDICINE

"I'M SORRY FOR HAVING TO DO THE INTERVIEW THIS WAY," SAYS CHARLES LEE, PH.D., BATTLING HARTFORD, CONN., RUSH-HOUR TRAFFIC WITH ONE EAR LISTENING FOR THE NEXT GPS DIRECTION. **"I'M ON MY WAY TO A RECEPTION WITH THE GOVERNOR.**

Charles Lee, recently named director of The Jackson Laboratory for Genomic Medicine in nearby Farmington, is used to urban New England traffic, having moved from Boston in late summer. But he doesn't know Hartford yet, and at one point he interrupts himself with a "darn, I think I might have taken a wrong turn" and apologizes again for the drive-time interview after getting back on course.

"It's been crazy busy." He laughs. "I guess this is my new norm."

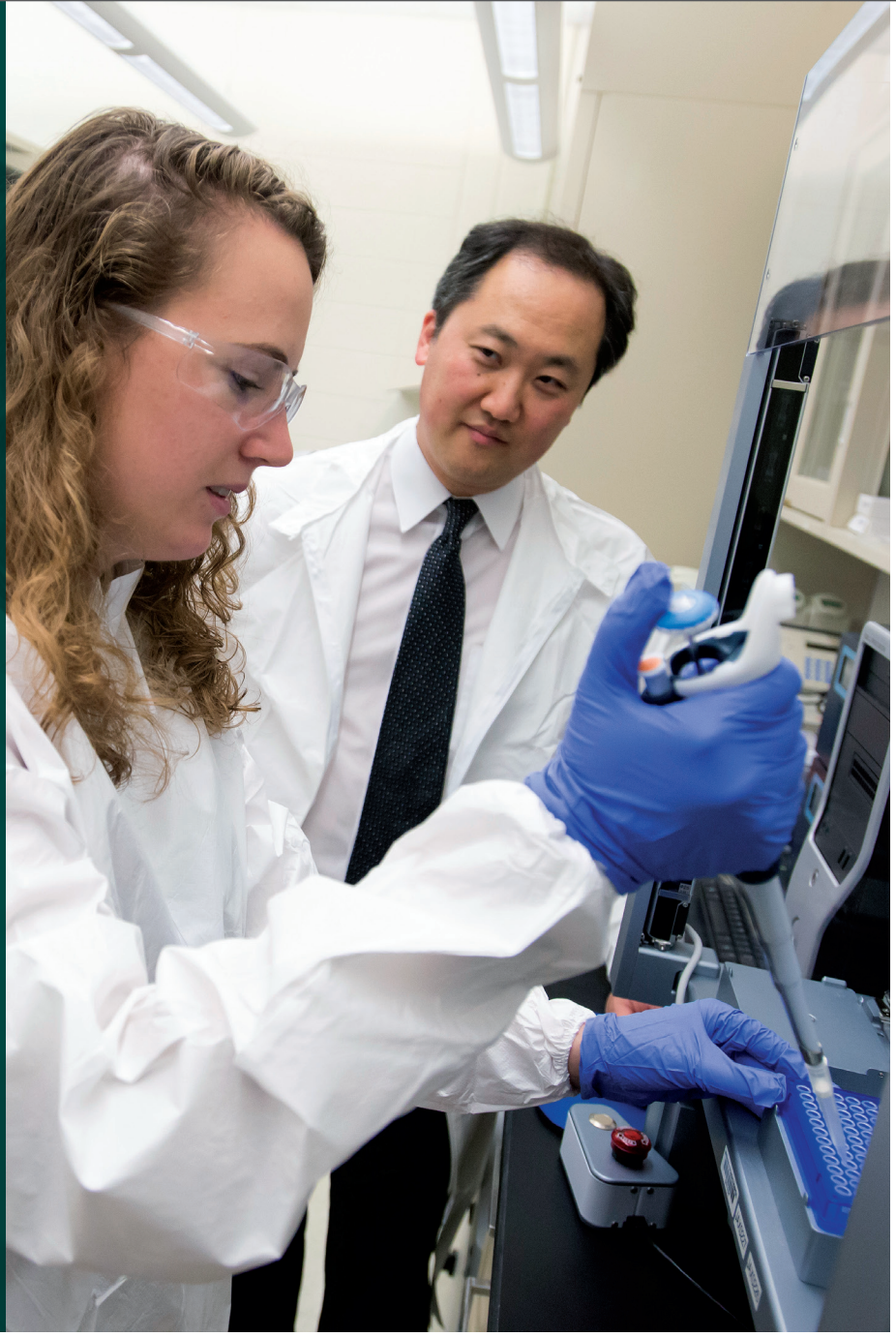
CHANGE OF FOCUS

Lee has a formidable record of success in human genetics research. So what led him to travel a different route, leaving an established and prestigious research position at Harvard Medical School (among other appointments) to lead what is essentially a start-up project in Connecticut?

"This is a really exciting opportunity to gather some of the best scientists from around the world spanning different disciplines and provide them with state-of-the-art technologies to further genomic medicine," says Lee.

And why JAX, so well known for its genetics work with mice, when Lee's career has focused on human genetics?

"Over the past few years, as we have amassed a huge amount of data from human genetics, we are also realizing how little we actually understand," says Lee. "About four years ago, I was talking with some senior scientists and they were adamant that with the advances in genome sequencing and analyses, we didn't need model organisms



LEFT Lee leads a research effort that is already well under way, with Research Assistant Eliza Cerveira and others working in JAX Genomic Medicine's temporary research facilities.

anymore, we just needed to sequence more people. Now we see that's not true. We need good model organism research to understand the biological implications of the sequence variants that are being uncovered."

Lee's move to JAX Genomic Medicine was greeted with enthusiasm throughout the biomedical research community. According to JAX President and CEO Edison Liu, M.D., Lee "is uniquely qualified to lead our entire effort around the clinical implications of genomic medicine. He represents the next generation of scientific leaders in translational science with national and global recognition."

PERSEVERANCE

Lee didn't set out to be a next-generation scientific leader. In fact, he was gearing up to be a medical doctor in college. But a brief foray into biomedical research after graduating from the University of Alberta in Canada in 1990 led to the co-authorship of a paper based on his summer research project.

"I think a lot of people get a 'rush' out of seeing their name in print for the first time," says Lee. "I did too, but more than that—I got a great deal of satisfaction knowing that I was uncovering some new knowledge (no matter how small) for the very first time. I couldn't shake that excitement, so I stayed in research and never did go to medical school."

Lee stayed in Alberta for his graduate work and obtained an M.Sc. in experimental pathology in 1993 and a Ph.D. in medical sciences in 1996. His

> "I GOT A GREAT DEAL OF SATISFACTION KNOWING THAT **I WAS UNCOVERING SOME NEW KNOWLEDGE** (NO MATTER HOW SMALL) **FOR THE VERY FIRST TIME.**"

> MY LESSON FROM THIS EXPERIENCE WAS TO **NEVER ASSUME ANYTHING. LET THE DATA SPEAK FOR ITSELF.**

postdoctoral work subsequently took him to Cambridge University in England, then to Harvard Medical School in Boston, where he trained and became board certified in clinical cytogenetics. His training went well, but it came with hardship and sacrifice.

"I went to Harvard Medical School with my wife Cecilia and my newborn daughter Annabelle, but the cost of living in Boston is quite high, and it was difficult to survive on my postdoc stipend alone," says Lee. "So my wife had to work, and she got a part-time job as an administrative assistant at the main Harvard campus in Cambridge, working mornings Monday-Friday. Daycare was too expensive for us, so I'd go to the main Harvard campus with Cecilia, and sit in the car in the parking lot, taking care of Annabelle—sometimes just reading scientific articles in the car while Annabelle napped—then go to work until 11:00 p.m. or midnight and certainly on weekends to get everything done. That went on for almost a year."

Lee continues, "I loved my work, but it didn't come easily to me. I had to put in the hours. It was very difficult, and even eventually led to some health issues, but it was just… just what we had to do."

THE BENEFITS OF TECHNOLOGY

With his postdoc complete, Lee became an instructor at Harvard Medical School in 2001 and then an assistant professor in 2003. As he built up his laboratory, he set out to understand more about the human genome. The opportunity to run a laboratory meant that Lee could dive headfirst into another key interest of his—technology. And early on, that interest yielded a significant discovery.

One of the newest technologies that Lee pursued and acquired at that time was array CGH (array-based comparative genomic hybridization), which was developed to survey gene copy-number variations—additions and deletions—across entire genomes. Lee and a postdoc in his lab, John Iafrate, got it on board and began to examine human clinical samples. They expected to see additions and deletions in some patient samples, especially in tumors, but were very curious to see if they saw additions and deletions when they compared the genome of one healthy individual with the genome of another healthy individual. When they saw what Lee now calls "blips" in the control data—DNA gains and losses throughout the genomes of even healthy control samples—Lee was actually not surprised.

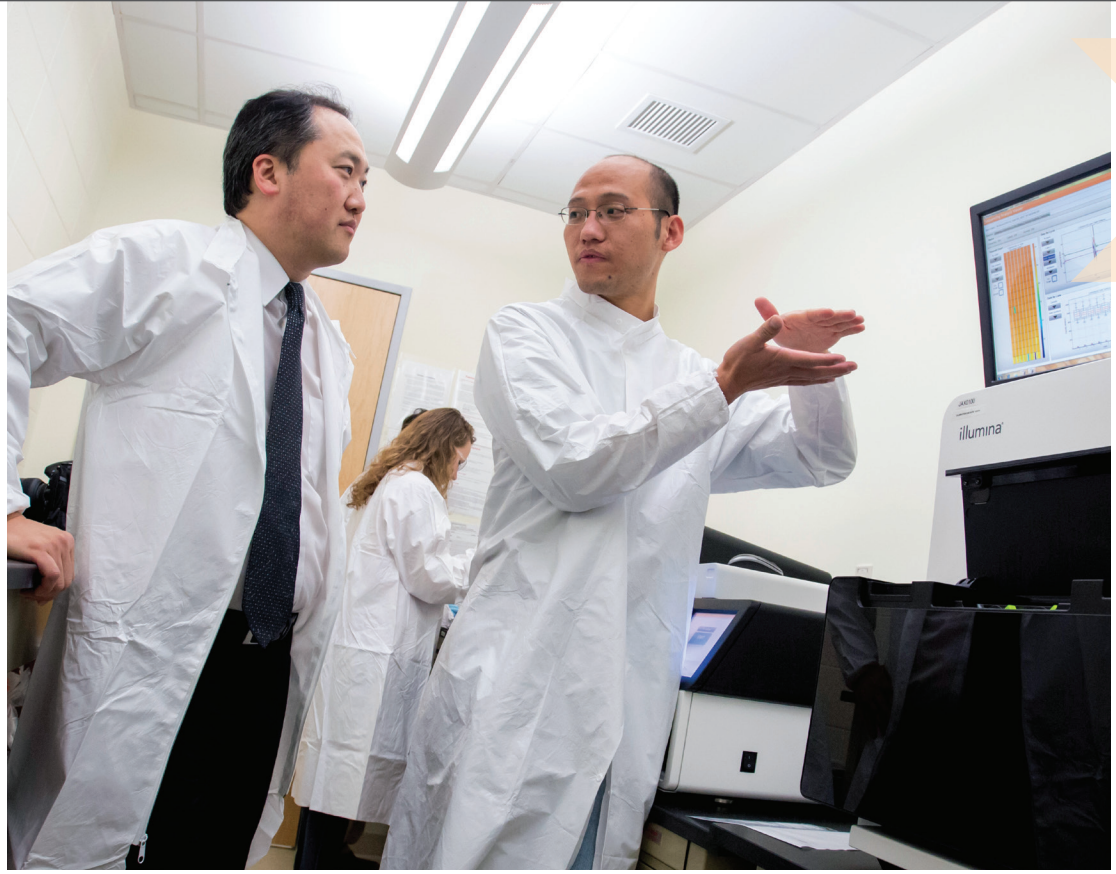
"I previously attended a talk by a pioneer of array CGH technology, Dr. Dan Pinkel, and one slide in his talk showed the same 'blips' in his control experiments," Lee recalls. "However, Dr. Pinkel did not point out the blips in the control experiments, but rather focused on the gains and losses identified in the cancer specimens. When I asked him about the blips in the control experiments, he seemed annoyed at my question and dismissed them as technical artifacts."

However, those "blips" weren't artifacts; they were real gains and losses of DNA. Lee's discovery that copy number variants (CNVs) are common in genomes of healthy individuals was a crucial step in human genomics research, and it has shaped the field in the decade since. The exact biological implication of most CNVs is still unclear, but it is now widely recognized that CNVs are very important to understanding human health and that single base changes or small mutations alone do not determine disease states and human individuality. The discovery was also crucial for accurately interpreting the tens of thousands of genetic test results performed around the world every year. Knowing what gains and losses are found in healthy individuals helps to differentiate those gains and losses that directly cause certain human diseases and medical conditions.

"My lesson from this experience was to never assume anything," says Lee. "Let the data speak for itself. It sounds easy, but it is actually hard advice to follow. It's something that I keep reminding every student that comes through my lab. But I sometimes wonder how many of the approximately 40 students that I have had over the years got it—really got it—the 'don't assume anything' concept."

Lee considers himself a simple man, and he tries to keep his research papers and scientific presentations simple as well. He also has a simple philosophy: focus on merit, seek quality over quantity, and value the students and staff who sacrifice a lot to perform good research, just as he has done. He reminds them that a scientist's reputation is built over a lifetime, but a single careless mistake can have profound implications to that reputation.

Visit **www.jax.org/thesearch/lee** to see Lee describe his vision for JAX Genomic Medicine.



LEFT Lee and Postdoctoral Associate Yuxiao Chang, Ph.D., discuss a DNA sequencing project. JAX Genomic Medicine's research focuses on human genomics and translating research results to human medicine.

A BRIGHT FUTURE

Lee's research in Boston gained him international accolades and a heavy workload. He received the 2008 Ho-Am Prize in Medicine, one of the highest scientific awards in Korea. He also won a Chen Global Investigator award from the International Human Genome Organization and is now an elected fellow of the American Association for the Advancement of Science. He ultimately carried appointments at Harvard Medical School, the Harvard Cancer Center, the Broad Institute and Brigham and Women's Hospital before joining JAX Genomic Medicine in August 2013. But it's clear he's lost none of his enthusiasm for discovering something new.

"There's still so much work to do in structural genomics," he says. "I'm fascinated by how structural variants can actually cause new phenotypes [traits]. We just published a new paper that looked at structural variation across primate species, and we found a gene in which there was a different copy number and a whole new function in rhesus macaques that wasn't there in other primates studied, including humans. In some cases, errors in DNA replication or DNA repair duplicate a portion of the genome, which leads to a new gene function, or activity in a new tissue where it was not originally meant to be."

In his leadership role, Lee sees several keys to JAX Genomic Medicine's success. In addition to recruiting leading researchers across several disciplines—and early recruiting has already built a stellar faculty nucleus—the researchers must actively interact with one another and have access to the latest genomic tools as well as massive computational and bioinformatics capability.

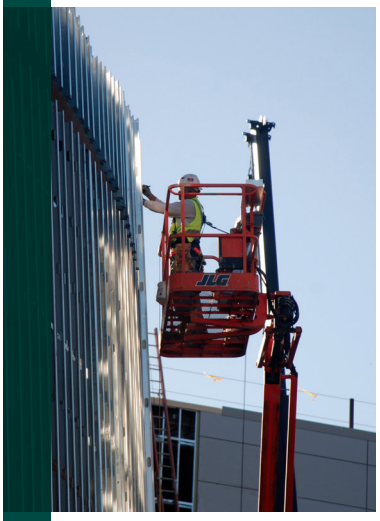
It's a huge undertaking, but Lee's commitment and expertise are translating well at JAX Genomic Medicine. David Valle, M.D., director of the Institute of Genetic Medicine at The Johns Hopkins University School of Medicine and JAX trustee, notes, "Charles Lee is an internationally recognized leader in molecular cytogenetics and the application of genomic medicine. His clinical expertise will advance the translational focus of JAX Genomic Medicine, and his international presence will broaden JAX's visibility globally."

LEAVING THE COMFORT ZONE

Having concluded his interview and safely navigated his way to the reception site, Lee is officially welcomed to Connecticut and JAX Genomic Medicine by Connecticut Gov. Dannel Malloy and JAX President Edison Liu. During his speech, Malloy, who threw his full support behind building JAX Genomic Medicine in Connecticut, jokes that he was very impressed with what Lee had accomplished in a very short time in Boston, but he expects even more now that Lee is in Connecticut. Then it's Lee's turn to talk.

"When I spoke, I confessed to the governor and the others in the room that I was way out of my comfort zone, that I didn't like being the center of attention," says Lee. "But to make a difference, to start a bold project like JAX Genomic Medicine, it required a lot of people having to leave their own comfort zones. The governor and his staff had to move the state out of its comfort zone and make significant investments to bring JAX Genomic Medicine and other important bioscience initiatives to Connecticut. Dr. Liu had to step out of his comfort zone in Singapore and return to the US to become the first non-mouse geneticist to lead JAX.

STATUS UPDATE:
JAX GENOMIC MEDICINE



The leadership and scientists at JAX in Bar Harbor had to step out of their comfort zone of focusing mainly on mouse genetic research to venture more into the realm of clinical and human translational research. Indeed, there are many that needed to take risks for us to be here. As a result, we are now all here, working hard every day, to make a real difference in the lives of patients burdened with a genetic disorder or other illness. I feel such positive energy from all of the JAX Genomic Medicine faculty and staff every morning that I come into work, and I realize that it's all worth it."

Lee's trip to the governor's reception foreshadows his work moving forward, embracing a new normal that is simultaneously difficult and rewarding.

"It's a privilege to have the opportunity to do something that goes far beyond ourselves, to contribute to breakthroughs that will benefit mankind," Lee says. "I'm really looking forward to taking this exciting journey ahead together, with my new colleagues at JAX and with my new neighbors in Connecticut." ●

The Jackson Laboratory for Genomic Medicine is rapidly taking shape in Connecticut. Here's a quick status update on the project.

As of mid-October, 77 people were on JAX Genomic Medicine's payroll, including 10 principal investigators and 48 Ph.D.s. The staff includes 21 people who were Connecticut residents at the time they were hired. At least 80 employees will be on board by the end of 2013, and 180 by this time next year when the permanent facility opens.

As these early hires work in leased laboratory and administrative spaces on the campus of the University of Connecticut Health Center (UCHC), construction of the 189,000-square-foot JAX Genomic Medicine facility nearby is on schedule and on budget. With each passing week, the new building assumes a visibly more finished status, and crews are working now to get the structure sheathed and weather tight before winter. About 200 workers are on the site each day, including carpenters, plumbers, electricians, masons, technology contractors, HVAC contractors and others. The construction value of the work being accomplished is about $1.5 million weekly.

Laboratory equipment, office furnishings, interior decor, landscaping, signage and parking will complete the project. By the time it is ready for occupancy in October 2014, the building will meet Gold-level standards for LEED certification, an internationally recognized measurement of environmentally responsible building design, construction and maintenance standards.

Photos: Janine Gelineau, UCHC

Visit **www.jax.org/ct** to learn more about JAX Genomic Medicine and see the latest photos of the new building taking shape.

Steve Munger sought out Jackson Laboratory Professor Gary Churchill, Ph.D., for his postdoctoral appointment.

Postdocs @JAX

by Meg Haskell • Photography by Françoise Gervais

Some of the ***MOST IMPORTANT*** members of The Jackson Laboratory's scientific community are here only a ***SHORT TIME***.

Postdoctoral researchers from universities all over the world compete for appointments at The Jackson Laboratory, where they will polish their research and lab management skills, submit their findings to scientific journals, and gain practice in writing and managing research grants. They typically spend between three and five years at the Laboratory, then use the skills and connections they've developed here to move on to professional positions at other research institutions and universities.

At any given time, about 40 postdocs work in the laboratories of JAX principal investigators on the Bar Harbor campus. Another 12 or so are at JAX Genomic Medicine in Farmington, Conn., although that number is growing daily as new investigators come on board.

JAX postdocs have access to all the Laboratory's scientific support services, unparalleled mouse and genomic resources, training programs, and numerous courses and conferences centered on research in genomics, genetic diseases and biomedicine. They are paid a modest stipend through a variety of sources: some are Jackson Laboratory fellows, funded by the institution itself; some are paid by their faculty mentors; and others come with their own research funding.

Postdocs are a welcome presence in the laboratories of most JAX investigators, including glaucoma researcher and Professor Simon John, Ph.D.

"These are high-level individuals, in terms of both their intelligence and their skills," he says. "They can and do work independently, but in the best case the relationship with the faculty mentor is a fun, mutually beneficial experience where you're synergizing off each other, challenging each other, and really getting a lot done in a laboratory environment.

"We need them to keep science going," John says. "They are the next generation of competent scientists who cannot only do the science but also run a laboratory."

A case in point is Steven Munger, who for the last two years has been working in the laboratory of Professor Gary Churchill, Ph.D., a statistical geneticist.

Munger earned his undergraduate degree in biology at the University of Michigan in Ann Arbor and completed a Ph.D. in genetics in 2010 at Duke University. He had a wide choice of postdoctoral options.

"I was good in the lab and I had a good grounding in genetics," he says of his formal education. "But what I really wanted to do was to work with large-scale data analysis, and I didn't really have the skill set to do that. So I persuaded Gary Churchill"—whom he had met at several conferences—"to take me on as a postdoc and to help train me in the computational aspects of genetics."

LEFT Assistant Professor Gareth Howell, who first came to the Laboratory for a postdoctoral fellowship in 2003, mentors current postdocs earlier this year. After a second postdoc in the U.K., he returned to work as a research scientist in the laboratory of Professor Simon John, then was promoted to the JAX faculty in 2012.

BOTTOM, RIGHT Munger teaches students bioinformatics at the MDI Biological Laboratory in Bar Harbor. His work involves intense data analysis as well as teaching and outreach.

Churchill, he notes, has an international reputation as a leader in bioinformatics, and the postdocs in his laboratory are invariably enthusiastic about their experience working with him.

When he finishes his postdoc appointment, Munger expects to land a teaching position at a major research university. But already he has made important contributions to the scientific community while making progress toward his own professional goals.

Working with Al Simons in the JAX Computational Services group and colleagues in Churchill's lab, Munger has developed a software package, called Seqnature, for constructing individualized diploid genomes for Diversity Outbred mice. This tool allows researchers to more accurately identify regions of the mouse genome that affect the expression of specific genes.

Munger is the lead author of a paper on Seqnature, currently in revision for a major scientific journal, which he presented in September at the annual meeting of the International Mammalian Genome Society in Salamanca, Spain. Professional papers published in peer-reviewed journals are an essential component of a scientist's CV and a deciding factor when qualifying for independent research funding. Presenting research findings at major scientific gatherings is also a coveted opportunity.

Munger also has seized every opportunity to teach during his fellowship at JAX.

Through his connection with Churchill's group, he has taught computational biology online to gifted high school students at magnet schools in Maine, North Carolina and Georgia. He has lectured Tufts and University of Maine graduate students about RNA/sequencing and complex trait analyses.

Visit **www.jax.org/education** to learn more about the postdoctoral experience at JAX.

He has presented his work at the Genetics Interest Group at the Laboratory and has spoken about high-throughput sequencing and systems genomics at JAX short courses for external investigators. He is scheduled to give an introductory talk on computational biology to University of Maine undergraduates this fall and will lecture at a short course on bioinformatics at the Mount Desert Island Biological Laboratory. Munger also has worked closely with JAX researchers to help them become more familiar with the tools of computational genomics.

"We all need to be doing more, working harder, to educate the public about the importance of the work we do," he says. "It's important to speak to our peers at scientific conferences, but we also need to do whatever we can to elevate the collective scientific literacy of our society."

Bright, ambitious postdocs like Munger are essential to the Laboratory's mission and future, says Tom Litwin, vice president for education at The Jackson Laboratory.

"Postdocs are fundamental to the Lab's intellectual fabric and scientific accomplishments," says Litwin. "They are important contributors to the faculty members' labs in which they work and the research they accomplish. While working at JAX, and when they complete their work and leave, they are our ambassadors to the broader world. We want to send them into the world as critical scientific thinkers and talented leaders who capably represent The Jackson Laboratory and the postdoc program itself."

JAX aims to attract bright young postdocs by offering them an enriched learning environment, says Litwin. In addition to the faculty researchers with whom they work most directly, JAX postdocs are encouraged to establish a network of other Laboratory scientists whose work complements their own. They participate in monthly forums on topics ranging from how to write an effective research grant application to ethical considerations in bioscience. They are offered opportunities to teach and mentor others, and they get help in applying for positions at research institutions and universities.

Litwin says it is essential to recruit the most promising young postdocs to The Jackson Laboratory, to provide them with the support they need and to demand their best work.

"If we are good mentors, if we expand and develop their scientific experience in meaningful ways, they will leave here well-positioned for appointments at major scientific and academic institutions," he says. "And they will in turn reflect well on the opportunities JAX offers, encouraging other highly qualified people to apply to our postdoctoral programs." ●

> ***"POSTDOCS ARE*** fundamental to the Lab's intellectual fabric and scientific accomplishments... they are ***OUR AMBASSADORS*** to the broader world."
>
> **TOM LITWIN** VICE PRESIDENT FOR EDUCATION

THE QUESTIONER

by Joyce Peterson - Photography by Françoise Gervais

JAX Professor, Executive Research Fellow and former Director Ken Paigen, Ph.D., explores the elusive basics of how mammals evolve and develop

Kangaroo,
naked mole rat,
whale, Tasmanian devil,
Thomson's gazelle, rhinoceros.
Mouse. Human.

THE ENGINE OF EVOLUTION,
which powers the astounding
variety of mammalian life,
IS GENETIC RECOMBINATION.

And the mammalian genome
comes equipped with a toolkit
of proteins designed to work
on that engine.

KEN PAIGEN
wants to figure out
how the tools work.

Paigen

was The Jackson Laboratory's director (the role now designated president and CEO) from 1989 to 2003. Since then he has moved back to the research bench as a JAX professor and executive research fellow.

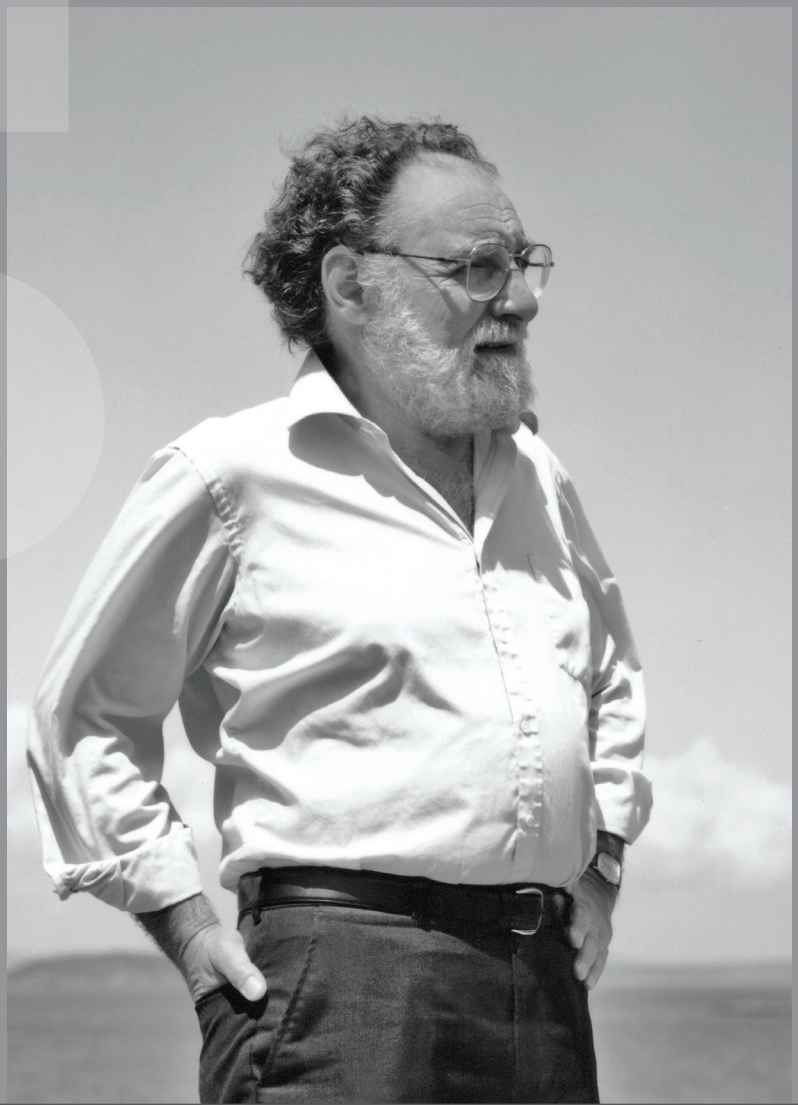
PRDM9

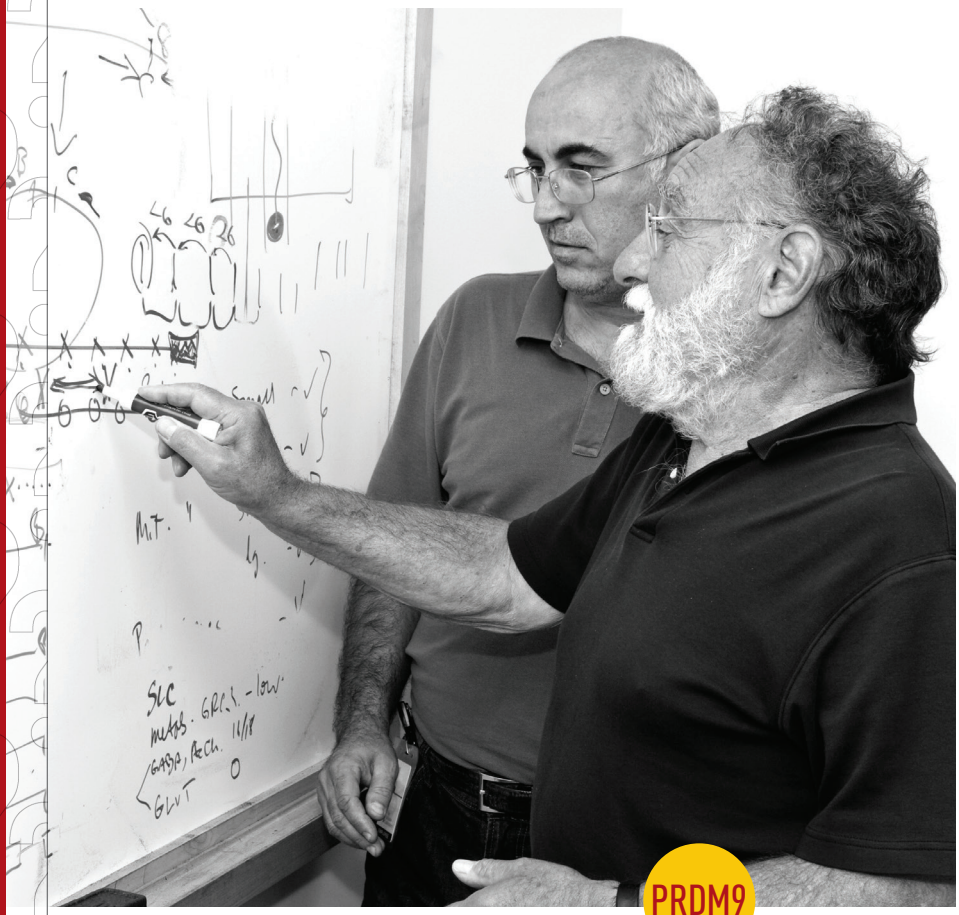
In late 2009 Paigen's laboratory published a paper in the journal *Science* showing that a protein known as PDRM9 turns certain locations on chromosomes into "hotspots" of genetic recombination activity during the first moments of reproduction. It was a hot moment for hotspots: Two other research groups, publishing in the same issue of the journal, identified PRDM9 as important in both mouse and human genetic recombination.

Paigen is the principal investigator of a new five-year, $8.2 million grant from the National Institute of General Medical Sciences of the National Institutes of Health. Together with collaborators Petko Petkov, Ph.D., Mary Ann Handel, Ph.D., Matt Hibbs, Ph.D., and Greg Carter, Ph.D., he will explore the key mechanisms for how PRDM9 reshuffles DNA during meiosis, the process by which egg and sperm divide their respective complements of chromosomes in half, providing one set each to the offspring.

"Defects in meiosis can result in infertility or subsequent embryonic loss," Paigen says. "Actually, up to half of all human pregnancies go awry due to spontaneous abortions or developmental defects. Those losses, which usually go unnoticed, are in large part the consequence of failures of the genetic recombination process."

With his beard, glasses, twinkling dark eyes and shock of curly gray hair, Paigen has the classic scientist "look." **IN FACT, HE HAS AN INTERNATIONAL REPUTATION AS A SCIENTIST'S SCIENTIST:** the quiet voice in the back of a packed lecture hall asking the question all the other researchers wish they had raised.





Research Scientist Petko Petkov works closely with Paigen to better understand the mechanisms of genetic recombination.

As challenges to human health go, Paigen says, "humans generally do fine at having babies. But meiosis is simply one of the most fundamental biological processes; there's a lot we don't know about it and science is about investigating the unknown. There's a need to question and explore how the world works, and you learn later on what the practical applications are.

"As Einstein said, 'What use is a baby until it grows up?'"

PRDM9 belongs to a family of proteins known as zinc finger proteins, which recognize specific sequences in DNA and regulate their function. Paigen notes that there are more than 800 zinc finger proteins in the human and mouse genomes.

A human is born with a complete set of chromosomes in every cell, with about 20,000 genes turning on and off to orchestrate changes in gene expression, and thereby the physiological changes that occur throughout a lifetime as shaped by environment (diet, exercise, sun exposure and so on). Zinc finger proteins are the cellular tools that enable these gene expression changes as a baby grows its first tooth, learns to swim, goes through puberty, gains the freshman 15 and finishes a first marathon at age 85.

"Approximately one out of every 25 genes codes for a zinc finger protein," Paigen says, "but the rules governing how they recognize specific DNA sequences are still obscure. While PRDM9 appears to function only during meiosis, it provides an exceptional opportunity to expand our understanding of those rules."

PATH TO RESEARCH

Paigen was born in 1927 at Hunts Point Hospital in the Bronx, N.Y. "I had a normal, middle-class upbringing," he says. "Father was a dentist, Mother stayed at home with my older sister and me."

What he calls the "formative educational experience of his life" started in the fourth grade, when he was selected to attend the Speyer School, an early experiment in magnet schools for students with high IQs, as well as a separate program for students with IQs under 90.

"Each semester we had to write a book detailing what we had learned about a given subject," he recounts. "One of our teachers was interested in antiques, and at the age of 11 I could tell you the difference between Chippendale and Hepplewhite furniture, though I couldn't possibly do it today."

Paigen's academic aptitude got him into the Bronx High School of Science and on to Johns Hopkins University as a pre-med student, in keeping with his father's wishes that he become a physician. "When I started college I didn't know there was such a thing as a Ph.D.," he says. "In my senior year we got a new professor who taught a course in cellular physiology (which nowadays would be called cell biology). I fell in love with it, and I found out you could actually become a scientist. Much to my father's distress, I got accepted as a graduate student at Caltech."

Ken and Bev Paigen
at home in Bar Harbor, 2002.

Paigen describes the job market for scientists facing him in 1950, after earning his Ph.D. in biochemistry, as "utterly and totally abysmal." But at last, after two postdoctoral stints, Paigen heard that the new Roswell Park Memorial Institute (now Roswell Park Cancer Institute) was looking for faculty, and he landed his first academic job there without even having to interview for it. Over his 27 years at Roswell Park, he would become the chair of the department of molecular biology.

Paigen and his wife, JAX Professor Beverly Paigen, Ph.D., faced some tumultuous times at Roswell Park and eventually decided to move to U.C. Berkeley, Ken becoming the chair of the department of genetics and Beverly a scientist in the Children's Hospital Research Institute. "The University was a great place," Paigen says. "We had flowers in our garden every day of the year, we had a sailboat in the Berkeley marina and went sailing on San Francisco Bay, we attended all the performances of the dance theater and the repertory theater, and we went skiing in Tahoe. But after seven years I was invited to become the director of The Jackson Laboratory."

TRIAL BY FIRE

For Paigen, joining The Jackson Laboratory in 1989 was a kind of trial by fire. After a visit to the Laboratory on May 10 of that year, having agreed to take the director's post in October, he returned to Bangor International Airport to drop off his rental car and fly home. A note was waiting for him at the rental car desk: "The Lab is on fire."

"I presumed this was a fire in a wastepaper basket," Paigen says, but then he decided it must be a serious situation, got back into the rental car and drove back to Bar Harbor.

"There's a place on Route 3 in Trenton, Maine," he recounts, "as you approach Mount Desert Island, where you make a turn and see the island's mountains for the first time. I could see an enormous plume of smoke. It looked like a volcano. And when I got to the Lab there was chaos."

A fast-spreading fire had started in Mouse Room 4 in the Laboratory's

mouse production facility. A few weeks earlier, Paigen had read an account of the Exxon-Valdez oil spill disaster in *The New York Times*. The article had detailed the errors in leadership, planning and communication that had exacerbated the problems caused by the spill, lessons Paigen kept in mind during the rescue process.

"As of that day I stepped into the director's job," he says, adding with a laugh, "I don't remember what I did with that airline ticket."

This major milestone in JAX history coincided with a turning point in mammalian genetics. The late 1980s brought the advent of gene transfer technology—the ability to engineer changes in a mouse genome in order to develop better models of human disease. The laboratory mouse was about to become the primary platform for genetics research, and The Jackson Laboratory was poised to take an even larger role in the international biomedical research community.

Paigen headed to Capitol Hill to convince the U.S. Congress that The Jackson Laboratory needed not only to rebuild, but to expand. With the Laboratory's counsel, Ken Trevett, and lobbying consultants Lloyd Mees and Susan Geiger, the JAX team met with members of Congress and made their case for funding.

Former U.S. Senator George J. Mitchell of Maine recalls the effort: "I worked closely with Ken and other Jackson Lab supporters to obtain funding that was crucial to rebuilding the Lab. It is in times of crisis that leaders are most severely tested, and the aftermath of the fire was a crisis. Ken was at all times strong and visionary, as he successfully led the effort. It was a pleasure for me to help restore the Lab, an important part of our economy on Mount Desert Island and a national treasure in medical advancement."

GROWTH AND OPPORTUNITY

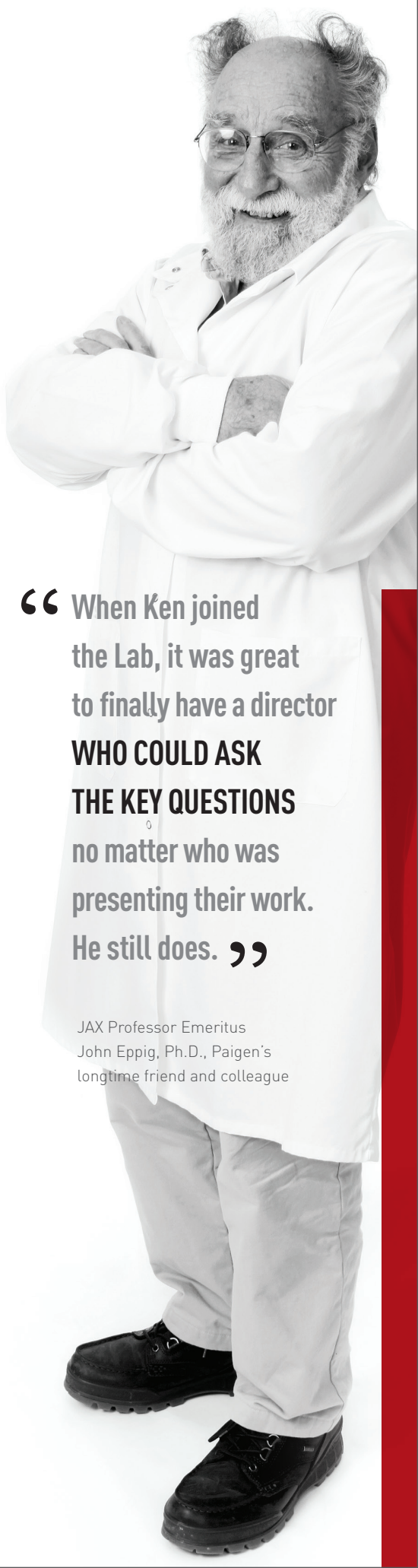
During Paigen's tenure as director, the Laboratory saw a doubling in its staff, from 548 to 1,162 employees, and its operating budget, from $25.4 million to $50.4 million. And the institution's role as the international hub of mammalian genetics also grew, with the expansion of the Mouse Genome Informatics research databases and distribution of hundreds of new mouse models of human disease to laboratories around the world.

JAX Chair Emeritus David Shaw had helped to recruit Paigen as director. "As chair of the board of trustees, I was grateful to be associated with such a talented and passionate director, and was only sorry that Ken's sailing days occasionally suffered from the heavy workload of historic opportunity, change and exponential growth. Ken is deeply committed to realizing the potential of genetics to improve human health and well-being. That commitment has been inspirational to me and many others associated with the Lab."

Paigen and JAX took a leadership role in settling one of the key research controversies of the past two decades. In the late 1990s, Harvard University obtained patents on a transgenic mouse capable of developing a human cancer. E. I. DuPont de Nemours & Co., which funded the development of the so-called "OncoMouse," retained intellectual property rights to the patent and sought to restrict the Laboratory's ability to distribute the mice. Working with Harold Varmus, M.D., the Nobel laureate who was then director of the National Institutes of Health, Paigen engineered an agreement whereby academic researchers had free access to the OncoMouse.

"Ken put the legal talents and immense prestige of The Jackson Laboratory on the line in this important cause," Varmus states. "And while we never completely voided the patent, he injected a high moral standard into the debate in support of what we now call 'open science,' a notion that underwrites more recent movements towards open access to the scientific literature and the greater use of research data. He was and is a proud warrior in such battles, showing others how to advocate for sensible policies that improve the conduct of science. JAX is justifiably proud of him!"

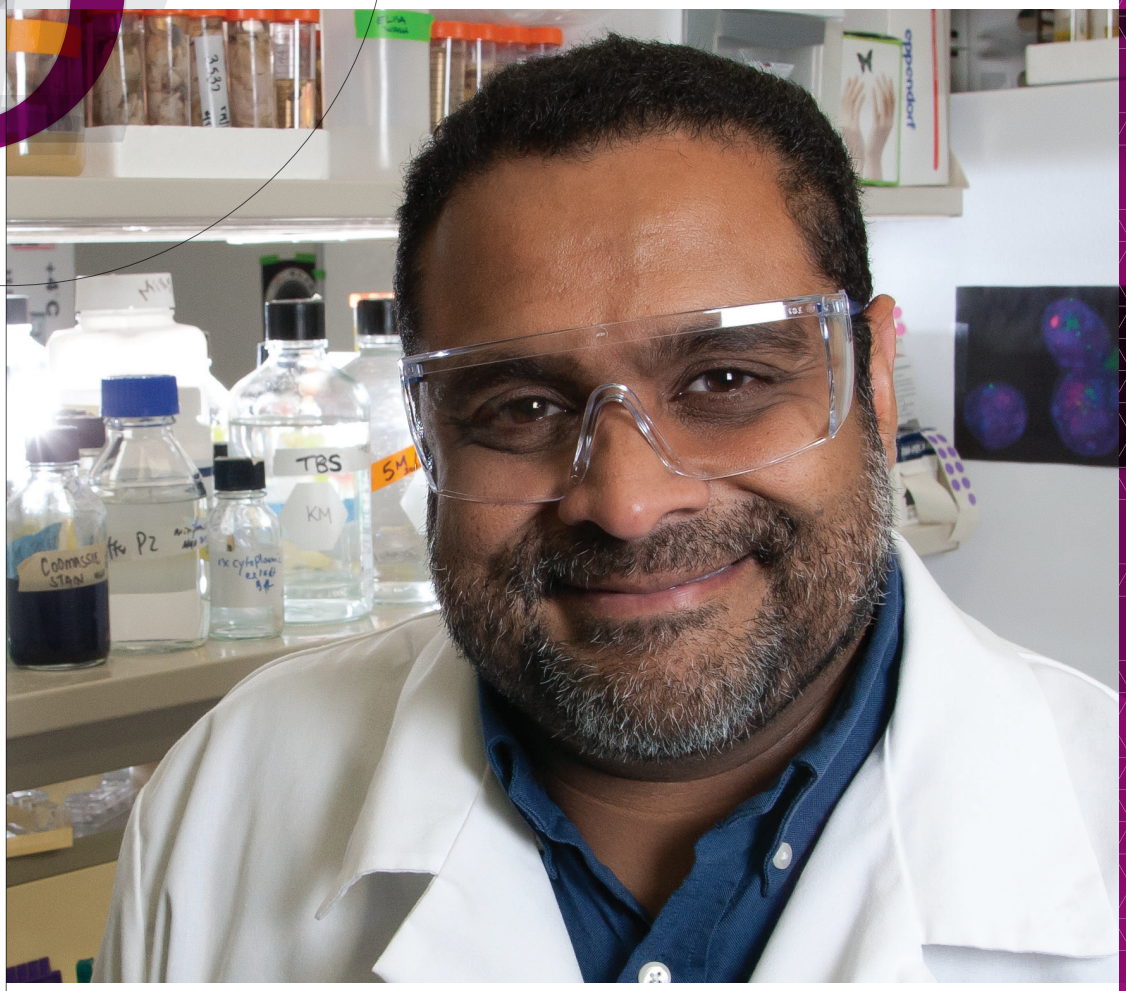
Now well into his ninth decade, Paigen shows no signs of slowing down. "After all these years I continue to be amazed by what happens in basic research. You start out studying one thing, like genetic recombination, and suddenly find your work is relevant to a host of subjects you weren't even thinking about when you started. It's one of the things that makes you want to come to work every morning." ●



"When Ken joined the Lab, it was great to finally have a director **WHO COULD ASK THE KEY QUESTIONS** no matter who was presenting their work. He still does."

JAX Professor Emeritus John Eppig, Ph.D., Paigen's longtime friend and colleague

5 questions



Muneer Hasham, Ph.D.

Associate Research Scientist
The Jackson Laboratory

Visit www.jax.org/thesearch/5-questions for bonus content from the interview.

Q *How did you get interested in science?*

A I grew up in Tanzania, and in Africa most kids don't have toys, so I played with nature. I used to save food so that I could grow different fungi on it, and have "battles" to see which kind would win. My mom was so mad when she found out, wasting good food like that! But that sort of thing gave me a love of biology.

Q *Tanzania? When did you come to the U.S.?*

A I went to an International School, which is about equal to high school here, then applied to colleges and universities all over—Turkey, Czechoslovakia and of course the U.S. I got a full scholarship to Bowdoin College here in Maine, plus work/study jobs on campus. I put myself through school working, but I was very fortunate to have the opportunity.

Q *So was basic research your first interest?*

A I thought I would go to medical school, then go back to practice medicine in Tanzania. But I realized that it wasn't lack of doctors that was killing people there, it was the lack of good medicine that was killing people. The doctors were doing their best, but it wasn't good enough; they needed better therapies. So I went to Temple University School of Medicine in Philadelphia on a Ph.D. track.

Q *What do you do at JAX?*

A I finished my postdoctoral training with (Associate Professor) Kevin Mills, and I've stayed in his lab as an associate research scientist. I really like the research he's doing, and my work has two main objectives. First, I'm studying a specific type of DNA damage that occurs particularly in immune cells, which can lead to immunodeficiency or cancer. I also study how the damage that causes the immunodeficiency can be turned around and be used *against* cancer, as a tool to target cancer cells, but not healthy cells and further develop better therapies.

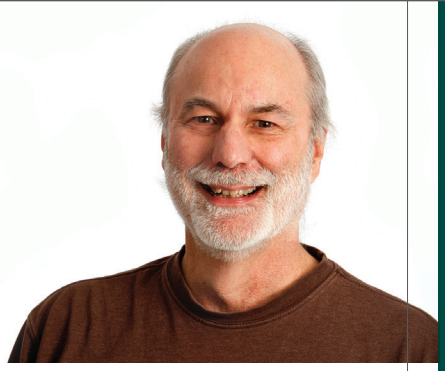
What I love about JAX is the camaraderie among principal investigators here, how easy it is to approach someone else and work together on a problem. You don't feel isolated in your lab. Of course, it's also the best place to use the best research platform there is to study human disease—the mouse—and gain a broad perspective on medical research.

Q *Do you like being in Maine?*

A I love Maine. I love the four seasons and being outdoors. I like being outside with my wife, who's from Maine, and my children, who are nine and three years old.

I enjoy being among mountains too. I used to be a mountain climber, and when I was 18 years old I climbed Mt. Kilimanjaro. I was strong as a bull! And it was amazing—the views from the mountain, the wildlife . . . I hope someday, given time and health, to continue my climbing. Climbing teaches you perseverance, which is a key component if one wants to remain sane doing research.

beyond the news



John Eppig, Ph.D.

A surprising twist in egg development

Although "eureka" moments are hard to come by, science still has its surprises, unearthed through months and years of hard, painstaking work. Take the research of Jackson Laboratory Professor John Eppig, Ph.D. Eppig's career has focused on the development of oocytes, the cells that become mature eggs in female mammals and, when fertilized by sperm, form the beginnings of life. A recent paper in the *Proceedings of the National Academy of Sciences* from Eppig and his team provides another piece of knowledge about oocyte development that, in this case, also brings with it something of a surprise.

Oocytes develop in ovarian follicles, lined with somatic (non-reproductive) cells that are vital to the development of mature eggs. Part of the development is the process of meiosis, which in humans divides the number of chromosomes in half from 46 to 23. Sperm also undergo meiosis, and fertilization provides the baby with 23 + 23 = 46 chromosomes. Oocytes have to enter what is known as meiotic arrest, however, in which they are held in a limbo-like state, sometimes for decades, before final development and ovulation as mature eggs.

Eppig has previously helped to describe the ways in which follicle cells play an important role in directing meiotic arrest and oocyte maturation. At the heart of it is a substance called cyclic guanosine monophosphate (cGMP), a messenger molecule vital to maintaining meiotic arrest. cGMP is transferred from the follicle cells to the oocytes, so it was thought that the follicle cells probably "direct" the actions of the oocytes. Now, Eppig's research shows that it's not so simple. Instead, there's a complex and nuanced conversation between the follicle cells and oocytes, with the oocytes themselves regulating the process by signaling the follicle cells.

Eppig's research shows that . . . there's a complex and nuanced conversation between the follicle cells and oocytes.

Oocytes are vital to reproduction and have been intensively studied for decades, so it would be easy to think that we know all about them. But as the paper indicates, they can still surprise even the most experienced researchers: "Thus, although the somatic compartment of ovarian follicles plays an essential role in the maintenance of oocyte meiotic arrest, as has been known for many years, this function of the somatic cells is surprisingly regulated by signals from the oocyte itself."

Wigglesworth K, Lee KB, O'Brien MJ, Peng J, Matzuk MM, Eppig JJ. Bidirectional communication between oocytes and ovarian follicular somatic cells is required for meiotic arrest of mammalian oocytes. *Proc Natl Acad Sci U S A.* 2013 Sep 24;110(39):E3723-9.

Our neighborhood

Val Scott (right) and Melissa Rockwood joined more than 80 riders on a mild early October morning in Bar Harbor for the inaugural Cookie's Ride to benefit cancer research at the Laboratory. Scott and Rockwood helped organize the event, which topped its $25,000 fundraising goal. •

Photograph by Rogier van Bakel

The Jackson Laboratory

Leading the search for tomorrow's cures

600 Main Street
Bar Harbor, ME 04609-1523

Two years ago Meghann Harris ran her first marathon. She successfully completed the Mount Desert Island Marathon and raised funds for research into Rett syndrome, an autism-spectrum disorder (ASD), at The Jackson Laboratory. This year Meghann's daughter Eliza, who has Rett syndrome, completed the children's race held in conjunction with the marathon. Recent Rett syndrome research successes at JAX and elsewhere provide optimism that better therapies may soon be available for Eliza and others with ASDs.

Photograph by Rogier van Bakel