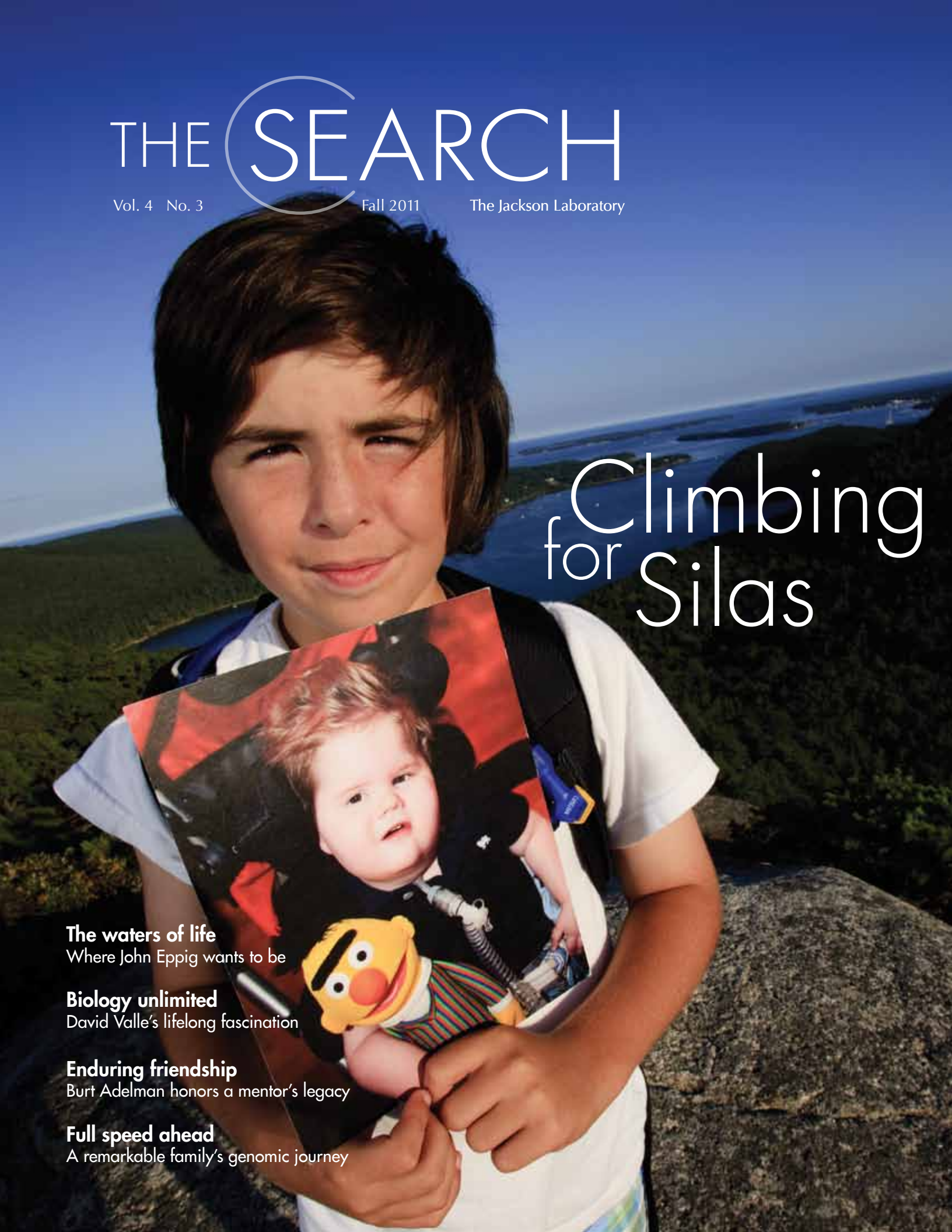
THE SEARCH

Vol. 4 No. 3 Fall 2011 The Jackson Laboratory



Climbing for Silas

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Biology unlimited
David Valle's lifelong fascination

Enduring friendship
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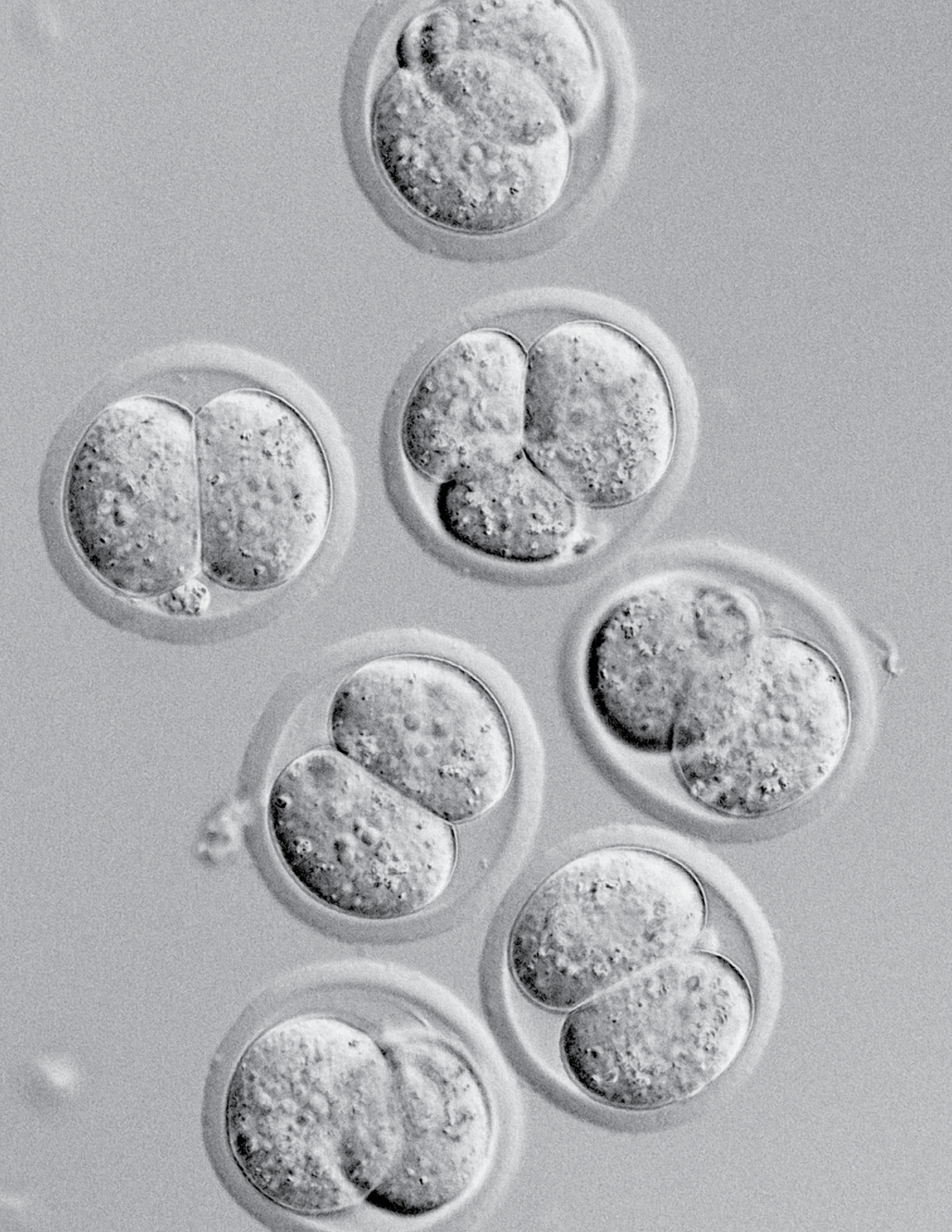
A remarkable family's genomic journey



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John Eppig, Ph.D., studies the complicated process through which a mammalian egg becomes ready for fertilization (page 22). This image captures a vital post-fertilization stage, just after the first cell division. These cells give rise to the trillions of specialized cells that make up an adult mammal. (Image is courtesy of James Denegre, Ph.D., and Adriane Betancourt.)

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Cover photo of Gus La Casse by Françoise Gervais

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Mission

We discover the genetic basis for preventing, treating and curing human disease, and we enable research and education for the global biomedical community.

Vision

Our mouse models and genetics research lead the world to solutions for cancer and other complex and intractable diseases.

Research programs

Cancers: brain, leukemia, lung, lymphoma, mammary, ovarian; cancer initiation and progression; cancer detection and therapies

Computational biology and bioinformatics: mouse genome informatics, comparative genomics

Developmental and reproductive biology: birth defects, Down syndrome, sex determination, aging, osteoporosis

Immunology: HIV-AIDS, autoimmunity, immune system disorders, lupus, tissue transplant rejection

Metabolic diseases: atherosclerosis, diabetes, hypertension, obesity

Neurobiology: blindness, cerebellar disorders, deafness, epilepsy, glaucoma, macular degeneration, neurodegenerative diseases

Printed September 2011

The Jackson Laboratory

Leading the search for tomorrow's cures

Introducing Edison Liu, M.D.

On August 26, The Jackson Laboratory named Edison Liu, M.D., as its new president and chief executive officer. Liu will officially begin his work at the Laboratory on January 2, 2012.

Liu is an international leader in cancer biology, genomics, human genetics and molecular epidemiology. He is the founding executive director of the Genome Institute of Singapore, building it in less than 10 years from a staff of three into a major research institute of 27 laboratory groups and a staff of 270. Before moving to Singapore in 2001, he was the scientific director of the National Cancer Institute's Division of Clinical Sciences in Bethesda, Md.

Regarding the hiring, Leo Holt, newly elected chair of the Laboratory's Board of Trustees, says, "Dr. Liu's arrival signals to a broad audience what the scientific world has always known: The Jackson Laboratory is a dynamic pivot point at the intersection of mammalian and human genetics. His talents run broad and deep, and his leadership is a great addition to the team that leads the search for tomorrow's cures."

Liu's experience with human genomics and clinical research strengthens the Laboratory's increasing focus on translational research and genomic medicine. He is serving his second term as the elected president of the Human Genome Organization (HUGO) and his own scientific research has focused on the functional genomics of human cancers, particularly breast cancer.

"The Jackson Laboratory is at a unique crossroads in its history," says Liu. "The options are all good. It's a matter of which is the best. I truly believe that independent organizations like The Jackson Laboratory, with a strong mission and not-for-profit structure but yet with revenues that would help support the scientific mission, are going to be one of the key models going forward to advance science."

Liu's appointment concludes an international search following the January 2011 departure of Richard Woychik, Ph.D., who served eight years as Jackson president and CEO. Woychik left to become deputy director of the National Institute of Environmental Health Sciences in Research Triangle Park, N.C.

Born in Hong Kong in 1952, Liu obtained his B.S. in chemistry and psychology, as well as his M.D., at Stanford University. He served his internship and residency at Washington University's Barnes Hospital in St. Louis, followed by an oncology fellowship at Stanford. From 1982 to 1987 he was at the University of California, San Francisco, first in a hematology fellowship at Moffitt Hospital and then as a postdoctoral fellow in the laboratory of Nobel Laureate

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J. Michael Bishop, while also serving as an instructor in the School of Medicine.

From 1987 to 1996 he worked at the University of North Carolina at Chapel Hill as an assistant professor in medicine and oncology at the School of Medicine, and rose to full professor directing the UNC Lineberger Comprehensive Cancer Center's Specialized Program of Research Excellence in Breast Cancer. He was also the director of the Laboratory of Molecular Epidemiology at UNC's School of Public Health, chief of medical genetics, and chair of the Correlative Science Committee of the national cooperative clinical trials group, CALGB. At UNC, Liu held faculty positions in the departments of medicine, epidemiology, biochemistry and biophysics, and in the curriculum in genetics.

In 1996 he was appointed director of the Division of Clinical Sciences at the National Cancer Institute. In this capacity, he was responsible for the scientific and administrative direction for the intramural clinical research arm of NCI consisting of 1,200 employees organized in 16 branches/ laboratories/departments, and led by 100 principal investigators.

In 2001 he was recruited as the executive director for the new Genome Institute of Singapore (GIS), tasked with developing the region's genomic research, infrastructure, and scientific human capital, and attracting R&D ventures in biomedicine into Singapore. Under Liu's leadership, the GIS grew into a major international research institute, with faculty in functional genomics, computational biology, population genetics and genome-to-systems biology. Liu also played major roles in the development of Singapore's larger R&D landscape.

Liu is also the recipient of a number of awards, including the Brinker International Award for basic science research in Breast Cancer, 1996, the Rosenthal Award from the American Association for Cancer Research, 2000, and the President's Public Service Medal for helping Singapore resolve the SARS crisis, 2007.

In his spare time, Liu pursues jazz piano and composition, and writes for the lay public in regional newspapers and magazines on science, medicine and society.

Watch an interview with Edison Liu at
www.jax.org/thesearch/vol4no3/news-notes

News & Notes

Laboratory recognized twice as a best place to work

The Jackson Laboratory has recently been recognized as one of the best places to work by two separate publications: locally, among all employers in Maine, and nationally, in the academic life sciences field.

In August, the Laboratory was named among the 2011 "Best Places to Work in Maine." The recognition is based on an evaluation of a company's workplace policies and practices, and on information collected through an employee survey. The program concludes with an awards ceremony in October, where the final rankings will be announced. Honorees will be profiled in a special publication by *Mainebiz* magazine.

The local honor came soon after *The Scientist* magazine named the Laboratory one of the 2011 "Best Places to Work in Academia" in the United States. The Laboratory ranked 13th among 40 top U.S. academic research institutions, with infrastructure, peer interactions and environment cited as its greatest workplace strengths. The rankings were published in the July 2011 issue.

Cancer treatment partnership with UC Davis, NCI

Many promising cancer treatments reach early clinical testing in humans, but only a very small percentage pass that stage and go on to benefit patients. A new partnership between The Jackson Laboratory, the UC Davis Cancer Center and the National Cancer Institute's Center for Advanced Preclinical Research (CAPR) is seeking to improve those odds.

The collaboration seeks to establish a uniform and controlled testing process to integrate data from mouse cancer model studies with patient clinical trial studies. The approach will help identify biomarkers, molecules that provide targets for candidate drugs and help predict when they will be most effective.

"There is an urgent need for more predictive models of human cancer for drug discovery," says Charles Hewett, Ph.D., executive vice president and COO of The Jackson Laboratory. "Unfortunately, nine out of 10 cancer drugs entering preclinical testing fail. This comes at great cost to the pharmaceutical industry and to patients. The integrated approach we have with CAPR and UC Davis targets these issues directly."

New approach may improve SMA treatment

Spinal muscular atrophy (SMA) is the most common inherited cause of infant mortality, affecting about 1 in 25,000 births. Now, Jackson Laboratory Research Scientist Cathy Lutz, Ph.D., has collaborated with researchers at Columbia University and other sites to develop a better way to treat the disease, with the findings appearing in the August issue of the *Journal of Clinical Investigation*.

The cause of SMA centers on a protein known as SMN. Reduced levels of SMN caused by gene mutations in motor neuron cells lead to progressive and ultimately fatal muscle degeneration. Working with a newly developed mouse model of SMA, Lutz and colleagues showed that restoring the SMN protein even after symptoms appeared could reverse the motor neuron degeneration.

But restoring the protein was most effective if done early. "There was a therapeutic 'window of opportunity' during which the mice responded best to the SMN treatment," says Lutz. The research is still in an early stage, but the results point to early screening of newborns and clinical SMN restoration as an effective potential therapy for this devastating disease.

Governor Paul LePage

Tumor Consortium grows

The Jackson Laboratory's Primary Human Tumor Consortium effort gained a powerful new partner with the addition of Scripps Translational Science Institute (STSI) of San Diego in June.

The Laboratory is building a library of primary human tumors with the goal of developing highly targeted cancer therapies. STSI will provide solid human tumor samples, which will be grafted into mouse models for study. The initial tumor genomic characterization data will be shared with all participating institutions, which also include the University of Florida, the Swedish Neuroscience Institute of Seattle and UC Davis Cancer Center.

Mouse models that can accept newly resected human tumors offer a highly productive way to develop and test cancer treatments. Mouse models of virtually any kind of cancer can be developed, providing a more individualized approach to finding new treatments.

Leo Holt named Board of Trustees chair

Leo A. Holt of Philadelphia became the new chair of The Jackson Laboratory's Board of Trustees at the board's Annual Meeting in Bar Harbor, Maine, in August 2011. Holt succeeds Brian Wruble, who stepped down after two terms as chair.

Holt is president of Holt Logistics Corp., a marine terminal and logistics systems developer and operator, with facilities in Philadelphia and Gloucester City, N.J. He has participated in the Laboratory's governance since 2004. He was elected to the Board of Trustees in 2007 and became vice chairman in February 2011.

"Like The Jackson Laboratory, we rely on our people for creativity, innovation and relentless pursuit of excellence," Holt says. "The successes we enjoy today are best safeguarded by never resting in this search, whether that is for solutions to complex logistics issues, work opportunity for our employees or in the search for tomorrow's cures at the Laboratory."

The Search is partially underwritten by the generous support of Walter and Dorsey Cabot on behalf of family members confronting cancer and the millions of others challenged by genetic diseases.

The Cabots invite readers of *The Search* to share their experiences with other readers. If you have a story related to the work of the Laboratory, please contact the editor at mark.wanner@jax.org.

Maine governor visits the Laboratory

Governor Paul LePage visited The Jackson Laboratory on August 4 to see how one of Maine's largest employers is generating jobs on its own campus and throughout the state.

Highlights of the visit included viewing the Laboratory's new energy center, which will replace about 1.2 million gallons of fuel oil each year with Maine-grown wood pellets, and meeting with Joan Malcolm Albee, a biomedical engineer who is working with technology and manufacturing companies throughout Maine to commercialize new laboratory tools and techniques.

The Laboratory is the largest employer in Hancock County. It receives about 95 percent of its budget from outside Maine while spending at least 85 percent within the state.

"The Jackson Laboratory has a long history in our state, generating more than 1,200 jobs in Hancock County and another 2,100 throughout Maine," says Governor LePage. "I commend the level of commitment their staff has had in our state."

Full speed ahead

By Mark Wanner
Photography by Françoise Gervais

Ten-year-old Scotty Wentzell is a boy on the go.

Recently he began to play tee ball and to surf in the Atlantic Ocean. He added those sports to horseback riding and swimming, both of which he began as a preschooler. And in the winter he's downhill skied since he was 5 years old. Scotty flat-out loves speed and the sensation of going fast.

It's an impressive list of activities, made even more so by Scotty's physical challenges. Scotty's health has taken Scott and Lisa Wentzell, Scotty's parents, on what his mother describes as an emotional roller coaster ride from the time he was born. It's a roller coaster that the North Yarmouth, Maine, family has ridden together, and it has led them to the edge of the genetic medicine frontier.

Mere days after Scotty was born, he nearly died from serious heart problems. Known as Tetralogy of Fallot, Scotty's condition is characterized by four serious heart defects and requires surgical repair. Scotty underwent successful open-heart surgery at five days old to address the most critical needs, then again at six months for a more thorough reconstruction.

For Scotty's parents, the most important thing was that after the initial scare, Scotty was out of danger. But when subtle problems with Scotty's development and progress alerted his parents and pediatrician that there may be a larger underlying disorder, they were referred to a geneticist.

Even then a diagnosis proved elusive, but over time the evidence pointed to a rare condition: Dubowitz syndrome. It not only has no cure, its cause is unknown other than the fact that it's a recessive genetic disorder. It's also very difficult to confidently diagnose—it wasn't recognized until the mid-1960s—as patients display a wide range of characteristics and symptoms, none of which are universal. Scotty, as it turned out, had more impairment to his cognitive development than many patients, but other than the initial heart malformation, has had relatively few medical difficulties.

So where is a parent to turn with such a diagnosis? The Wentzells found two highly effective resources through clinical experts and athletic programs. Medically, they were able to begin working with Dr. Gerald Cox, who holds positions at Boston Children's Hospital, Harvard Medical School and Genzyme. The leading expert on Dubowitz in the eastern United States, Cox works with many Dubowitz patients and even holds an annual "Dubowitz day," at which many Dubowitz families gather for appointments and sharing information.

"I met Scotty, his parents Scott and Lisa Wentzell, and his grandfather several years ago in my Genetics Clinic at Children's Hospital Boston," says Cox. "While Scotty has physical and communication challenges, none of this seems to slow him down. He has a zest for life and a sparkle in his eye."

But the vast majority of Scotty's time was to be spent outside of a doctor's office. The Wentzells, avid skiers who both worked at Sugarloaf Mountain Resort during the 1990s, brought Scotty into their world of movement. Unable to verbalize or walk unassisted as a young child, he nonetheless began swimming at age three, and horseback riding and skiing by age five.

"Scotty's gross motor skills have come a very long way," says Scott. "He began walking when he was six, and he gets better and better in all the activities. He's very solid on a horse at this point and absolutely loves to ski."

"Scotty can't play a lot of team sports like other kids do," adds Lisa, "so we looked for therapeutic activities like the swimming and horseback riding, which he does through a program called Riding to the Top. But we also want things we can do as a family, and the skiing has been great for that."

While the family concentrated on helping Scotty, Dr. Cox was learning about genomics. The first human genome sequence was published in 2003 and continued progress in the field offered hope that someday the root cause of Dubowitz syndrome could be found through genome

Scotty celebrates the successful toss of a bean bag through a shape board at "Riding to the Top."

"It's doubtful Scotty will be able to live on his own, and I'm prepared to be with him."

Lisa Wentzell

sequencing. Scott also learned more about genetics and genomics through his work as marketing manager for Thomas Moser, a high-end furniture manufacturer. When Thomas Moser teamed with The Jackson Laboratory on some events, Scott saw the research side of the genetics field and the exciting possibilities it offered.

"Rapid DNA sequencing technology is now able to cost-effectively sequence the coding regions of all human genes," says Cox. "By comparing the DNA sequences of a few affected individuals with the same rare genetic condition, changes in the same region of DNA can be found that identify the disease gene."

It was Cox who referred the Wentzells to the National Institutes of Health (NIH) for a new research study. The Wentzells' trip to the NIH facility in April 2010 left them impressed on several fronts.

"We went to the National Human Genome Research Institute (NHGRI) in Bethesda, Md., for three days of testing and working with the scientists," says Scott. "It's an amazing facility, very impressive and tightly run. Despite the strong security there we were treated incredibly well—it was like a Disney experience."

To the Wentzells' knowledge, Lisa was the second woman in the world to have her genome fully sequenced after actress Glenn Close. But while the sequencing itself has become progressively faster and less expensive, analysis is still painstaking, and the Wentzells are awaiting the study's findings with great anticipation.

"New large-scale sequencing technologies have successfully identified genes for many rare genetic conditions," says Julie Chevalier Sapp, the NHGRI genetic counselor who is working with the Wentzells. "Our laboratory has used whole genome and whole exome sequencing to discover the genetic causes of a handful of rare conditions and we hope that our application of these techniques to Dubowitz syndrome will be successful as well. Scotty Wentzell is a special young man who is truly a joy to be around; it's been a real pleasure to partner with amazing families like his to work toward a common goal."

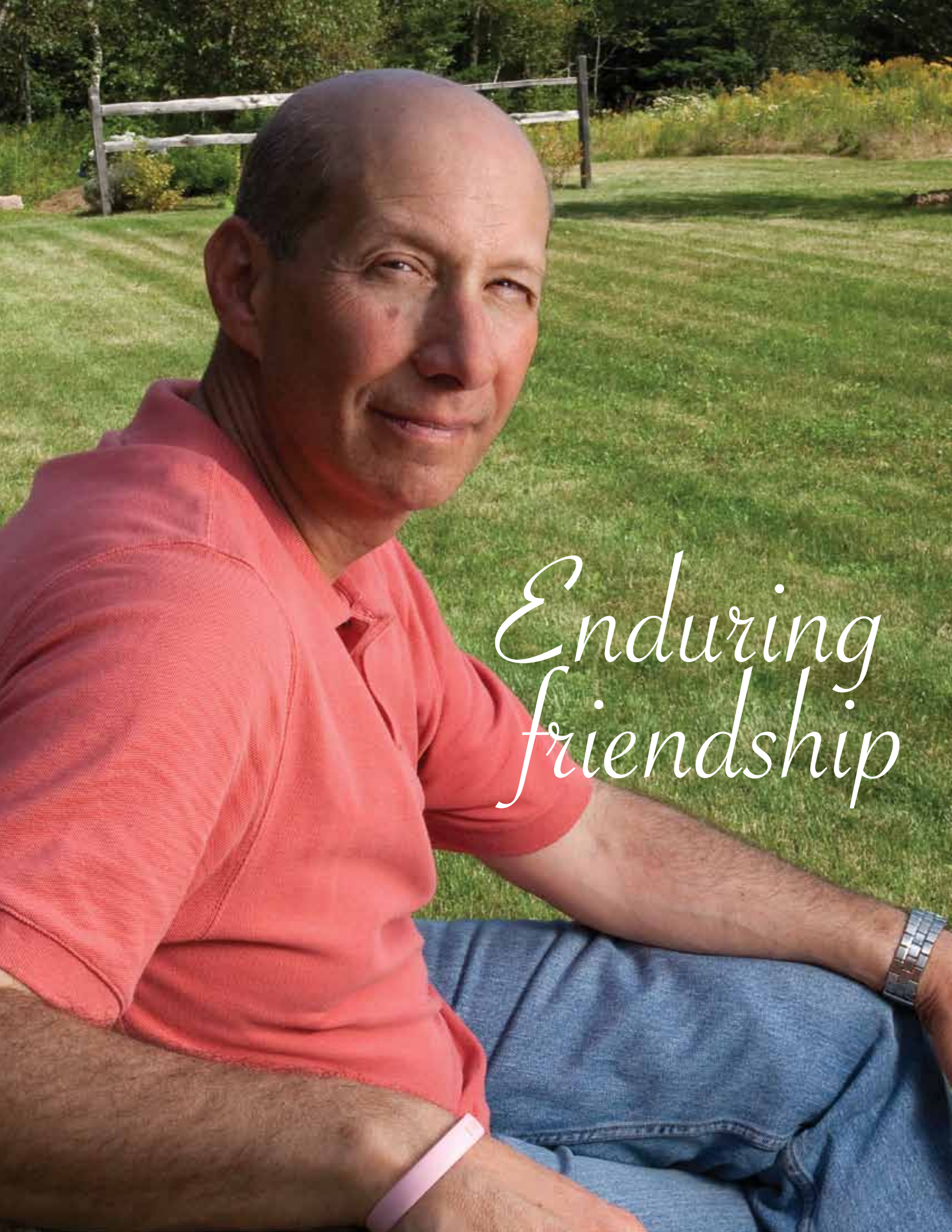
While the NIH works behind the scenes to tease out the syndrome's root genetic cause, the Wentzells continue their efforts to expand Scotty's abilities and experiences. Lisa has stayed home with Scotty since his birth and coordinates the logistics for his many activities. She has also benefited from some robust community resources, including the special needs program in the Cumberland/North Yarmouth public schools.

"I was apprehensive before Scotty went to the public school for kindergarten, but it's been a great program and a great experience for him," says Lisa. "Scotty loves school and his classmates are very supportive and welcoming. He's like a celebrity in the community, and when we are at the grocery store and other places around town we're always getting stopped by people who know him and want to say hi."

Although Scotty does not speak, he effectively uses a visual technique called picture exchange communication—which employs a book with picture images—to communicate. Both parents have also seen significant strides in him this year as he learns colors, letters and numbers, and it remains unknown what his learning potential actually is.

"It's doubtful Scotty will be able to live on his own, and I'm prepared to be with him," Lisa says. "There's a strong group of parents of kids with special needs here, and we're talking about buying a house where they can go after they leave school to spend time together and have programs to help them. Then again Scott and I sometimes talk about how fun it would be to drive off together with Scotty in an RV someday and tour the country for a while. In the end, we want to find new things to do and have fun together as a family."

Scotty and his mother, Lisa, take a breather after his riding is done for the day.


Enduring
friendship

Burt Adelman's personal and professional adventures as a lifelong learner found him doing research at The Jackson Laboratory as a 19-year-old member of the Summer Student Program's Class of 1971.

Now a physician immersed in developing new drug therapies for multiple sclerosis and other genetic diseases, Adelman says it was a summer that validated his budding passion for science.

"I came here as a college fella, from Trinity College in Connecticut," Adelman says, looking back. "I was a junior, as I had started college when I was 16. That summer was an experience that confirmed that I was excited about science and passionate about research and wanted to work in a lab, and it certainly strengthened my desire to go to medical school. I met some great people while I was here."

Among those people was Chen Kang Chai, a Jackson Laboratory principal investigator who served as young Burt Adelman's mentor throughout that summer. Throughout his long and productive career at The Jackson Laboratory, Chai was a vocal and active supporter of the Summer Student Program, which has been providing hands-on research opportunities for high school and college students for more than 80 years.

Adelman and his learned mentor would become friends. Their extended families remain close, 40 years later. For more on the enduring friendship between the two families visit www.jax.org/thesearch/vol4no3/adelman.

While at the Laboratory that summer, Adelman spent time with another Trinity College student, Dean Hamer. Now a prominent geneticist at the National Institutes of Health, Hamer is the author of *The God Gene*, and other, by Adelman's assessment, "somewhat controversial" books grounded in genetics.

"Dean and I both had our own individual research projects that were assigned by the scientists in the labs we were working in," Adelman recalls. "But Dean cooked up another project on his own that had to do with extracting RNA from mouse pituitary glands. So we worked on that one at night. I had a great time."

After graduating from college, a scholarship took Adelman to Cornell University's medical school in midtown Manhattan after he completed another research fellowship at a New York University medical center. His medical career included time in both clinical and industry settings, and he joined Biogen, Inc., in Cambridge, Mass., as director of medical research in 1991.

He retired in 2007 as Biogen's executive vice president for portfolio development, and is currently scientific advisor to Eleven Biotherapeutics in Cambridge, which is focused on developing protein-based therapies for improving human health and treating disease.

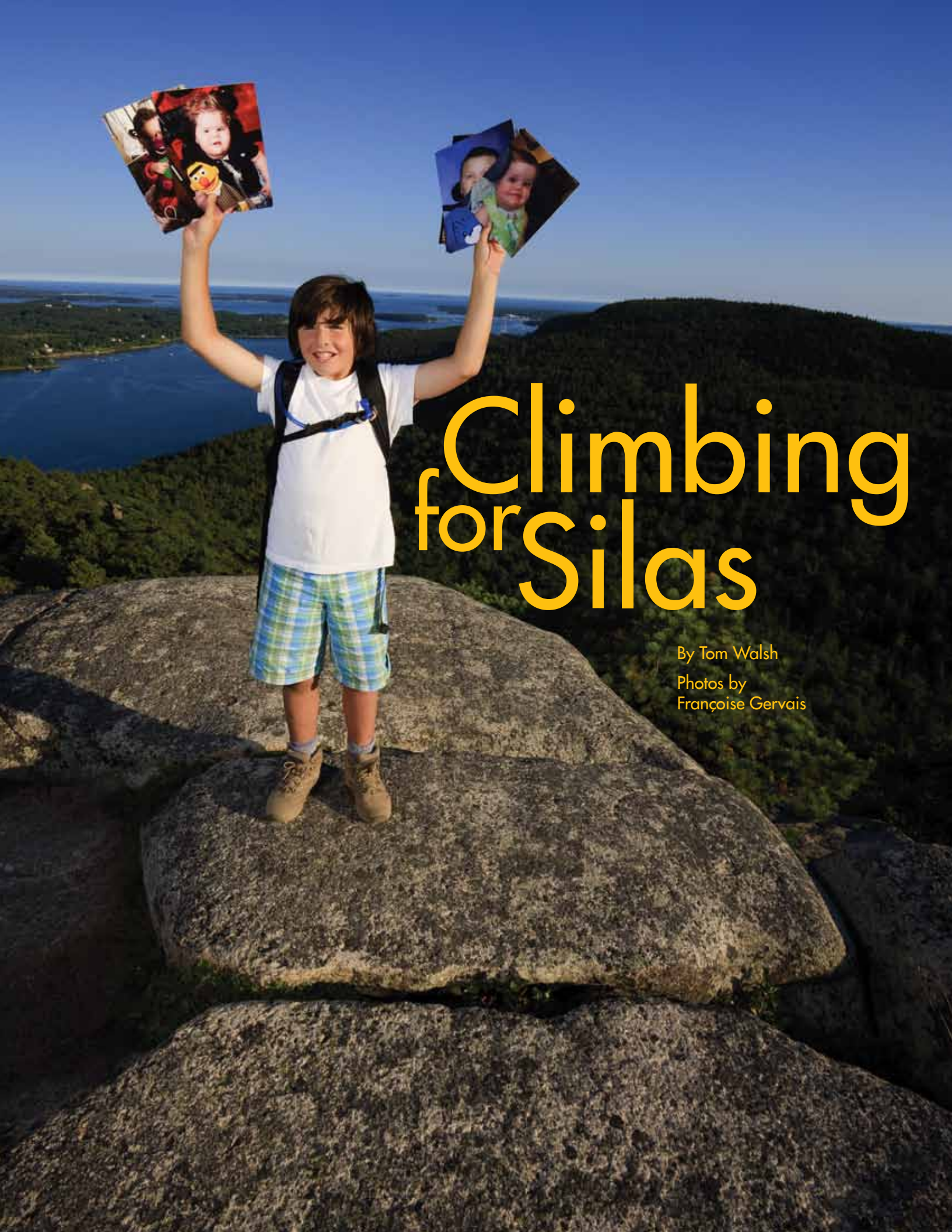
Adelman and his spouse, Lydia Rogers, divide their time between their home in suburban Boston and their home on Mount Desert Island. The couple's friendship with Chen Kang Chai and his spouse, Ling Chi Chai, blossomed and flourished over the years, with the Chais' children, Leon and Jeanne, becoming close friends as well. When Chen Kang Chai died at age 95 and Ling Chi Chai died at age 87—four days apart in November 2010—the Adelman/Rogers family was eager to find a way to honor them.

"Both of them had important careers at the Lab," Adelman says. "We thought that the most appropriate way to honor them and their contributions to science and to the community here would be to do something through the Lab that would recognize and remember them."

A gift from the couple has endowed a new lecture series named in honor of the Chais. The first such lecture was held last July on the first day of the two-week annual Short Course on Medical and Experimental Mammalian Genetics. The speaker was Eric Green, Ph.D., director of the National Human Genome Research Institute, a division of the National Institutes of Health.

"Dr. Chai was a geneticist first and foremost," Adelman says of his late friend and mentor. "Lydia and I decided the annual Short Course would be the right avenue to celebrate and remember the Chais."

Burt Adelman, M.D., at his Mount Desert home.



Climbing for Silas

By Tom Walsh

Photos by Françoise Gervais

Gus La Casse did some math.

What he concluded was that if each of 25 mountain treks could attract pledges, that money would provide a tremendous boost for SMARD research at The Jackson Laboratory and, he hoped, help find a cure.

"My mom works at The Jackson Lab, and one day she came home and told me about SMARD," Gus La Casse said in July. "It's pretty rare, but there are quite a few kids in America and kids all over the world who have SMARD. And nobody has a cure."

That insight distressed Gus, who is into climbing and hiking and who realizes that kids with SMARD will never do either. He decided he would spend much of his summer, in effect, doing that for them, while seeking pledges to fund research. It was, Gus says, a "good summer vacation deed."

Most people have never heard of SMARD, an acronym for spinal muscular atrophy with respiratory distress, which Jackson Laboratory Associate Professor Greg Cox, Ph.D., describes as "the rarest of the rare" in terms of genetic-based, neuromuscular degenerative diseases.

"Until recently, I had never heard of it, nor have most physicians," says Cox. "It's a very debilitating infantile disease. Most of these children don't live more than two or three years. SMARD is a very early onset motor neuron disease. Motor neurons are the neurons in your spinal cord that extend into every muscle in your body. When these motor neurons get sick—and with SMARD, they actually die—there's no way to trigger voluntary muscle response, which includes breathing and swallowing. It's a recessive disease. You have to have two parents who carry the mutation to have a fear of a child developing SMARD."

Regrettably, Cox notes, he can count on the fingers of one hand the number of research laboratories worldwide that are exploring the biomolecular complexities of SMARD. Researchers in those labs make use of a mouse model of SMARD provided through The Jackson Laboratory.

It was Greg Cox who discovered the genetic mutation that causes this currently incurable disease that kills infants and toddlers through muscle atrophy and paralysis. While SMARD affects fewer than 1,000 American children at any given time, each case is devastating for the families involved.

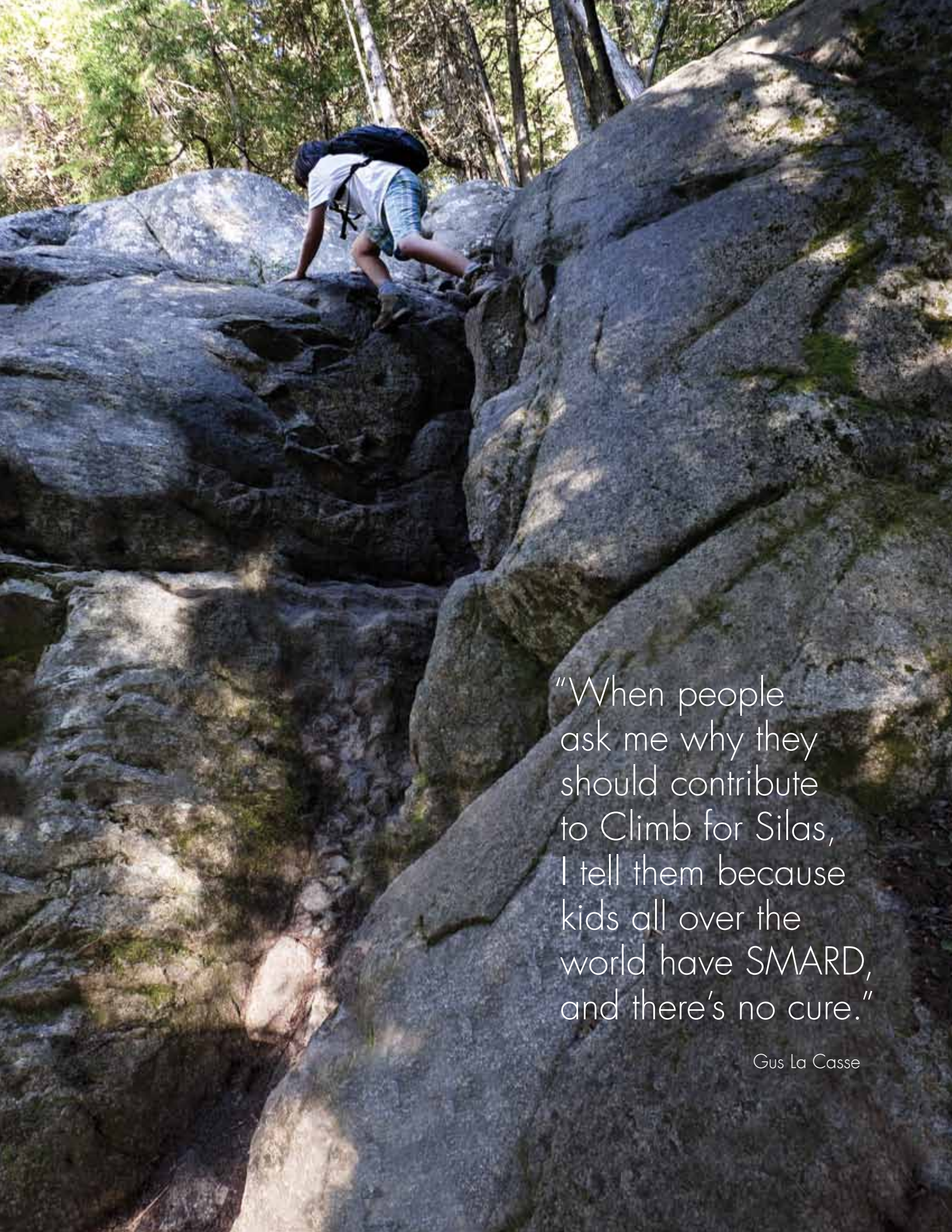
Among those families are the parents and grandparents of Silas Werner. As a newborn, Silas baffled a small army of Pittsburgh, Pa., pediatricians before he was finally diagnosed with SMARD, at age three months. After an original diagnosis of botulism and a prognosis of full recovery, agonizing months of hospitalization finally revealed a diagnosis of SMARD. His parents were devastated.

When Gus, whose parents Renée and Joe both work at the Laboratory, first heard of Silas and SMARD, he was moved to act.

"I do a lot of things that involve movement, like hiking and climbing," he says. "So I decided I would raise money by doing something for these young kids with SMARD that they will never be able to do, like go hiking. In hiking, you have to breathe a lot, and these SMARD kids will never breathe on their own."

Over his summer break from grade school, Gus trekked up and down 25 mountain trails, most of them within Acadia National Park on Mount Desert Island. His final climb on July 31 was a steep ascent to the summit of Mount Katahdin, Maine's highest peak at 5,268 feet. It was five miles straight up, and five miles straight down. Among those joining him in the trek was Greg Cox, who joined Gus on many of his climbs. "He doesn't

Gus La Casse, triumphant, on the summit of Acadia Mountain.



"When people ask me why they should contribute to Climb for Silas, I tell them because kids all over the world have SMARD, and there's no cure."

Gus La Casse

get tired," Cox says of Gus' ambition. Apparently, neither does Greg Cox, according to his wife.

"The last couple of weekends have been very hot here on Mount Desert Island," Kathy Cox wrote in late July on the Facebook site Gus created to promote the project. "But Gus, Renée, Greg and team kept hiking for SMARD families. We are so proud of you."

Gus set an ambitious goal for his fundraising in hopes that Greg Cox can hire a postdoctoral researcher to focus on gaining a better understanding the disease. To spread the word about his project, he was interviewed on a morning talk radio show and wrote an op-ed that he sent to the editorial pages of daily newspapers throughout Maine.

"When people ask me why they should contribute to Climb for Silas, I tell them because kids all over the world have SMARD, and there's no cure," he wrote. "It's important that people like Greg Cox find a cure."

Gus has never met Silas, but plans to. He's been communicating with Lisa and John Werner, Silas's parents, by e-mail, as well as other SMARD families he's tracked down online, including a family in England.

"There's another kid, Dakin, who lives in Texas," Gus says. "He's four years old, which is quite old for a kid with SMARD. I also heard that there's a SMARD kid in California who is 18, which is very unusual."

The dust has settled on his summer of climbing, and Gus is back into his usual school routine. But he continues to work toward his fundraising goals to support research and discovery on behalf of a far-flung community of children and parents to whom he is now firmly connected.

View more from Gus's hikes at www.jax.org/thesearch/vol4no3/smard-champion

Silas Werner is beloved for his sweet disposition.

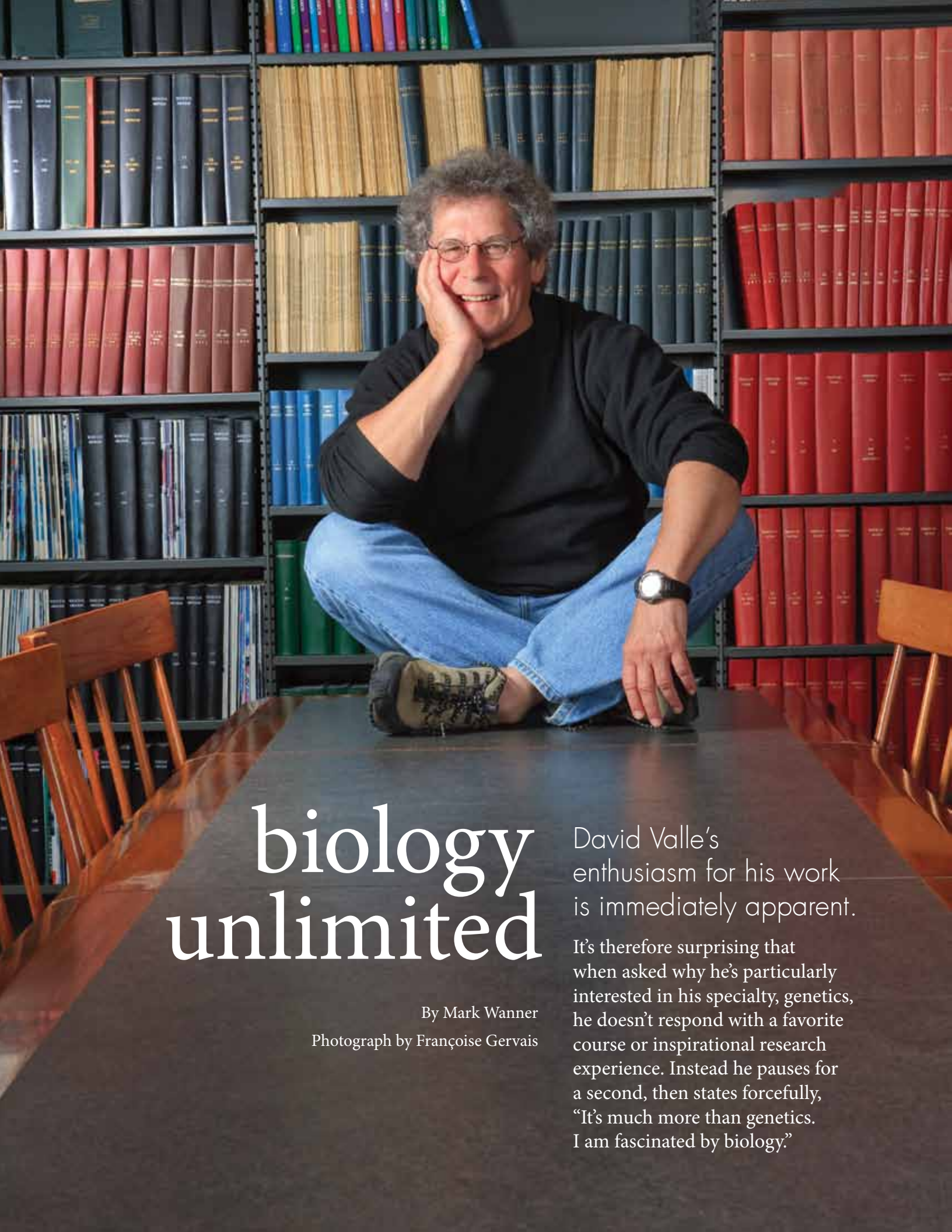
Silas Werner, the boy who inspired Gus La Casse to climb and raise money for SMARD research, is now 2.

Despite his condition, his parents say that Silas radiates joy through his happy smile. Speaking haltingly through a ventilator, Silas has now mastered "mama" and "papa," much to the delight of his parents. Silas' nurses describe him as "having the sweetest disposition of any baby we've ever met."

Nonetheless, Silas requires the around-the-clock care provided by his parents and by visiting nurses. Lisa and John Werner have mastered what Lisa terms "special needs boot camp" to meet Silas's needs.

The Werners are part of the close network of SMARD parents who now have newfound hope for the future. They recently learned that The Jackson Laboratory has a laboratory making strides in SMARD research. They are actively raising funds to support the research and, hopefully, advance the understanding of the disease to the point that doctors can one day help Silas and his peers.

Contributions to support the fundraising efforts of Gus, Renée and Joe can be made by visiting http://genetichealth.jax.org/climb-for-silas.



biology unlimited

David Valle's enthusiasm for his work is immediately apparent.

By Mark Wanner

Photograph by Françoise Gervais

It's therefore surprising that when asked why he's particularly interested in his specialty, genetics, he doesn't respond with a favorite course or inspirational research experience. Instead he pauses for a second, then states forcefully, "It's much more than genetics. I am fascinated by biology."

While many of his scientific peers focus on narrow specialties with laser intensity, Valle's enthusiasm for the broader subject hasn't dimmed since he spent as "much time as possible" as a young boy scrambling through the woods of upstate New York. It has led to wide-ranging professional interests, which are reflected in his current titles at Johns Hopkins University: The Henry J. Knott professor and director of the Institute of Genetic Medicine as well as professor in the departments of Pediatrics, Ophthalmology and Molecular Biology & Genetics.

Nature first sparked Valle's scientific interest. His early nature rambles in the woods led to many captured frogs and snakes and a strong desire to learn about animals. He recalls becoming very excited as a 4th grader when he learned that biology was an official course in 7th grade. Faced with a student with three years of pent-up anticipation, the school's biology teacher further fed Valle's enthusiasm by providing him with extra resources, including a microscope he was able to take home. That teacher was the first of many "really superb teachers and mentors" who both nurtured and shaped Valle's love for science.

Ironically, however, lacrosse may have influenced his choice of undergraduate school as much as biology.

"I played lacrosse in New York, but I went to high school in Kansas City after my family moved there," says Valle. "Most people in the Midwest had never heard of lacrosse back then. One day a guy saw me bouncing a ball off a wall, and it turned out he had played lacrosse at Duke. So we would play catch, and he told me about his experiences there."

To benefit from Duke's biology department—and lacrosse program—Valle first had to withstand a formidable parental challenge. His dad, who worked in insurance, lobbied for Yale or Wesleyan, in part because of their proximity to Hartford, the industry's epicenter.

"I stuck to my guns," says Valle. "I was the only one in my immediate family who was so interested in science, and I don't think it was something they fully understood. But to his credit, my father was okay with it in the end. And off I went to Duke without having ever actually seen the campus."

At Duke, Valle "clicked" with Professor Calvin Ward, a fly geneticist, and began an exploration into various aspects of genetics that has continued to the present day. But it was medicine, not basic science research, that Valle chose as a career, attracted by what he calls its humanistic side.

At Duke for medical school as well, Valle soon found himself in formidable company. "I remember doing weekly rounds with a terrific group, seeing pediatric and adult patients with genetic and biochemical diseases," he says. "They were led by my friend and mentor Jim Sidbury, a biochemical geneticist who later became director of the National Institute of Child Health and Human Development. The group also included Harvey Cohen, who went on to be chair of pediatrics at Stanford, Jim Wyngaarden, who went on to be director of the NIH, and Bill Kelly, who was later dean of the medical school at the University of Pennsylvania. That was very exciting."

Valle went on to do his residency in pediatrics at Johns Hopkins, where he has stayed since. The chair of pediatrics, John Littlefield, soon suggested that Valle attend a course in Maine led by Victor McKusick of the Medical Genetics Clinic at Johns Hopkins. Valle did attend the Short Course on Experimental and Medical Genetics at The Jackson Laboratory for the first time in 1976, but not as a student—he was named to the faculty.

Valle took over as co-director of the Short Course (as it's commonly known) with McKusick in 1992 and by now has taught on its faculty for 35 years. The two became friends and colleagues through the years and enjoyed the process of setting up the course each year together. Valle now works with new co-directors after McKusick's death in 2008, but the reasons for his commitment to the course remain rock solid.

"The Short Course introduced me to the Laboratory and through it the tremendous power of mouse genetics. Also, teaching is the best way to learn, and every year the Short Course explores a wide variety of interesting and important topics."

Which is just the way Valle likes it, expanding his knowledge and pursuing his fascination for all things biological.

David Valle, M.D., chairs The Jackson Laboratory's Board of Scientific Counselors.

5 ques

tions...

Mark Sobczak, Computer Technician, The Jackson Laboratory

Q: Are you originally from Maine?

A: No, I grew up and went to high school in the Buffalo, New York, area. I first came to the Maine coast, at Winter Harbor, when I was in the Navy.

Q: When did you join the Navy?

A: What I learned at college was that I wasn't quite mature enough to get a lot out of it at that time. So I joined the Navy, and that's where I began to work with computers. I retired in 1996 after 20 years.

Q: How did you come to the Laboratory?

A: I moved to Maine and applied to the computing department in 1996 after leaving the Navy. There wasn't a job for me there, but I was hired to work in a mouseroom in December. I worked there for about 18 months, then, after a very short time in customer service, I went to IT as a computer technician.

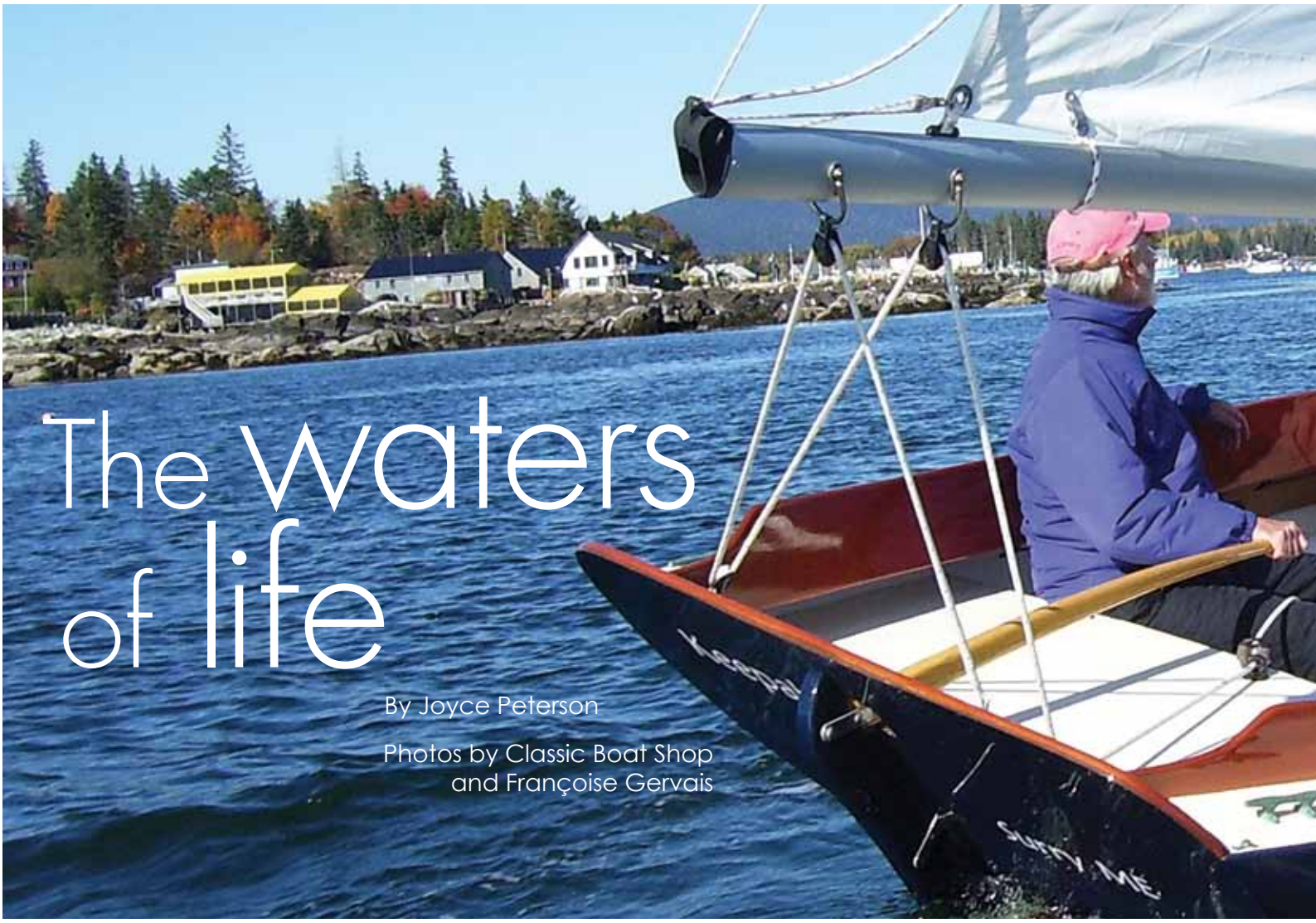
Q: What do you do in your job?

A: I help people use their computing equipment, whether it's setting up hardware, helping them with software upgrades that IT pushes out, getting them up and running after power glitches, that sort of thing. But given how dynamic the computer field is, the specifics of what I do are always changing.

Q: Do you like your work?

A: I love working here! I've always liked taking things apart—fortunately, during my time in the Navy I learned how to put them back together again too [laughs]. And 11 years ago I was diagnosed with multiple sclerosis, and everyone has been helpful and willing to work with me. My supervisor in particular has been my guardian angel through it all.

Visit www.jax.org/thesearch to watch the video and learn more about Mark's time in the Navy.



The waters of life

By Joyce Peterson

Photos by Classic Boat Shop and Françoise Gervais

John Eppig, Ph.D., is somewhat obsessed with water.

It dates back to childhood, when his first scientific samples came from local ponds. "I've always been a scientist," he says. "By the sixth grade I was always looking into a microscope. My mother used to worry about all the murky-looking jars in my room, filled with stuff I had collected."

Now the renowned Jackson Laboratory reproductive biologist insists upon a very specific source of Mount Desert Island spring water for use in his lab. And his favorite place to unwind is on Blue Hill Bay at the tiller of his sailboat, Keepah. Eppig, recently elected to the National Academy of Sciences, grew up sailing on the North Shore of Long Island, N.Y., and rediscovered his boyhood passion a few years ago, when injuries sidelined his wicked tennis game.

Initially fascinated with the metamorphosis that transforms tadpoles into frogs, Eppig was inspired to study developmental biology at Villanova University. He continued his graduate studies at Catholic University in Washington, D.C., followed by a series of graduate positions at the University of Tennessee and Oak Ridge National Laboratory. "I never did study metamorphosis," he laughs. "All my work involved frog eggs."

His first teaching post was at Brooklyn College. While there he met Professor Ed Leiter, who was to become a distinguished diabetes researcher at The Jackson Laboratory. At the time, Leiter was doing summer work in Bar Harbor, and he encouraged Eppig to visit as well. Soon thereafter Leiter moved full-time to Maine, and a year or so later, in 1975, Eppig followed suit, joining the Laboratory staff and shifting his focus from amphibians to mammals.

Hundreds of research publications have followed, as have dozens of awards including the Gregor J. Mendel Honorary Medal for Merit in the Biological Sciences, bestowed in 2002 by the Academy of Science of the Czech Republic; the 2007 Pioneer in Reproduction Research Lectureship Award from the Frontiers in Reproduction Research Program; and The Jackson Laboratory Award for Scientific Achievement.

The research conducted in Eppig's lab for the past 30 years had a common theme: to develop culture systems that support the *in vitro* development of egg precursor cells, known as oocytes. His research successes include achieving the first complete *in vitro* development of mammalian oocytes into a complete organism, the famous mouse known as "Eggbert."

Water underlies his most celebrated scientific achievements. Cell culture depends on controlling environmental factors to an almost fanatical extent, and for decades Eppig has used only water from an undisclosed local spring. His longtime research assistants Marilyn O'Brien and Karen Wigglesworth collect the precious water every few weeks, in every season of the year, and distill it for the experiments. Wigglesworth jokes, "John has always been afraid Marilyn would leave here and get a tanker truck full of this water, and drive it around to labs around the country."

Wigglesworth and O'Brien describe the Eppig lab as a fun and challenging place to work. "However, you have to like puns," Wigglesworth says. "The other day John came into the lab while I was preparing oocyte culture medium and asked what

John Eppig (stern) and friend enjoy a brisk fall day aboard Keepah.

I was doing. I said, 'I'm making medium,' and he said, 'Yes, but will it be a happy medium?'"

Jackson Laboratory Senior Research Scientist Mary Ann Handel, Ph.D., is a longtime friend and colleague of Eppig's—the two of them were postdocs together at Oak Ridge National Laboratory, and they recently shared duties as coeditors of *Biology of Reproduction*, the journal of the Society for the Study of Reproduction (SSR). Handel describes Eppig as a "brilliant, original thinker and experimentalist. But I bet he'll say the thing he's most proud of are his students. He's a great teacher."

Barbara Vanderhyden, Ph.D., Corinne Boyer Chair in ovarian cancer research at the University of Ottawa, was one of three postdoctoral associates in Eppig's lab in the late 1990s. "John's lab was a really fun and stimulating environment. He was always challenging us to try new ideas."

At last year's annual meeting of the SSR, when Vanderhyden was elected president, Eppig received the organization's most prestigious honor—the Carl G. Hartman award. Vanderhyden says the thing she admires most about Eppig as a scientist is that "he never steps away from a challenge. And the biological system he has chosen to study is certainly among the most challenging."

He's also "simply brilliant," she adds. "He thinks out of the box. You never know where his ideas are coming from, and they're always illuminating."

With characteristic self-deprecation, Eppig declines the "brilliant" label his colleagues insist on using, but does acknowledge that he's "…very imaginative. If you had to be a very bright person to be a successful scientist, I would never have been a successful scientist." He says his best skill is figuring out, "if I were in Mother Nature's shoes, how would I do this?"

Last year Eppig published a paper in *Science* about the molecular and cellular players in ovaries that control the timing of egg development in mammals, including humans. What Eppig and his research team found was an intricate interrelationship of signaling between the oocytes themselves and the surrounding cumulus and follicular granulosa cells.

"Far from being a passive passenger on the Good Ship Follicle," Eppig says, "it looks like the oocyte is the captain of the ship."

However, Eppig adds, "I do wonder whether the follicle cells are also affecting how the 'captain of the ship' is making decisions. That's the question I would most like to resolve."

For several years Eppig has worked at home on Tuesdays. "He always says he gets more work done," O'Brien says, "and so do we!" Wigglesworth explains, "He'll come in and say, 'I've thought of a better idea for that experiment' after we've already set it up, and then we have to start over."

In 2003 Vanderhyden and almost all of Eppig's other past graduate students and staff surprised him with a symposium and party in honor of his 60th birthday. "People came from all over the world—China, Japan, Czech Republic, Scotland, Canada," says Wigglesworth. "It was a real testimony to John as a scientist and mentor."

Fine days often find Eppig aboard Keepah, pushing off from the dock at the shore of his home. There's a charming story behind the name of the sloop. "Janan, my wife, handed me a brown paper bag on our 25th wedding anniversary. Inside was a toy sailboat with a check taped to it and a note that read 'Go buy a sailboat.' When I told our local boatbuilder that this would be a gift from my wife, he paused a moment and said, 'She's really a keepah'—which is Downeast Maine for 'keeper.'"

It's with a certain pride that Eppig notes that Keepah doesn't have a motor. Instead he has only his skill as a sailor to navigate the craft. "I've only needed a tow once," he says, "when the wind totally died on us."

And so it's fitting that his work has led him here, at home on the open waters of Blue Hill Bay.

Marilyn O'Brien at the source of the Eppig lab's precious water.

Beyond the news

What is a laboratory mouse?

What, genetically, are laboratory mice? It's a very important issue. A lack of genetic diversity limits the potential for new research discoveries and makes it much more difficult to translate findings in mouse models to human medicine.

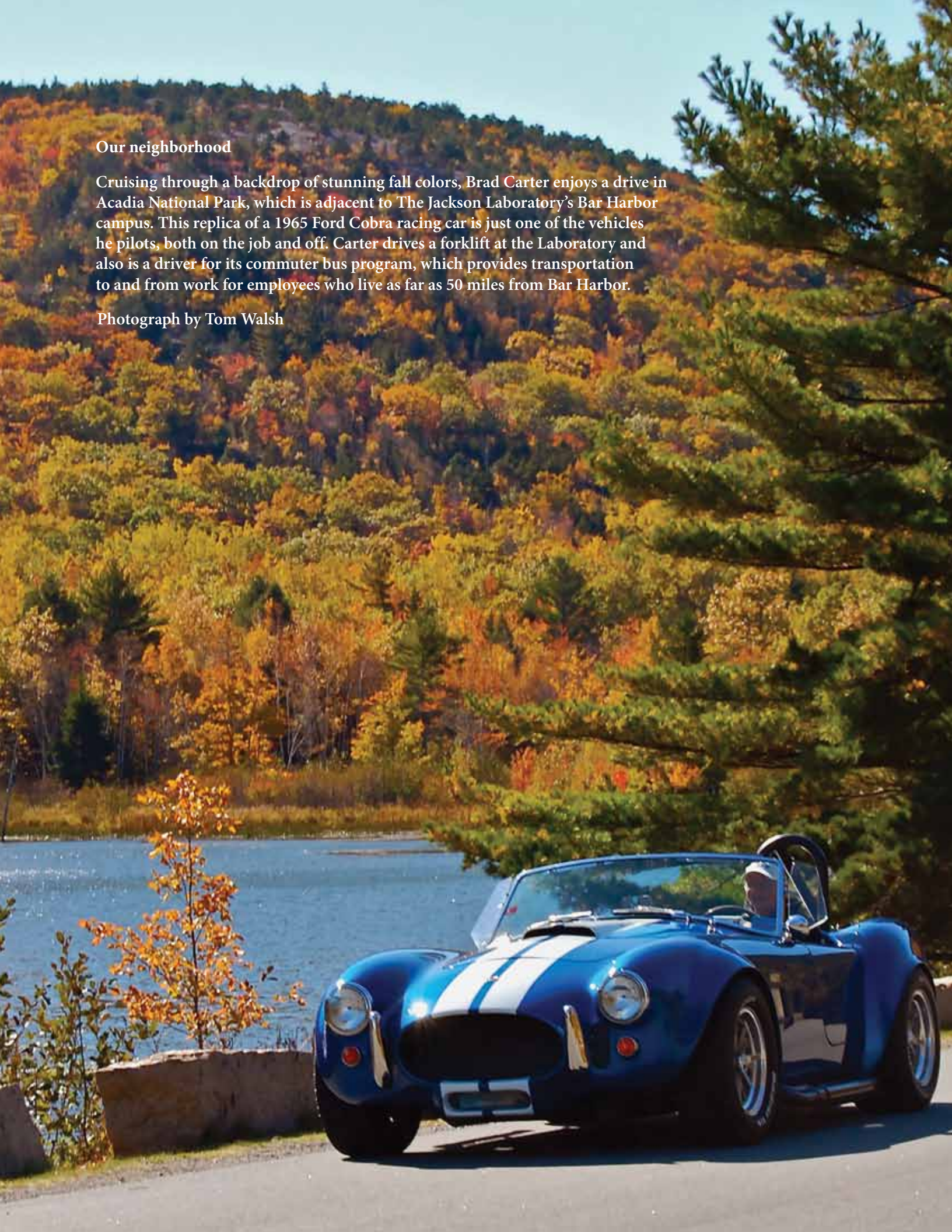
Did the mice originally come from several different wild and domestic mouse species? Or are they almost entirely descended from the domesticated "fancy" mice popular in the late 1800s? It seems like a basic question, but until recently researchers didn't know for sure. And for Jackson Laboratory Professor Gary Churchill, Ph.D., not knowing was unacceptable. "It's embarrassing," he says, "to have such a highly used model organism and not really understand what its relationship is to the wild."

Gary Churchill, Ph.D.

Now Churchill and Fernando Pardo-Manuel de Villena, Ph.D., of the University of North Carolina, Chapel Hill, have led an international effort to provide a definitive answer. In a paper published in *Nature Genetics*, they conclude that most laboratory mice represent limited genetic diversity and are derived almost entirely from mice kept and traded as pets in the 19th century.

Churchill and Pardo-Manuel de Villena have been working for almost a decade to make laboratory mice more effective for translational research. The Collaborative Cross and Diversity Outbred mouse population projects have included wild-derived strains to greatly increase genetic diversity and more accurately model human genetics. These mice provide 45 million sites of genetic variation, nearly four times more than can be found in standard laboratory mouse strains. "All these variants give us a lot more handles into understanding the genome," says Churchill.

Yang et al. 2011. Subspecific origin and haplotype diversity in the laboratory mouse. Nature Genetics 43:648-655.



Our neighborhood

Cruising through a backdrop of stunning fall colors, Brad Carter enjoys a drive in Acadia National Park, which is adjacent to The Jackson Laboratory's Bar Harbor campus. This replica of a 1965 Ford Cobra racing car is just one of the vehicles he pilots, both on the job and off. Carter drives a forklift at the Laboratory and also is a driver for its commuter bus program, which provides transportation to and from work for employees who live as far as 50 miles from Bar Harbor.

Photograph by Tom Walsh

The Jackson Laboratory

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On a visit to The Jackson Laboratory on June 29, Congressman Mike Michaud disembarks from a commuter bus, part of the energy-saving fleet for which he helped secure funding.

Photograph by Jennifer Torrance