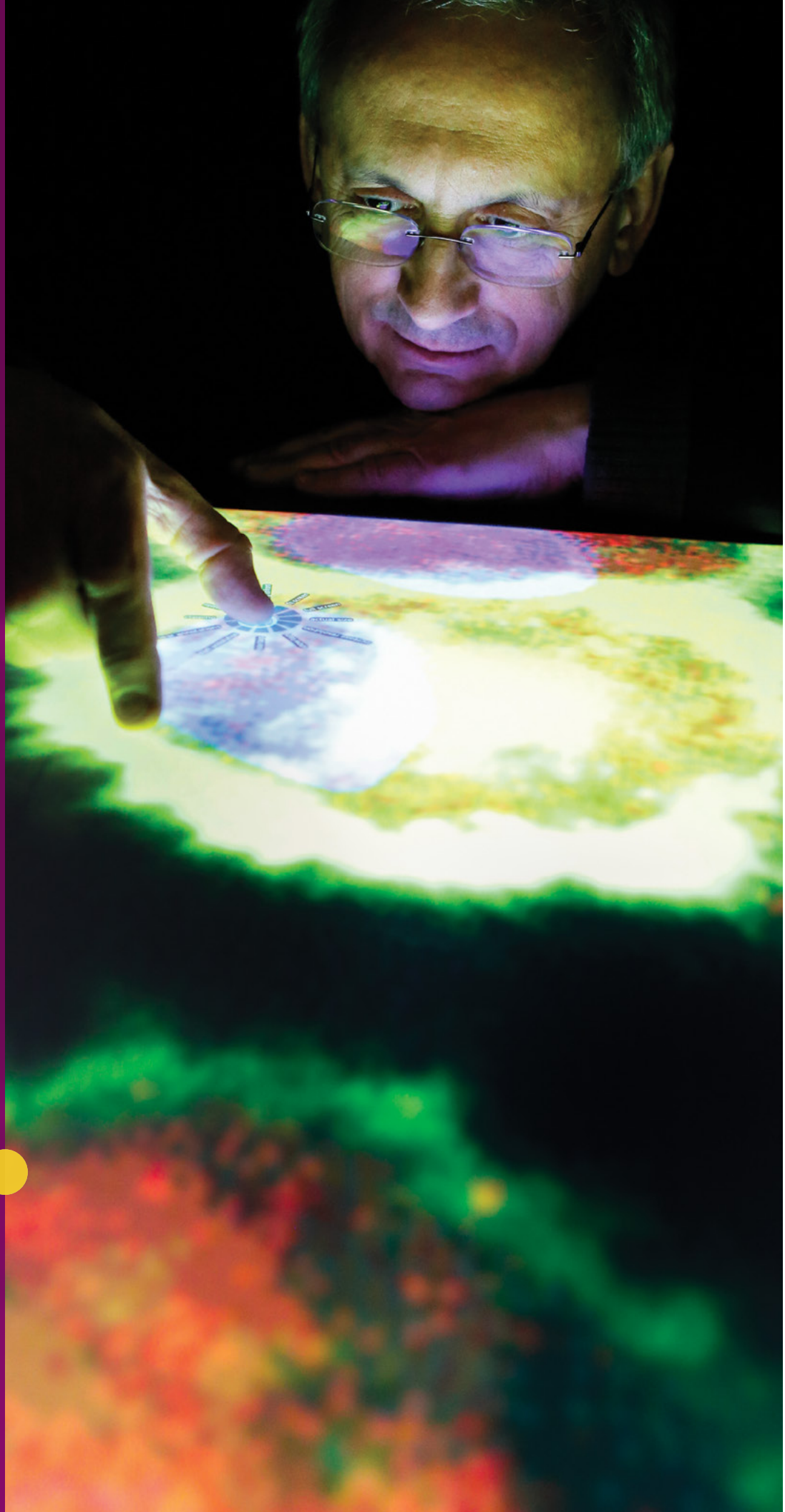
THE SEARCH

SPRING 2014 • VOL.7 • NO.1 • THE JACKSON LABORATORY



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THE SEARCH

A PUBLICATION OF THE JACKSON LABORATORY

LEFT RNA used to be seen as having limited functions, mostly carrying out the process of converting DNA code to working proteins. Researchers now know RNA plays far more roles in each cell, and RNA research is growing in importance. Unfortunately, the RNA molecules themselves are difficult to work with and tend to degrade quickly. Here, RNA samples awaiting analysis are kept stable in Eppendorf tubes on ice. *Photograph by Françoise Gervais*

Cover photograph by Jennifer Torrance

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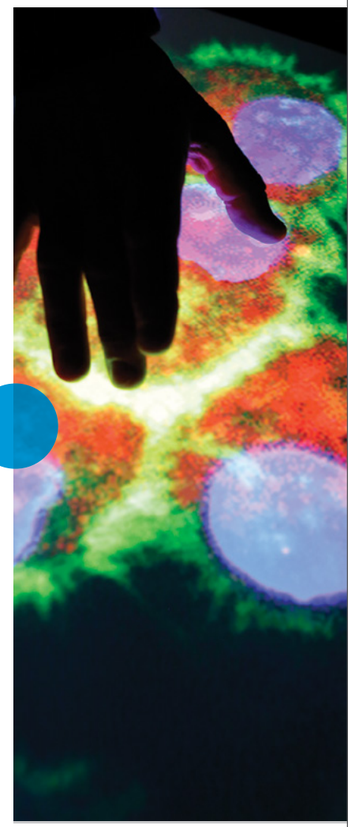

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Printed April 2014

The Jackson Laboratory
Leading the search for tomorrow's cures

President's message

Our bodies are made up of a lot of cells. The latest estimates put the number at around 100 trillion, give or take a few.

Large as that number sounds, our own cells are vastly outnumbered by fellow organisms we carry within and on us: the microorganisms that make up what is now called the microbiome. For every cell that's ours, there are approximately 10 microbial cells, for a total of 1 quadrillion additional cells. We have long known the consequence of having too many of the nastier varieties—infectious disease. But only recently has the nuanced interplay between ourselves and our microbiomes become better known and appreciated, and there is growing evidence that microorganisms contribute to our wellness as well as to disease.

The Jackson Laboratory has been investigating the genetic material contained within each and every mammalian cell for more than 80 years. How does it function, and what happens when proper function is somehow disrupted? The answers gained while working to answer those simple questions have contributed greatly to medical progress and promise much more to come. But now JAX is expanding its research to embrace our quadrillion fellow travelers and how they influence human health, both for better and for worse.

Having George Weinstock, Ph.D., join our faculty was a terrific step forward. George helped lead the human microbiome project, which gathered essential data about the microbiome at various sites in and on our bodies. Building on this foundation, scientists can investigate how the microbiome varies between sites and between individuals and how those variations contribute to health and disease.

Another new faculty member, Jacques Banchereau, Ph.D. (profiled on page 16), looks at the microbiome from a different angle—how the body responds immunologically when things go awry. And while immunology encompasses a far wider scope, including autoimmune disease, cancer immunotherapy and much more, infectious disease response is an important component of the expanding immunology program.

Overall, JAX research still focuses on mammalian genetics and genomics. But bringing our microbial community into the picture expands our knowledge of how our bodies work and increases our ability to improve human health.

Edison Liu, M.D.
President and CEO, The Jackson Laboratory

news&notes

JAX awarded Korean grant for cancer genomics project

The Jackson Laboratory, in collaboration with Seoul National University, will receive a five-year, $7.5 million grant from the South Korean government for a large-scale cancer genomics project employing the latest sequencing technology and special JAX mouse models that can host human tumors.

"This is a wonderful example of the international collaborations that JAX is building to rapidly advance its research mission," says Charles Lee, Ph.D., scientific director of The Jackson Laboratory for Genomic Medicine and leader of the JAX component of the project.

Lee, who is also a distinguished visiting professor at Seoul National University, will work with principal investigator Jong-Il Kim, M.D., Ph.D., of the Seoul National University College of Medicine and other academic collaborators in Seoul. During the first phase of the grant (2013-15), Kim and colleagues will collect and store tumors from patients with gastric, breast, colon, lung and rare cancers, and sequence and determine the genomic signatures of those cancers. Lee will lead the development of hundreds of new mouse model systems for gastric, breast and other cancers that will be made available to the worldwide scientific community.

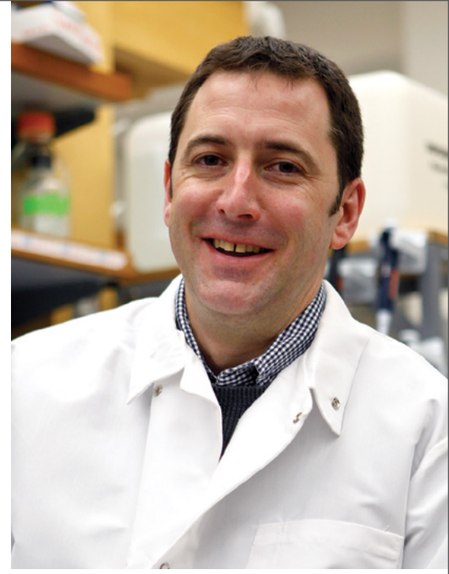
Jeffrey Chuang receives grant for RNA-protein research

Jackson Laboratory Associate Professor Jeffrey Chuang, Ph.D., has been awarded a two-year grant totaling $519,750 from the National Human Genome Research Institute for his studies into how genes are regulated and expressed.

Chuang researches the regulatory effects of RNA-protein interactions. "Gene regulation at the RNA level is central to many human diseases," says Chuang, "including cancer, muscular dystrophy, and many of the most common learning disabilities. Advances in understanding the underlying mechanisms of RNA-protein interaction have great value for improving health."

DNA provides the blueprint for building and running a living organism, but some proteins in the cell act like change orders in a construction plan. Binding to DNA molecules, these proteins can change how genes are expressed. While DNA-protein interactions for hundreds of proteins have been cataloged and studied, protein interactions with RNA, molecules transcribed from the DNA template that perform a variety of functions, are less well known.

"Scientific understanding of RNA-level gene regulation is rudimentary, despite the fact that this type of regulation probably influences the function of most genes," Chuang says. "Excitingly, several groups around the world, notably our collaborators in the Brenton Graveley lab at the University of Connecticut, have started to generate new types of experimental data on RNA-protein interactions."



Gareth Howell wins Rudin Glaucoma Prize

Assistant Professor Gareth Howell, Ph.D., is one of two winners of the prestigious 2013 Lewis Rudin Glaucoma Prize from The New York Academy of Medicine (NYAM). The prize recognizes the most significant scholarly article on glaucoma published in a peer-reviewed journal in the prior calendar year.

"For the first time in the history of the Rudin Glaucoma Prize, two prizes will be awarded. Each is a truly novel and transformative paper and the culmination of years of research that was done despite the universal feeling that neither could ever be accomplished," said Dr. David Abramson, chair of the Lewis Rudin Prize selection committee and chief of ophthalmic oncology at Memorial Sloan-Kettering Cancer Center.

Howell's paper, "Radiation treatment inhibits monocyte entry into the optic nerve head and prevents neuronal damage in a mouse model of glaucoma," was published in the *Journal of Clinical Investigation*. The study was performed while Howell was a research scientist working with Howard Hughes Medical Institute Investigator Simon John, Ph.D. Howell is now an assistant professor at the Laboratory and is using genetic and genomic approaches to understand neurodegenerative diseases including glaucoma, dementia and traumatic brain injury.

JAX researchers show that acarbose extends life span

A research team led by Professor David Harrison, Ph.D., reported in December 2013 that acarbose, a drug that is frequently prescribed in Europe for type 2 diabetes, extends the life span of mice. Interestingly, male mice show a more pronounced effect than the females. The study, prepared in collaboration with groups at the University of Texas Health Science Center at San Antonio, the University of Michigan and other institutions, appears in the journal *Aging Cell*.

Though the mechanisms behind the life-span-extending effects of acarbose have yet to be determined, reducing insulin levels could be a factor, says Jackson Laboratory Senior Research Scientist Kevin Flurkey, Ph.D., a co-author of the study. "Acarbose inhibits digestion of complex carbohydrates. It diminishes the release of glucose into the bloodstream from the food you're digesting, preventing insulin spikes."

In 2009, under the Interventions Testing Program of the National Institute on Aging that also funded this research, the Harrison lab reported that rapamycin significantly extends the life span of mice, the first demonstration of a pharmaceutical intervention to do so in mammals.

In related research, also reported in *Aging Cell*, the researchers at the three participating institutions also showed recently that the life span-extending effects of rapamycin vary with both dosage of the drug and gender of the mice, with greater effect in females than males.

A. Karolina Palucka joins JAX Genomic Medicine

Internationally recognized clinical oncologist and cancer immunologist A. Karolina Palucka, M.D., Ph.D., joined The Jackson Laboratory for Genomic Medicine faculty on March 1 as professor and associate director of cancer immunology.

Science magazine recognized cancer immunotherapy as the "Breakthrough of the Year" in 2013, and Palucka is one of the leaders in this field. Her research exploits dendritic cells, which control the body's immune response to tumors, as the basis for new vaccines against melanomas and other human cancers.

In a recent interview in the journal *Nature,* Palucka described how she used this approach to treat the pancreatic cancer of Nobel Prize winner Ralph M. Steinman using dendritic cells—the very cells Steinman and colleagues had discovered. "Although we can't say for sure that this treatment was responsible, Ralph survived for 4.5 years after his diagnosis—something that only around 5 percent of patients with this disease achieve," she told the interviewer.

"The diagnostic aspect of genomic medicine is very important, but so is the therapy component," says Charles Lee, Ph.D., scientific director of JAX Genomic Medicine. "We need to keep coming up with creative ways to utilize a person's genetic information to develop novel and effective therapies to human diseases. Dr. Palucka has had amazing success in this area and I am absolutely delighted to have her join our team here in Connecticut."

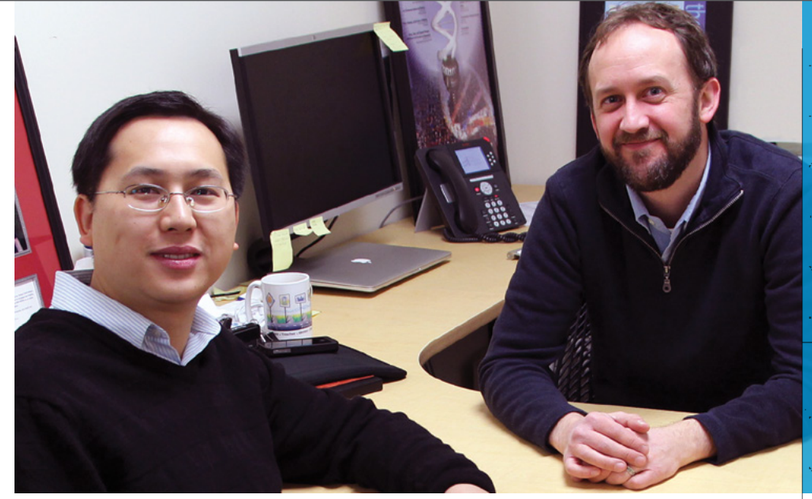
Edison Liu named 2014 Chen Award recipient

The international Human Genome Organisation (HUGO) has named Jackson Laboratory President and CEO Edison Liu, M.D., as the recipient of the 2014 Chen Award for Distinguished Academic Achievement in Human Genetic and Genomic Research

In 2010, Yuan-Tsong Chen, M.D., and Alice Der-Shan Chen established the Chen Award to celebrate research accomplishments in human genetics and genomics, and to recognize the tremendous impact that genetics and genomics have had on the improvement of health and treatment of diseases. The annual award honors the achievements of a biomedical scientist who has made significant contributions to genetics and genomics. As the 2014 awardee, Liu will receive a $10,000 award and plaque, and will present a plenary lecture at HUGO's annual meeting in Geneva, Switzerland, on April 30.

HUGO is an international organization dedicated to coordinating research in the human genome and fostering collaboration among scientists through meetings and educational programs. Part of HUGO's mission is to encourage public debate and provide information and advice on the scientific, ethical, social, legal and commercial implications of human genome projects.

Zhengqing Ouyang and Michael Stitzel



JAX, UC Davis extend, expand partnership

The Jackson Laboratory and the University of California, Davis are expanding their 15-year collaboration to provide mutual support in research infrastructure and educational programs.

The new agreement will enable UC Davis to fully utilize JAX's Sacramento-based infrastructure to reduce long-term capital and operating expenses, while providing flexibility to the UC Davis investigators and administration in pursuit of their research results.

"This new memorandum of understanding between JAX and UC Davis not only stretches research dollars through collaboration, but also enables two nonprofit organizations with similar missions to recruit world-class scientists and contribute to the Sacramento region's life sciences momentum," said Auro Nair, Ph.D., general manager of JAX® Mice, Clinical and Research Services. "UC Davis has been a key ally over the last decade as we grew from 50 employees in 2008 to nearly 200 employees at our Sacramento facility."

Harris Lewin, Ph.D., UC Davis vice chancellor of research, said, "As UC Davis grows to meet its strategic imperatives, The Jackson Laboratory's world-class mouse infrastructure and scale in Sacramento can provide a measure of capital and operating flexibility for the University, which should result in more innovative, efficient and scientifically substantive collaborations in the future."

Three JAX faculty among GenomeWeb top young genomics researchers

Every year GenomeWeb, an influential online site that focuses on genomics research, identifies and profiles 20 of the most promising up-and-coming researchers. This past year's list, released in late December, includes three JAX researchers—Zhengqing Ouyang, Ph.D., Michael Stitzel, Ph.D., and Haoyi Wang, Ph.D.—who are just beginning their careers as principal investigators.

"Having three investigators on this list of 20 really speaks to the exceptional talent of the scientists we have recruited to our research team," says JAX President and CEO Edison Liu, M.D.

All three came to JAX after postdoctoral appointments with pioneering genomics researchers. Their work moving forward will explore important yet very different areas of genomics investigation.

In December 2012, Ouyang began work at JAX Genomic Medicine as one of its first faculty members after completing a postdoctoral appointment with Michael Snyder, Ph.D., at Stanford University. He uses computational methods to explore non-coding RNA, which is transcribed from DNA but doesn't code for proteins. Long considered "junk" in the genome, recent research has indicated that such RNA is very important for proper genomic and cellular function. Ouyang is using statistical and computational methods to identify non-coding RNA and tease out its function on a genomic scale.

Stitzel joined JAX Genomic Medicine in September 2013 after completing a postdoctoral appointment at the NIH in the lab of NIH Director Francis Collins, Ph.D. He investigates the genomics underlying type 2 diabetes. Early genomics studies have turned up many associations between the disease and genetic variants, but the signals are weak. Stitzel is looking at pancreatic islet cells (which secrete insulin), identifying variations in gene regulation and expression found in diabetes patients. In particular he is looking at the effects of epigenetic changes (modifications to the genome that don't alter the DNA sequence), such as changes in chromatin structure and DNA methylation, on gene expression.

Wang, who will ultimately divide his research time between JAX's Bar Harbor, Maine, campus and China, is currently finishing his postdoc work with Rudolf Jaenisch, Ph.D., at the Whitehead Institute. He will work to develop innovative new gene-targeting technologies, and he has expertise with TALENs and CRISPR/cas, the leading tools for actually editing genes within the genome. His long-term goal is to better understand diseases and defects associated with the Y chromosome.

Willys Silvers, seen here with his toy poodle Gigi, began collecting Pennsylvania Impressionist paintings with his wife Abigail in the 1980s. Their gallery is now displayed in the house of Silvers' daughter and son-in-law.

# of medicine, mice & miracles

BY JOYCE PETERSON
PHOTOGRAPHY BY JIM GRAHAM

WILLYS SILVERS AND THE JACKSON LABORATORY

"I've had one of the most fabulous lives of anybody," says Willys Kent Silvers, Sr., Ph.D. "And when you get down to it, it's all due to my association with The Jackson Laboratory."

In that case, The Jackson Laboratory has a lot of which to be proud. Silvers has had a distinguished career in biomedical research and academic leadership, including 31 years at the University of Pennsylvania and decades of service to the Laboratory. One of his books is still a go-to classic of scientific literature.

Silvers likes to point out that he was born in 1929, the year of The Jackson Laboratory's founding. He graduated from high school in 1946, "right when all the veterans from World War II returned," he says, so when he enrolled at Johns Hopkins University as a pre-med student, most of his classmates were older men attending on the G.I. bill. "College was not a joyful experience," he says.

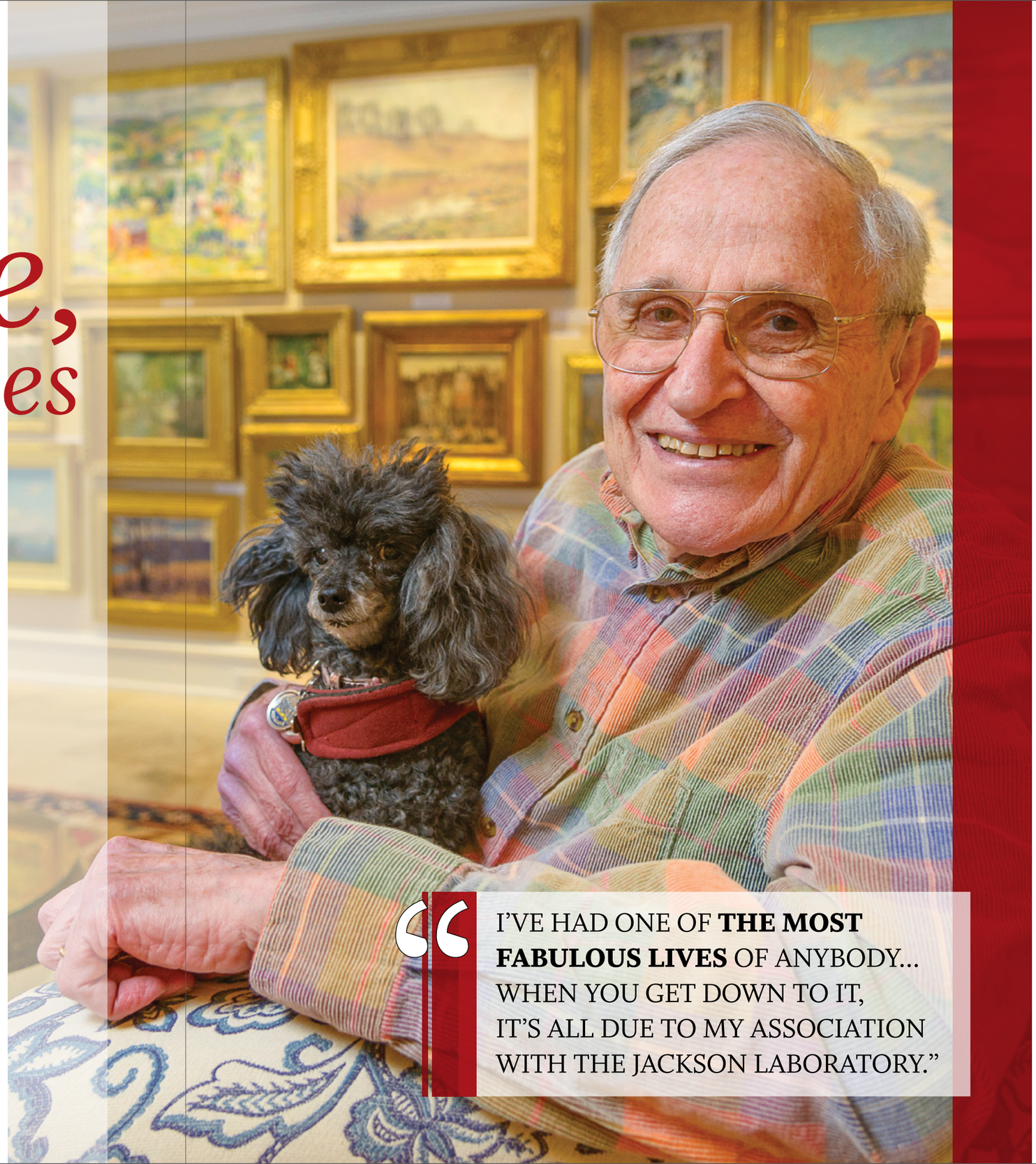
One day during his junior year, on his way out of the biology building for the day, Silvers noticed a flyer promoting The Jackson Laboratory's Summer Student Program. "I thought, gee whiz, this sounds like a nice way to spend the summer," he reminisces, "and it will probably help me get into med school, so why not look into it?

"Seeing that flyer was the first miracle!" he exclaims.

Silvers spent the summer of 1949 as a Jackson Laboratory intern, assisting psychologist Joseph Royce with his behavioral studies of dogs. The following summer he won a scholarship for another summer at JAX, "not because of the outstanding research I had done," Silvers says with a chuckle, "but because I was always willing to volunteer to help wash the dishes in the central dining hall!"

During his time at The Jackson Laboratory, Silvers says, "I met two of my best, lifelong friends," Henry J. Winn, Ph.D., and Lloyd Guth, M.D. Guth is an eminent neuroscientist and a pioneer in the study of spinal cord injuries at the NIH, University of Maryland and College of William and Mary; Winn, an immunologist, was on the JAX faculty before joining the surgery department at Massachusetts General Hospital.

Silvers got to know Jackson Laboratory founder and then-director C.C. Little. "I adored 'Prexy,' as everyone called him. He was definitely a very positive figure in my life. Indeed, he told me I reminded him of himself when he was younger. He was an



> "I'VE HAD ONE OF **THE MOST FABULOUS LIVES** OF ANYBODY... WHEN YOU GET DOWN TO IT, IT'S ALL DUE TO MY ASSOCIATION WITH THE JACKSON LABORATORY."

LEFT The history of mammalian genetics through the 1950s is captured in this extraordinary photograph of four generations of scientists. William Castle, far left, pioneered the field of mammalian genetics, beginning his research soon after the rediscovery of Mendel's laws of inheritance in 1900. Among his students were JAX founder C.C. Little and Sewall Wright, second from left, who is one of three scientists credited with developing a mathematical basis for modern evolutionary theory. Longtime and renowned JAX researcher Elizabeth "Tibby" Russell, second from right, worked with Wright at the University of Chicago in the 1930s as a Ph.D. student. Silvers, far right, worked in Russell's lab during his time at JAX.

BELOW LEFT Silvers met his wife-to-be Abigail Adams at JAX, and their wedding cake had a mouse decoration on top. Abigail Silvers went on to graduate from the University of Pennsylvania Medical School and her successful medical career included an appointment as medical director of cancer programs at The Bryn Mawr Hospital.

exceedingly charming individual and always willing to spend time with me."

C.C. Little's grandson, Philadelphia architect and Jackson Laboratory Trustee Sam R. Little, has known Silvers for many years. "When I first became involved with the Laboratory, Willys cared that I should know what made the place so special. With his very personal recollections of the close-knit scientists, the excitement of the work they were doing, and how it changed his life, Willys made the earlier days come alive for me. It also speaks of the legacy which now helps give the Laboratory its promise for the future."

That second summer Silvers worked with the legendary Elizabeth "Tibby" Russell, whose contributions include the first successful bone marrow transplantations in mice to cure anemia. But it was at the end of that summer that Russell's mentoring really kicked in.

"I had not been accepted to medical school, and I really didn't know what I was going to do," he recounts. "And Tibby suggested I apply to the zoology department at the University of Chicago, where she had received her graduate degree. And somehow she was able to get me accepted!"

Silvers became a student of Sewall Wright, Russell's mentor. Together with C.C. Little, Wright had been a student of William Castle's at Harvard's Bussey Institute—a veritable "who's who" of 20th century American mammalian geneticists.

Silvers earned his Ph.D. from the University of Chicago, conducting his thesis research at JAX in Russell's laboratory. While Russell's research at the time was primarily in hematology and germ cell genesis, she continued her early work in pigment cell genetics as a kind of "hobby." And, Silvers says, "although my research eventually became more focused in transplantation immunology, I too had a lifelong interest in pigment cell genetics, starting with my dissertation."

During that time Russell had a summer student named David Baltimore, who along with another JAX student that summer, Howard Temin, would go on to win the 1975 Nobel Prize in Physiology or Medicine. "Tibby asked me to supervise David, but he was so bright he didn't need any help," Silvers recalls.

Silvers' association with Russell was also responsible for the next step in his career: an NIH postdoctoral fellowship at Brown University with Herman B. Chase, one of Russell's former University of Chicago classmates under Sewall Wright.

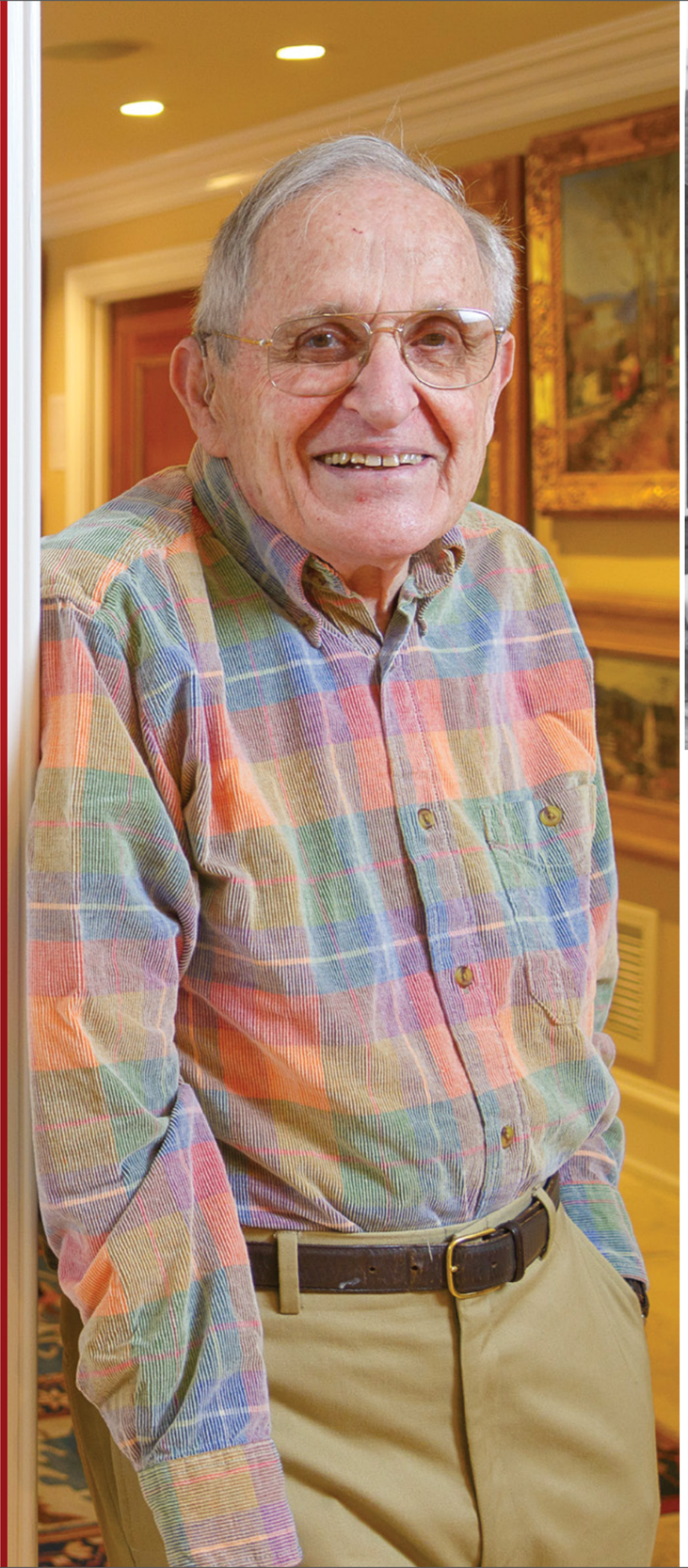
Next came what Silvers calls "another miracle." In the summer of 1956, he returned to Bar Harbor to finish his postdoctoral training in Russell's lab. "A young woman named Abigail Adams, who had just graduated from Mount Holyoke, was spending her second summer as Tibby's student," he recounts fondly. "Towards the end of the summer, I asked her out for a date, and a few weeks later I proposed to her."

However, Adams had been accepted at the University of Pennsylvania Medical School, and in the 1950s med school and marriage didn't generally mix, especially for female students. Silvers finally persuaded her to choose marriage just a few weeks before she was due to start her first classes. "But it was soon obvious to me that my bride was exceedingly unhappy in giving up medical school." Soon Silvers accepted a staff position at The Jackson Laboratory, again in Russell's lab, and his wife was accepted at the University of Vermont School of Medicine, the young couple resigning themselves to a long-distance relationship.

But in the spring of 1957, right on schedule, yet "another miracle." Rupert Billingham, whom Silvers had first met during his postdoc years, offered Silvers a position at The Wistar Institute in Philadelphia, and Abigail Silvers was accepted at the UPenn Medical School right across the street from Wistar. She, who was one of only six women in a class of 125, excelled in her studies, completing her internship at The Bryn Mawr Hospital and becoming board certified in internal medicine, hematology and oncology.

While building their careers in Pennsylvania, the couple also had two children, daughter Deborah and son Kent.

In 1965 the University of Pennsylvania started one of the first departments of



Silvers first came to JAX in 1949 as a summer intern looking to improve his transcript for med school. He poses with his fellow students (back row, third from right) in front of the old Lodge, an iconic Laboratory building that served many functions over the years.

medical genetics, and recruited Silvers as an associate professor in the department. As this department subsequently became the department of human genetics and finally the department of genetics, Silvers served as acting chair for nine years.

"In my three decades at Penn," Silvers says, "what I enjoyed most was my association with students, and I was chair of the genetics graduate program for 12 years." It's not hard to imagine the extroverted Silvers as an outstanding teacher; he won the university's Mary F. Lindback Award for Distinguished Teaching, and a Dean's Award in Graduate Teaching.

Silvers published *The Immunobiology of Transplantation* with Rupert Billingham, in 1971. Around 1975, Silvers was asked to compile a list of genes affecting coat color in mice, his lifelong research "hobby." "I realized it had been years since anybody had written a review article on the subject, and that was 'The Coat Color Genes in Rodents and Carnivores' by C.C. Little."

Once Silvers wrote the review article and compiled the list of genes, he realized he had a book's worth of material. He sent the manuscript to scientific publisher Springer Verlag. The publisher in turn sent the book to the top expert in the field for review: none other than Elizabeth Russell. "She gave it a great review!" Silvers says. Silvers' *Coat Colors of Mice* was so successful that after 35 years it is still in demand and is now available on The Jackson Laboratory's website.

"My primary research interests have been pigment cell biology and transplantation biology, and I'm proud to have written books on both subjects," Silvers says.

Throughout the 1980s, Silvers served on The Jackson Laboratory's Board of Scientific Overseers (now the Board of Scientific Counselors), chairing it from 1986 to 1989.

Silvers retired from the University of Pennsylvania in 1996, but continued to do research at the Fox Chase Cancer Center, also in Philadelphia, as a visiting scientist. There he collaborated with Beatrice Mintz, Ph.D., whom he had met at The Jackson Laboratory when she was a summer investigator in Tibby Russell's lab. Silvers' work with Mintz focused on the development and treatment of melanomas.

In 2004 Silvers terminated his research efforts when his wife was diagnosed with lung cancer. Despite her own illness, she was active as medical director of hospice, counseling other cancer patients. She died in 2005.

Abigail Silvers had a distinguished career as an oncologist and hematologist in private practice and in academic and leadership posts, including medical director of cancer programs at The Bryn Mawr Hospital and clinical assistant professor of medicine at Thomas Jefferson University.

Silvers now lives in Gladwyne, Pa., with his daughter and son-in-law (and his 13-year-old toy poodle, Gigi). Their house includes a gallery exhibiting the collection of Pennsylvania (New Hope School) Impressionist paintings that Will and Abigail Silvers assembled starting in the 1980s.

In his younger years, Silvers, like many mouse genetics researchers, collected pictures of mice. He and his wife donated his first art collection—including original prints by John James Audubon depicting different species of mice, rats and other small mammals—to JAX, where they now grace the library and North Research Building of the Bar Harbor campus. The Silvers have also been philanthropic supporters of the Laboratory, including establishing the Elizabeth Russell Scholarship Fund.

In reminiscing about his lifelong connection to Bar Harbor, Silvers says, "from summer student to the chairman of the Board of Scientific Overseers, I don't think anyone else has been in as many different positions at The Jackson Laboratory.

"And it all started when I saw that summer student notice when I was a junior at Hopkins. A notice that, because it luckily caught my eye, resulted in a graduate degree, a productive research program, a wonderful wife, two wonderful 'F-1s' [genetics-speak for offspring] and wonderful friends. A fabulous life indeed!"

Elisabeth Adkins is the first student in the "JAX track," a joint mammalian genetics graduate program between Tufts University and the Laboratory. Butterflies are a symbol for lupus, the focus of her research.

SEEKING the genetic underpinnings of LUPUS

by Jacqueline Mitchell
Photography by Jennifer Torrance

Lupus is one of the most enigmatic of diseases. It can take years to diagnose, marked as it is by a laundry list of seemingly unrelated symptoms: fever, fatigue, rashes, hair loss, sensitivity to light, seizures and even psychosis. Nearly 2 million Americans have some form of lupus, an autoimmune disorder in which the immune system wages war on the body's own cells and tissues. More than 90 percent of those who suffer from it are women, and there is no cure.

Elisabeth Adkins, a doctoral student at the Sackler School of Graduate Biomedical Sciences at Tufts University, is trying to decode the genetic underpinnings of the disease, a crucial step in combating it. She's working in the lab of Derry Roopenian, a clinical professor at Tufts School of Medicine and a professor at The Jackson Laboratory, and is the first student to take advantage of the mammalian genetics "JAX track," a joint program of the Sackler School and JAX. The program, launched in 2011, offers students in Tufts' genetics program—which emphasizes human disease—in-depth training in mammalian genetics, an increasingly recognized need in biomedical research.

Established as a cancer research center in 1929, The Jackson Laboratory is famous for its mice. It maintains a "library" of special strains of mice that make it easy to study certain diseases in humans. The type of mice that Adkins and Roopenian use arose accidentally, through mutation; they begin to exhibit lupus-like symptoms by the time they are four weeks old. It's a lesser-known strain of mice, but a potentially promising one. "We think it's one of the better models," says Adkins, who received a 2013 Gina M. Finzi Memorial Student Summer Fellowship from the Lupus Foundation to support her research. "We see a lot of the same indicators [in these mice] that human lupus patients have."

One such indicator is kidney failure, something that human lupus patients often died of before steroids were used to manage the disease. Adkins' mutant mice die of kidney failure before they are eight months old. The normal life span of mice is two to three years.

With Roopenian as her mentor, Adkins is studying these doomed mutant mice to figure out the mechanisms behind the onset of disease. The mutation causes the mice to produce too much of a protein called interleukin 21, or IL21. Roopenian's team has known for awhile that this protein has something to do with lupus. Normally, it helps the immune system respond to infections. But the scientists found that, when produced in excess as it is in their strain of mutant mice, IL21 leads to the symptoms of lupus.

"It turned out that it wasn't just lupus, but many other autoimmune disorders, too," says Roopenian. "We focus on lupus so we aren't going in 20 different directions at a time."

Now Adkins is studying the specific immunity cells (a subset of T helper cells) that produce the protein. Her goal is to figure out exactly how IL21 contributes to lupus, how it's produced and how it functions. Her work has already led to one significant finding.

Adkins found that these cells exist in healthy mice, even when they are not undergoing an active immune response. "That was a surprise. No one would have expected that," says Roopenian.

Next, the scientists want to figure out how those cells develop in normal mice, information that could illuminate what exactly goes wrong when lupus occurs. That would not only open the door to new therapies; it could have diagnostic value, too.

"Historically, lupus has been extremely hard to diagnose. A lot of our effort is to understand the mechanisms much better so it will be easier to predict when people are showing early signs of it," says Roopenian.

It was serendipity that put Adkins, who has been interested in science and medicine since high school, on the JAX track in 2011. After studying genetics as an undergraduate at Central Connecticut State University, she knew she wanted pursue a Ph.D., but she wasn't sure if she wanted to focus on genetics or immunity. The mammalian genetics program allowed her to marry her two interests. The JAX track, she says, also gives her access to the breadth of research at Tufts and the depth of genetic expertise at The Jackson Laboratory.

"It's nice to have the two names together," she says of the new program. "It adds more weight to what I'm doing."

"Liz has an innate drive to think scientifically and to come up with answers," Roopenian says of Adkins. "As the first [JAX track] student, she is really setting a high bar for everyone else."

Originally published in *Tufts Now*
http://medicalxpress.com/news/2014-01-genetic-underpinnings-lupus.html

Understanding IMMUNOLOGY

Where disease research starts

BY MARK WANNER • PHOTOGRAPHY BY JENNIFER TORRANCE

"Understanding immunology provides insight into all human disease."

It's a bold statement from someone working at a genetics laboratory, but Jacques Banchereau, Ph.D., is bold as well as confident. He has spent his career pushing the envelope with his research, always seeking to translate discoveries to clinical progress. He now brings his perspective and experience to The Jackson Laboratory. In his role as director of immunological sciences, he will begin a human immunology program at the The Jackson Laboratory for Genomic Medicine facility in Farmington, Conn. He will also lead a significant expansion of immunology research across all JAX campuses.

Banchereau comes to JAX after a stint at Roche Pharmaceuticals, and he knows the research landscape from both academic and corporate perspectives. "Jacques Banchereau is a distinguished and world-renowned immunologist," says Jackson Laboratory President and CEO Edison Liu, M.D. "We look forward to the exciting opportunities for partnerships between JAX campuses and other institutes afforded to us by his extensive network of colleagues. He is a tremendous addition to our faculty."

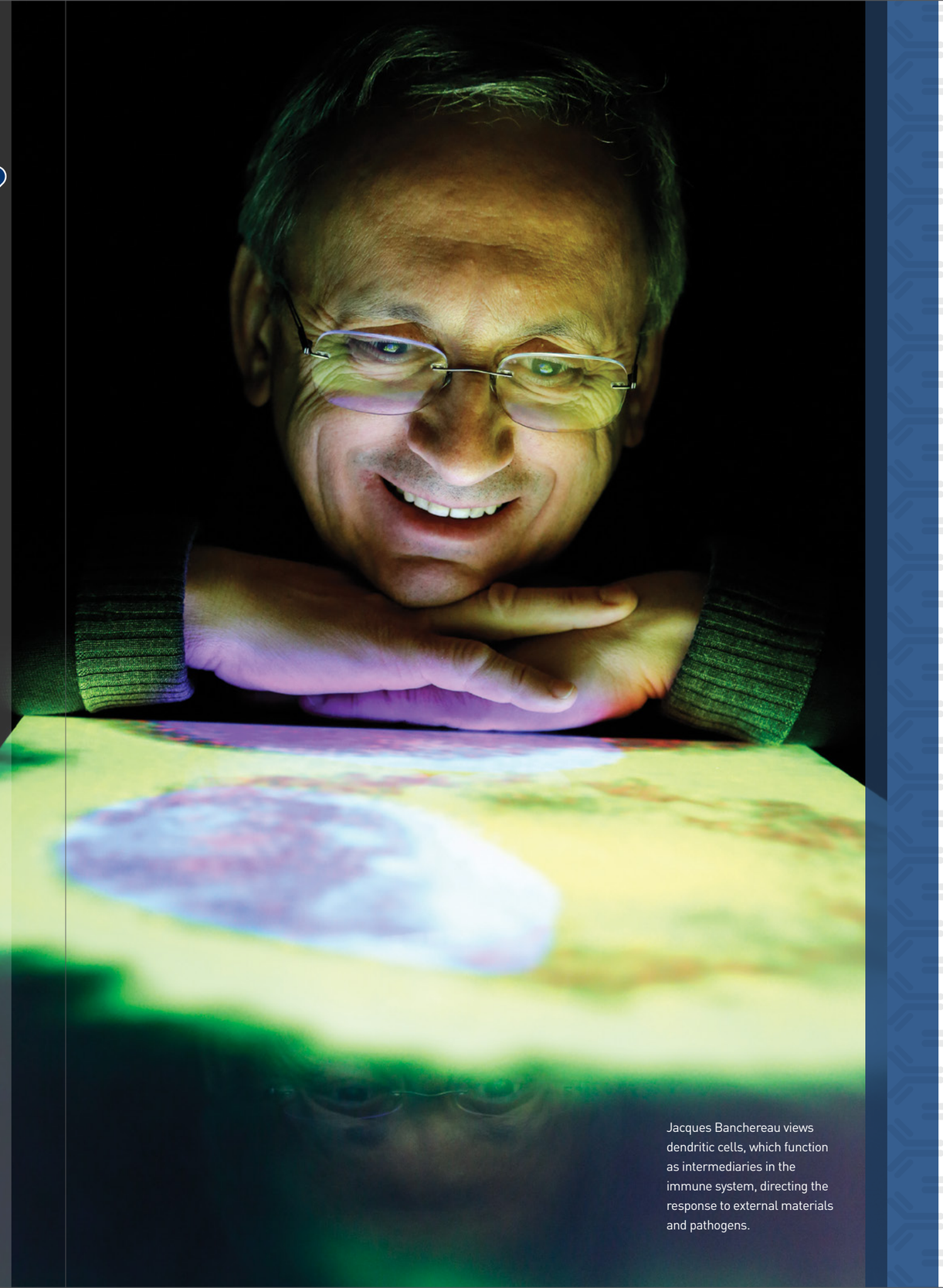
Banchereau sees unprecedented opportunities at JAX, built upon its formidable history and its current core of highly accomplished immunology researchers. He envisions the program as a triangle that will provide the potential to understand diseases better than ever before.

"At one corner you have human patients with disease and samples from those patients," says Banchereau. "Then you have research expertise and technology to work with the samples and data. Finally, you have the mice, which are the best models for human disease and allow discovery that you can take back to the patients. JAX has a unique situation, which completes the triangle with the absolute best personnel, experimental models and resources available. It is a winning combination."

RESEARCH HEYDAY

Banchereau's use of a geometric figure to capture how the pieces fit together at JAX is fitting. As a child growing up in the French town of Angers, he first became interested in science via mineralogy when he was only 8 or 9 years old. He was, and still is, "absolutely mesmerized" by crystals, and he still collects them as well as fossils five decades later.

Angers (pronounced Ahn-zhay) is in the middle of the Loire Valley, a region renowned for its wine. Banchereau retains his love of French culture, including good food and wine, but his early career path brought him to the United States, if only temporarily. While training in clinical pathology, he traveled to New York City



Jacques Banchereau views dendritic cells, which function as intermediaries in the immune system, directing the response to external materials and pathogens.

Cytokine Biology

Even scratching the surface of cytokine biology is daunting. For example, an exciting research area right now involves the interleukin 17 family of cytokines and their corresponding receptors. They are known to play a key regulatory role in host defense (immune response to external infectious microbes) and inflammatory disease processes, but important details of their function remain unclear. What is known is that IL-17s alone constitute an elaborate and nuanced system of signaling and response. According to a review published last year in the *Nature* journal *Emerging Microbes & Infections:*

Functional receptors for IL-17 family cytokines often exist in the form of heterodimers, with IL-17RA as a common subunit. For example, the receptor complex consisting of IL-17RA and IL-17RC recognizes IL-17A and IL-17F, whereas IL-17RA pairs with IL-17RB, followed by binding to IL-25.

Got that? What's more, IL-17 is only one of many families of cytokines, and the complexity has made immune response research both challenging and exciting.

to perform research in a laboratory at Columbia University's College of Physicians and Surgeons. It was only for a year, but it had a major impact on his moving forward.

"I learned good English and 'learned' New York City," says Banchereau. "Most of all, I confirmed that I really wanted to do research. I looked at clinical pathology as a good fallback position though."

Banchereau's tenure in that "fallback" career lasted exactly one day in October 1981. The very same day he started a professorship in clinical pathology in Paris, he quit in order to accept an offer to join a startup institution funded by the pharmaceutical company Schering Plough.

The startup had a very specific goal: work with human cytokines, the cell-signaling proteins vital to immunological function. The chain reaction that leads to immune response—antibody production, macrophage (killer cell) activation, and so on—has many components, and the roles of cytokines were only beginning to be discovered.

In the early 1980s, cytokines were not only an exciting research area, but knowledge of them was quite new. Banchereau, who had done his dissertation research on lymphokines (a particular class of cytokine), jumped at the chance to continue working with them when he received the offer. He soon found himself directing the new institute near Lyon, advised by two Nobel laureates (Paul Berg and Arthur Kornberg) and other high-level scientists and administrators. The excitement echoes in Banchereau's voice 30 years later.

See more photographs at www.jax.org/thesearch/immunology.

> JAX HAS **A WINNING COMBINATION** THAT WILL ALLOW US TO PURSUE ANSWERS TO THE BIG QUESTIONS IN IMMUNOLOGY. IT'S **A PERFECT STORM** IN THE RIGHT SENSE.

"It was an extraordinary adventure," he says. "A really, really exciting and exceptional time. The work was divided between California and France, working with both mouse models and human immunology. We discovered many exciting things, including human IL (interleukin) 4, 5, 10 and 13. My lab cloned and characterized human IL-17. It was the heyday of biotech."

STARTING ANEW

The work evolved over the years, however, and after a decade Banchereau's priorities began to diverge from those of his company. Desire to take his research closer to patient interaction and benefit drew him back to academia, this time launching another startup institution for the Baylor Healthcare System based in Dallas. While the move away from industry may not have been surprising to his friends and colleagues, the geographical destination certainly was.

"Many people in France had this idea about Texas, that it's awful, full of burning oil wells," says Banchereau with a chuckle. "Fortunately I'd had the privilege of doing a two-month sabbatical at the University of Texas Southwestern in Dallas, so I knew the reality was totally different. In those days Baylor had a vision to create a program in human immunology that was a bit ahead of its time and recruited me to lead it."

What started as a chair and an office grew steadily to a well-funded institution employing 125 people when Banchereau left in 2010. One of his significant achievements while at Baylor was a study of children with systemic onset juvenile arthritis, done with collaborator Virginia Pascual, Ph.D. Genomics studies revealed that the disease might be caused by interleukin 1 (IL-1), and Pascual used an approved but rarely used drug—an IL-1 receptor antagonist—to treat two patients resistant to every previous therapy. Within two days their chronic fevers disappeared, and within weeks that arthritis subsided. There is now an IL-1 antibody therapy approved, and about 70 percent of patients have a nearly complete response for a disease that less than 10 years ago had no effective treatment.

PERFECT STORM

Banchereau has a broad view of the work to be done at JAX. "Yes, we want to study cancer immunology, but we also have priorities for autoimmunity and inflammation, infectious disease, the importance of the microbiome in the development of diseases and more. We have a lot of collaborators excited to work together, and we want to leverage our strengths and use mouse models to precisely reproduce human disease and immune response."

Of course, JAX has a long and illustrious history of immunology research. George Snell won the Nobel Prize for his work on the major histocompatibility complex, a key component of the immune response to foreign substances. And JAX's current immunology program includes award-winning research into type 1 diabetes and lupus.

In addition, immunologist and JAX Professor Leonard Shultz, Ph.D., developed the NSG mouse that provides the cornerstone for much of the upcoming mouse modeling work in cancer and infectious diseases (see page 30). Shultz is particularly intrigued by the potential for tumor immunology research as the program evolves.

"At JAX we have a unique resource, these mice and the knowledge of how to use them," says Shultz. "Moving forward, we'll need to focus on specific disciplines like cancer immunotherapy and integrating the new principal investigators into the group."

The recent recruitment of JAX Professor Karolina Palucka, Ph.D. (see News & Notes) from Baylor immediately strengthens the cancer immunology effort, an area that is sure to grow. She and Banchereau previously developed a dendritic cell-based vaccine to treat patients with metastatic melanoma and HIV. Some patients have seen spectacular remission of the melanoma, but in Banchereau's words, "not enough yet." He plans to continue studies to improve the clinical vaccine outcomes by combining them with selected anti-cancer agents.

"I'm very excited to work with colleagues who bring an array of expertise to bear, and to have everyone working together," says Banchereau. "JAX has a winning combination that will allow us to pursue answers to the big questions in immunology. It's a perfect storm in the right sense."

PDX and avatars:

Novel ways to improve cancer therapies

BY MARK WANNER & MEG HASKELL • PHOTOGRAPHY BY JENNIFER TORRANCE

> **“THIS DISEASE COULD COME BACK ANYTIME,** ANYWHERE IN MY BODY, AND BE STAGE 3 OR STAGE 4 BEFORE WE KNOW IT’S THERE. **”**

Trish Ropp, who was diagnosed with cancer in 2012, is taking on new challenges, such as lobstering with a citizen’s license.

In 2012, after a routine mammogram revealed a suspicious spot in her left breast, Trish Ropp of Bar Harbor, Maine, learned she had cancer.

Although important progress has been made in identifying and treating some common forms of breast cancer, the disease remains a scary diagnosis. Ropp’s was especially so. Her cancer is classified as “triple-negative” breast cancer—TNBC—and it is impervious to the most advanced, targeted cancer therapies.

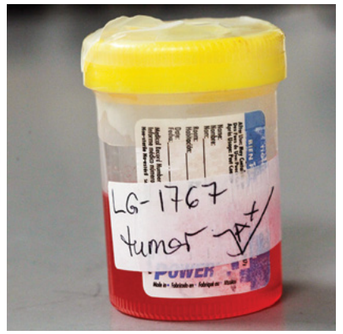
“I generally feel most things in life can be dealt with,” Ropp says, “but I know this disease could come back anytime, anywhere in my body, and be stage 3 or stage 4 before we know it’s there.”

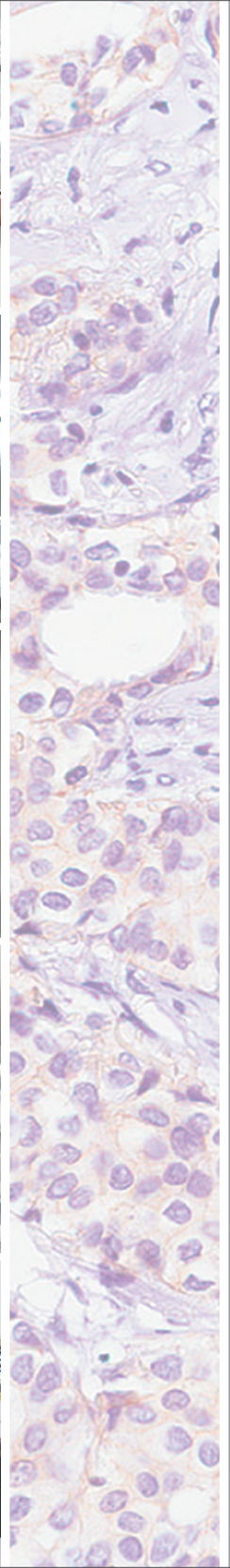
The TNBC study

Cancer is a highly complex disease, and what works to stop it in the laboratory often doesn’t work in patients. Efforts are under way to bridge the gap from research to medicine, however, and The Jackson Laboratory is spearheading an important one with the Maine Cancer Initiative. Researchers at the Laboratory are teaming with Maine’s top clinical centers to study cancer, and they have launched the Maine Triple-Negative Breast Cancer Study.

Despite significant advances in science and medicine, breast cancer remains the most frequent cancer diagnosis for women throughout the world, and the second-highest cause of cancer deaths among women in the United States. One in every eight women born in the U.S. today will be diagnosed with breast cancer at some point in her life. Only about 20 percent of breast cancer cases in the U.S. fall into the TNBC category, according to the National Cancer Institute. But because of its aggressive behavior and because no effective drug targets have been identified, it has a higher mortality rate than other forms of breast cancer.

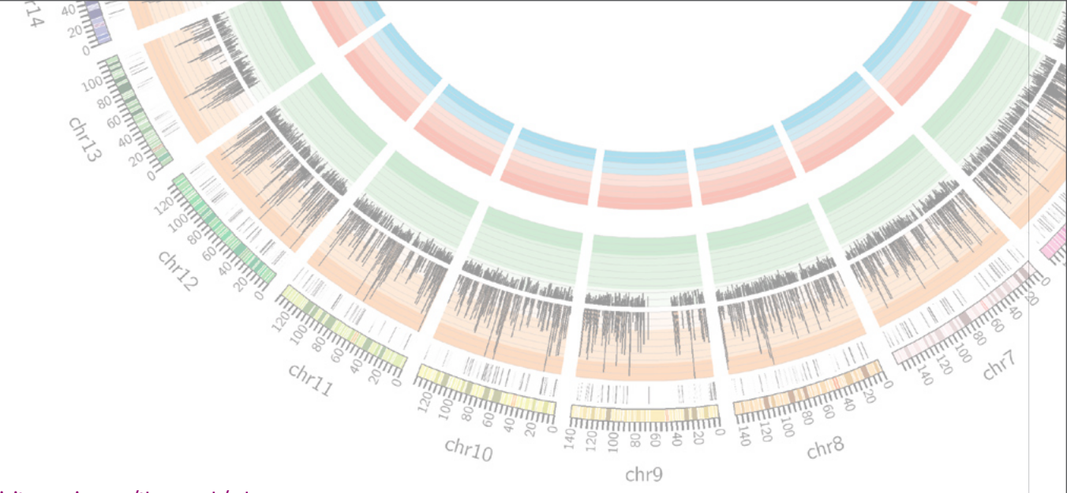
In the TNBC study, breast tumor tissue from patients like Trish Ropp will be shipped to the Laboratory, where a portion of each tumor will undergo genome sequencing. The remainder will be implanted into specialized mice with a suppressed immune response that enables them to host human tissues. These recipient mice will then be tested with drugs that match the treatment of the tumor donor. The goal is to demonstrate if response to treatment in the mice mirrors that observed in individual patients.





LEFT Work on the PDX resource at JAX's Sacramento facility involves the intake of human tumors and implantation of them in specially bred mice. The resulting data will improve understanding of tumor growth and help identify therapeutic targets. The background image shows the structure of a ductal cell carcinoma of the breast from the tumor of an 89-year-old patient.

RIGHT A Circos plot shows gene interactions in the tumor pictured to the left.



Visit www.jax.org/thesearch/pdx for more images and information.

"This is a study with a vision," says Professor Carol Bult, Ph.D., who heads the project at the Laboratory. "The Triple-Negative Breast Cancer Study brings together expertise in cancer genetics and clinical oncology from across the state to work collaboratively, using the power of emerging genome technologies and animal models to develop precise, individualized therapies for Maine cancer patients."

Building the PDX resource

Like most research initiatives at JAX, the TNBC Study uses mice as models for human disease. In this case, the mice are a launching point for exciting projects that quickly mesh biomedical research with human patients and human medicine.

The mouse in question is known as NSG, short for NOD scid gamma, developed by JAX Professor Leonard Shultz, Ph.D., after years of advanced immunology work. NSG mice have immune system deficiencies that allow them to accept xenografts—implanted tissues from other species, such as human tumor tissue—and can even be engrafted with functional human immune cells. They therefore provide an advanced, realistic research platform for a number of human diseases that can be hard to recreate in mice, including cancer.

Over the last four years, the Laboratory has built a comprehensive platform for genome sequencing, data analysis and drug studies to advance the development of new, targeted cancer therapies. The Laboratory has implanted human tumors from a wide range of cancers into NSG mice to create what are called patient-derived xenografts, or PDX. PDX tumors are grown and expanded in the mice, yielding information about how the cancers change over time as well as a hugely valuable data and research resource for studying human cancer.

It's a challenging process, and not all tumors "take" and grow in mice. Nonetheless, JAX has established more than 300 PDX models from patient tumors so far, including bladder, brain, breast, colon, kidney, lung, ovarian, pancreatic, skin and other cancers. The Laboratory is now targeting high-risk, metastatic tumors for the PDX program, including those that have or acquire resistance to targeted therapies.

"The PDX program is a great place for us to start," says Thomas Openshaw, M.D., a medical oncologist who heads up cancer research at Eastern Maine Medical Center's Cancer Care of Maine in Brewer. "It allows us to identify different drugs that can be used on the xenograft, to zero in on what a particular patient's tumor might respond to."

A focused outgrowth of the PDX program, the Maine TNBC study may be small in scope, but it establishes critical infrastructure for growth in the emerging field of genomic medicine, says Susan Miesfeldt, M.D., a medical oncologist and director of the Cancer Risk and Prevention Program at Maine Medical Center in Portland.

"The goal is to start building bridges between basic research scientists and clinicians caring for women with triple-negative breast cancer," she says. "We have never done a project like this. We're all incredibly busy clinically, but now we have The Jackson Laboratory as a scientific partner to help ground the project. This pilot project will really help to establish and build the infrastructure for the future."

Progress toward patient avatars

While the PDX program provides a solid foundation of knowledge and resources, the benefits to patients are indirect. The next step in the cancer xenograft story is to use a similar platform to create "avatars," mouse stand-ins for specific human patients in which therapeutics can be tested and treatments refined. Eventually, researchers expect to be able to assign a team of mouse avatars to a specific patient, so testing of second-line drug therapies can take place while the patient undergoes initial standard of care treatment. Although a full-blown clinical trial of this patient-specific avatar model may take a few years, the Maine TNBC study will pave the way, Openshaw says.

"Clinical research is a rising tide that lifts all boats," he says. "It allows us to think more deeply and be better informed, with enormous benefits for the patients and clinicians in our practice and for the people of Maine."

Hope for the future

For Trish Ropp, that future is unknown. Still, she remains philosophical about her cancer and its treatment.

"It could be years before they crack whatever code there is," she says. "And this cancer of mine could come back anywhere—my brain, my liver, my lungs. And if it comes back, the chemo I had this time won't be much use to me. So what I really have to fight with now is my own good health and my commitment to exercise, diet and serenity."

She credits scientific research for having improved the outlook for breast cancer patients in the past, and takes inspiration from patients who have tried out new drugs and procedures as they have become available. She has told her physicians that she would be honored to have her cancer tissue used in the new pilot study.

"I understand there is no gain to me directly," she says. "But in a small way, maybe I can help grow our understanding of what makes triple-negative breast cancer what it is. We're very lucky that most breast cancers are very treatable now. It would be nice if triple-negative were treatable, too."

by Meg Haskell
Photography by Stanton Short & Rogier van Bakel

GP GENETICIST PHILANTHROPIST

Weslie Janeway's many contributions to JAX

Scientist, investment professional, author and philanthropist: Weslie Janeway is all of these, and, since 2002, a thoughtful trustee and supporter of The Jackson Laboratory. With the evolution of The Jackson Laboratory for Genomic Medicine in Connecticut, she says, personal philanthropy, unrestricted in its use, must play an increasingly important role in supporting the Laboratory's mission.

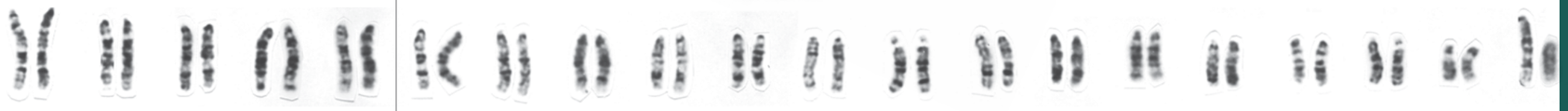
At a recent board meeting, Janeway, the vice chair, was everywhere—checking in with organizers in the lobby, debating one-on-one between sessions in the main meeting room, taking part in an animated lunch-table discussion.

"Weslie Janeway is a remarkable individual—simply one-of-a-kind," says President and CEO Edison Liu, M.D. "She is a philanthropist-turned-scientist, and her contributions to JAX have been enormous. As CEO, I have relied on her keen sense of observation and her sage advice on many matters related to Laboratory management. Her intellect, her generosity and her sense of style leave a lasting impression."

At the end of a long day of providing and processing information at the board meeting, Janeway shared her views on science, philanthropy and the future of The Jackson Laboratory.

Weslie Janeway studied genetics in England and spent the summer of 2009 at JAX studying chromosomal alterations.

We cannot just sit back and wait for the government to fully fund science.



Janeway is originally from Rhode Island, but her family has summered in coastal Maine for decades. Like many seasonal residents, she was aware of the Laboratory's presence in the area but knew little about it.

"I had heard The Jackson Laboratory was an economic engine for Hancock County, but I didn't know much more than that, except about the mouse-production business that so many people think of," she said. But in 2002, Dr. Ann Hirschhorn—a longtime friend, JAX board member and alumna of the JAX Summer Student Program—brought her to visit the Bar Harbor campus, where she learned about the important genetic discoveries taking place there.

"It became apparent to me right away that if you're going to be part of Hancock County, you should really be part of the Laboratory," she says. "I wish more people felt that way."

She has served on the JAX Board of Trustees since that time, and her generous giving has supported essential growth at the Laboratory, including a 2009 leadership donation to fund new research positions.

After joining the board, Janeway made it her business to learn more about the world of research. In 2006, when she and her husband, economist William Janeway, moved to England, she entered genetics research. Given her growing interest in the work taking place at The Jackson Laboratory, she said, a science education "just seemed like the right thing to do." Janeway's earlier education includes a bachelor's degree in political science from Barnard College and a master's degree from Brown University, also in political science.

In Cambridge, she first joined the lab of renowned American stem cell researcher Roger Pederson at the Cambridge Stem Cell Institute, conducting classic research using both mouse and human cell lines to study post-conception differentiation. With Pederson's impending retirement, Janeway moved to the lab of Mark Kotter, M.D., Ph.D., to study neural cell repair following damage due to trauma or neurological diseases.

Later, in 2009, Janeway spent an absorbing summer at JAX, studying cytogenetics with James Denegre, Ph.D., who at the time was the senior manager for imaging sciences and worked in the windowless lower levels of the Bar Harbor campus. Janeway refers to it as "the summer of the basement" and recalls it as a deeply rewarding experience.

"I learned a great deal," she says. "In Cambridge, we had developed stem cell lines with somewhat damaged chromosomes. At JAX, we regressed those stem cells to determine how meaningful the chromosomal alterations were. We learned that the cell lines were still viable despite the changes."

That summer, Janeway's respect for The Jackson Laboratory deepened. She especially enjoyed her working relationship with cytogenic technologist Ellen Akeson, whom she calls "one of the many people at the Laboratory who is doing amazing work—she is really a national treasure."

Denegre, now program manager of the Knock-Out Mouse Project (KOMP) at JAX, remembers well Janeway's summer in his lab.

"I was asked if I would take her on as an intern," he says. "All I knew was that she was a trustee with some scientific background. Then I learned she had been studying with Roger Pederson, and my respect notched way up. She has a very inquisitive mind, and she was committed to completing her study."

Janeway, a dedicated supporter of science and culture, believes public support for scientific research is essential, the way it is for schools, highways and healthcare.

"There are things a just society should provide for people," she says. "Privatization and entrepreneurship are often held up as panaceas for financing our institutions, but they're not always the answer."

Janeway has contributed greatly to the Laboratory's recent growth. She was joined by Maine's leading politicians for the ribbon cutting for the East Research Building (above left, third from the right) and broke ground with then-President and CEO Richard Woychik, Ph.D., for the new importation and cryopreservation facility (above right).

Weslie Janeway is a remarkable individual—simply one-of-a-kind. Her intellect, generosity and sense of style leave a lasting impression.

EDISON LIU PRESIDENT & CEO

However, she adds, "We cannot just sit back and wait for the government to fully fund science. Government agencies are, by their nature, risk-averse. We need private philanthropy to support more promising young investigators and to fund our overhead costs."

While commercialization of some JAX discoveries may yield important revenues, Janeway says philanthropy will remain an essential funding source as the Laboratory heads into a future that includes expansion into clinical genomics. She recognizes that there are steep philanthropic challenges ahead, especially with recent fluctuations in the national and world economies.

"People who serve on charitable boards are there to forward the mission of their institutions," she says. "But with changing economic times come changing pressures and competing interests for philanthropic dollars."

For example, she says, "A lot of younger philanthropists really like the idea of direct, grassroots investment in specific disease areas of research. But the institutions backing those operations are only as stable as the founder. When that person moves on or changes focus, the funding is lost."

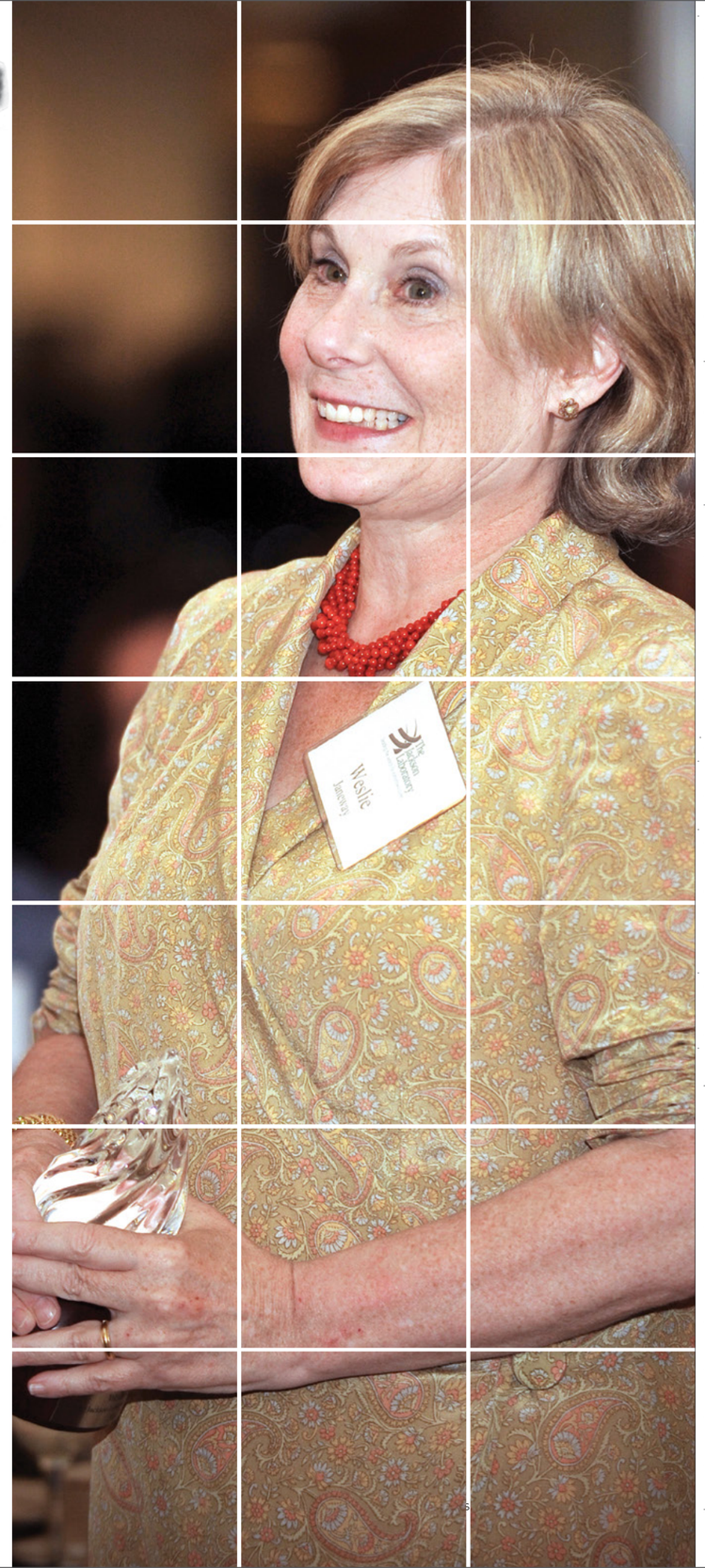
Even in tough economic times, she notes, wealth changes hands from one generation to the next, and many aging philanthropists elect to channel some of their resources to causes that inspire them rather than to their families.

"There is really a lot of opportunity now, some of it from unlikely sources," she says.

The challenge, Janeway says, is to attract high-level giving that supports not only the exciting new work of clinical genomics, but also the basic research that has been the JAX hallmark for eight decades.

"It's easy to get focused on clinical research at the expense of basic science," she says. "There's no doubt that translational science is the future of genetics, but it's important to maintain our leadership in basic research, too. Our move into clinical genomics presents us with great challenges and great opportunities. But for basic research or translational science, there will always be an important place for quality institutions like The Jackson Laboratory."

Janeway received the 2009 Chairman's Award at the Laboratory's Annual Meeting for her many contributions to JAX.



5 questions

Dave Walton

Manager, Software Engineering
The Jackson Laboratory

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

Q *What did you do before coming to JAX?*

A I grew up in southern Maine—Kittery Point—and graduated from the University of Maine with a computer science degree and math minor. During my education I gravitated toward scientific applications, not business, and after working at the University of Southern Maine for a couple of years in data processing, I came to the Laboratory in 1992 when an opportunity opened to write database applications. I became very interested in the research and took the Genetics course here, then moved to Mouse Genome Informatics (MGI), the online database and bioinformatics resource hosted by JAX, for the first time after a couple of years and helped design our first web interface.

Q *Did you work with MGI until you moved to scientific computing?*

A No, in 1996 I moved to Boston to work for a startup company. That began a time when I worked for five companies in about eight years. Startups folded, I was at Nortel when they closed a facility and laid off the entire staff... it became pretty difficult. It was good to come back and rejoin MGI.

Q *What does scientific computing do?*

A Our job is to be faculty focused. We build tools that help faculty do their research, developing and programming the kinds of applications and databases that you can't buy off the shelf.

Q *What are some specific examples?*

A We are optimizing command line programs that run on high performance computing clusters to help faculty work with massive data sets, developing small databases and web interfaces, developing image analysis tools, helping researchers visualize data, and a lot more. I lead a group of six now, and we work on a wide variety of projects.

Q *How did you get into that kind of work?*

A You might say I lucked into it, but I ended up where I want to be. I enjoyed working in MGI, but then computational sciences saw the need to automate data analysis and sharing for faculty, and I was hired to do that. It grew from there, and I find the work very fun and interesting. There are new projects all the time, I get to meet new faculty and solve different problems. Maybe it's that I have the right job for someone with a short attention span!

beyond the news

Cancers are heterogeneous.

Progress toward better therapies for leukemia

That short sentence explains a lot about why cancers are so difficult to treat. It means that cancers are not the same—between types of cancers, between cancers in different individuals, even between cancer cells within the same person.

So how do you figure out what's different in cancers so you can develop new therapies in the face of those differences? Experiments can't be done ethically within the patients, who need the best available treatment, and fast. Using human cancer cell lines helps, but the crucial interplay between the cancers and their host environments is absent. Animal models also help, but cancers in research animals such as mice are different from those in humans.

Enter the NSG mouse, developed by Jackson Laboratory Professor Leonard Shultz, Ph.D. NSG mice have impaired immune systems, so they can accept and grow human cancer cells like those grown in glass dishes. But the cells can be studied within a living system, better modeling the patient environment.

Take recent research into T cell acute lymphoblastic leukemia, an aggressive blood cancer. Scientists discovered mutations that activate a particular gene, NOTCH1, that can play a key role in the disease. It followed, therefore, that inhibiting it should stop the disease, which it does. Briefly. Clinical tests of inhibitors showed that the response was much more transient than hoped, indicating that at least some cancer cells had escaped the treatment. But how? Researchers couldn't investigate further within the human patients, so one group turned to cell line investigations to learn more about what was happening in the patients' cancer cells. They then worked with NSG mice to test what they had learned, and the results are encouraging.

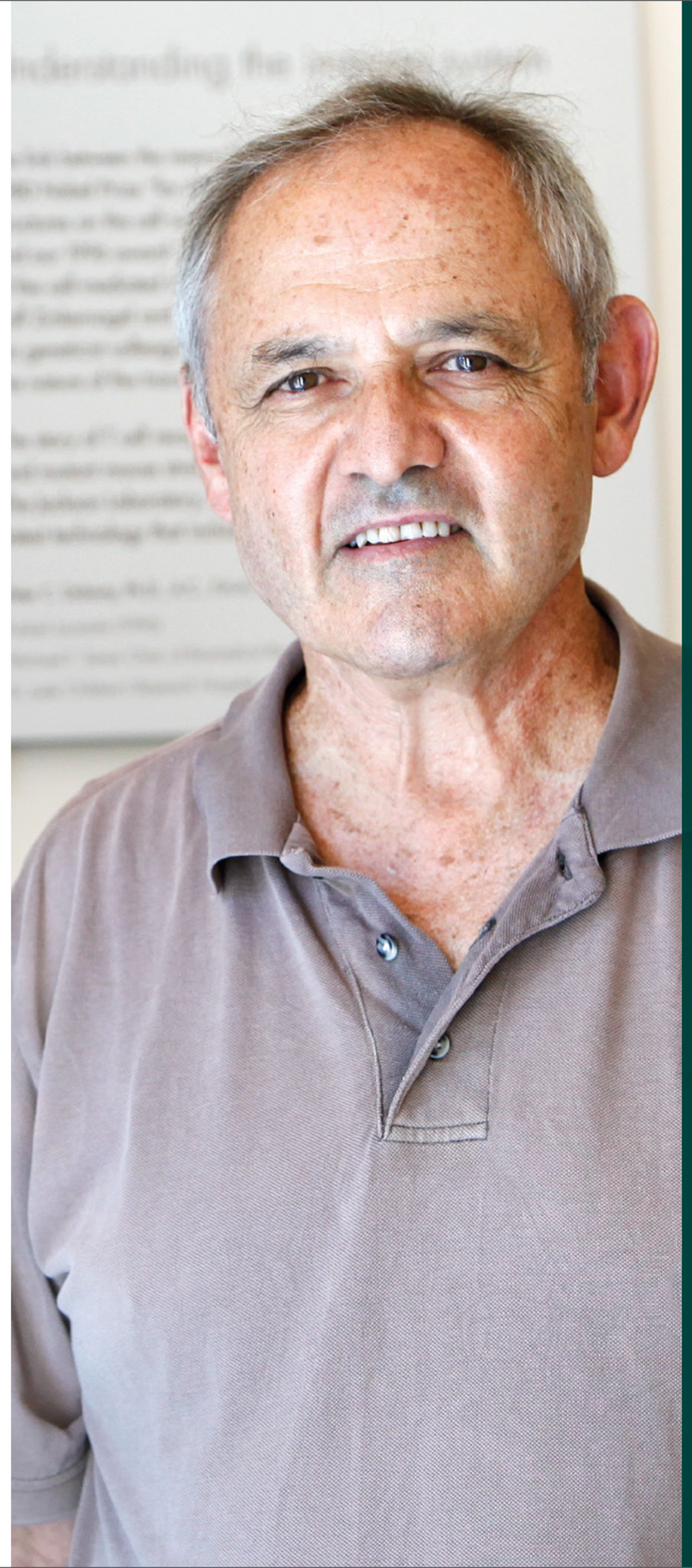
A paper published in *Nature Genetics* on March 2, titled "An epigenetic mechanism of resistance to targeted therapy in T cell acute lymphoblastic leukemia," shows their findings. The group, led by scientists at Harvard Medical School and including Shultz, found a small population of leukemia cells that survive treatment, which they called "persister" cells. Apparently persister cells don't need NOTCH1 to proliferate, relying instead on a different mechanism. But when the inhibitor was removed, they were quickly able to express genes in the NOTCH1 pathway, showing that the difference is not in the DNA sequence itself. Instead, it's epigenetic, meaning that chemical modifications are made to the DNA rather than to the DNA sequence itself, as in genetic mutations.

Essentially, persister cells, which make up well under 10 percent of the total cell population, survive NOTCH1 inhibition through epigenetic adjustments. But what if their ability to make epigenetic changes was also shut down?

After identifying the likely mechanism through which persister cells make their epigenetic modifications, the researchers theorized that a treatment that combines inhibition of both NOTCH1 and the epigenetic changes might improve outcomes. Using NSG mice implanted with human patient leukemia cells to test their idea, the researchers confirmed that the combination therapy is far more effective than either inhibitor administered alone.

Given that therapeutic resistance remains a major challenge in cancer treatment overall, the findings provide important insight into an epigenetic mechanism for drug resistance and how it might be overcome. Using the NSG mouse for confirmation is a vital step to bringing a more effective combination therapy to the clinic for the benefit of leukemia patients.

Knoechel B, et al. 2014. An epigenetic mechanism of resistance to targeted therapy in T cell acute lymphoblastic leukemia. *Nature Genetics* doi:10.1038/ng.2913.



Leonard Shultz

The Jackson Laboratory

Leading the search for tomorrow's cures

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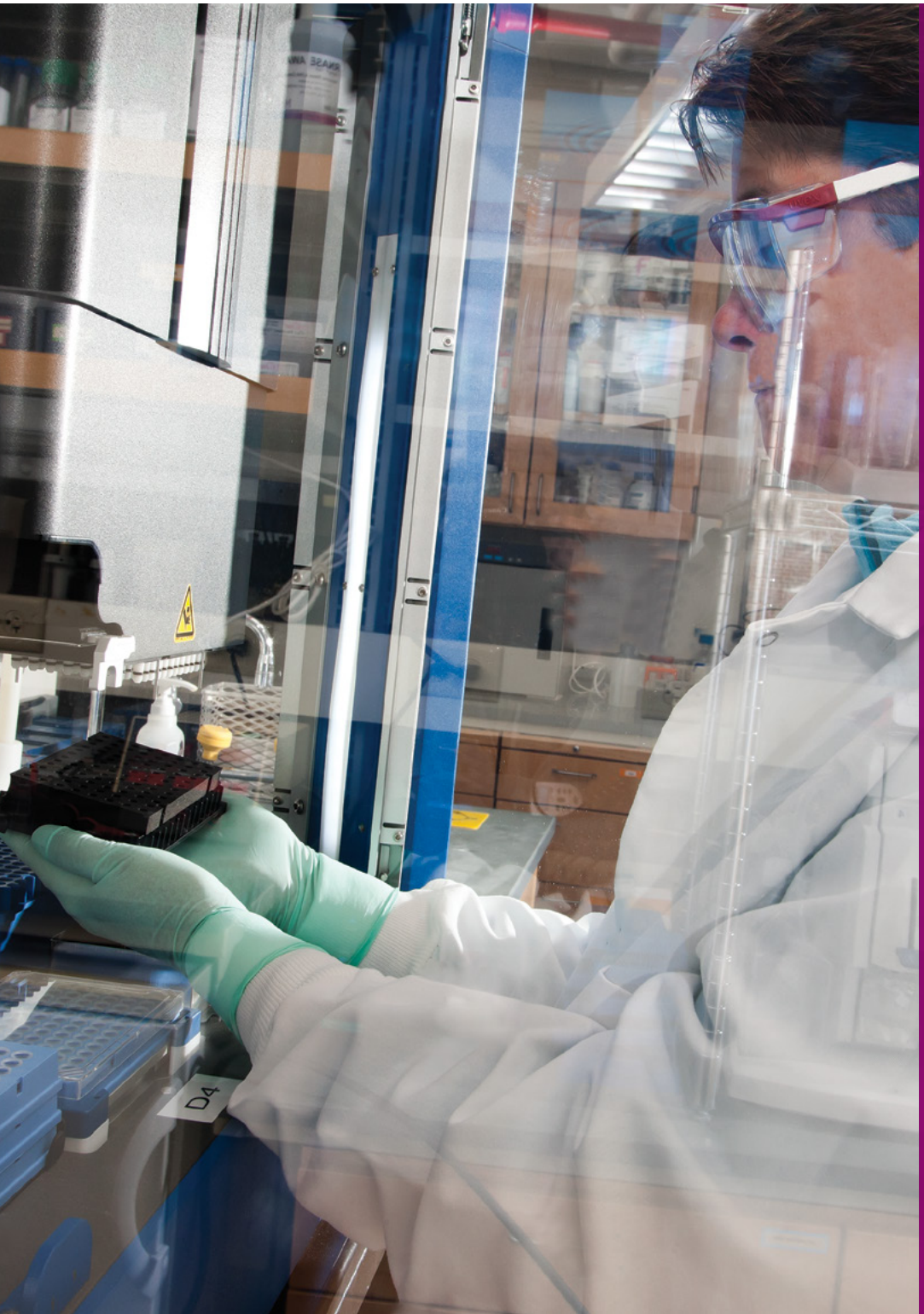

Sandy Daigle, high-throughput sequencing specialist, prepares an automated process in the clinical genomics and translational technology laboratory.

Photograph by Françoise Gervais