THE SEARCH

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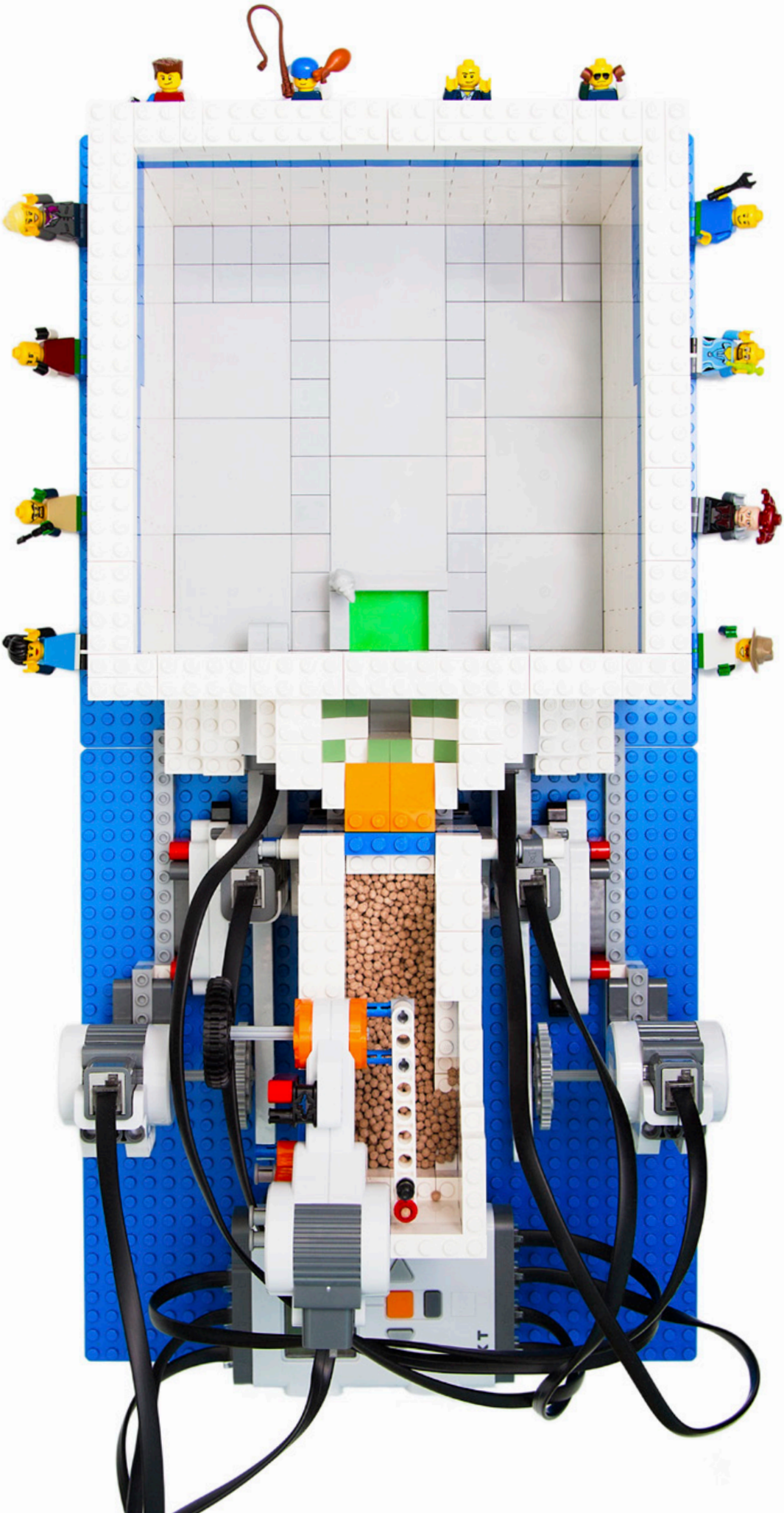

THE SEARCH
A PUBLICATION OF THE JACKSON LABORATORY

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JAX Associate Professor Elissa Chesler and her student intern Andy Gallup used the familiar LEGO® building brick system to study addiction behaviors. Story begins on page 18.
Photo by Marie Chao

LEFT
Photo By Marie Chao

The Search

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

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Bar Harbor, Maine
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The Jackson Laboratory
Leading the search for tomorrow's cures

President's message

ONE JAX — ACCELERATING DISCOVERY AND CREATING A HEALTHIER FUTURE

From our new scientific director in Bar Harbor to the outgoing chair of our Board of Trustees, from faculty researchers to alumni — the people you will meet in the pages of this *Search* issue are all visionaries who are deeply committed to advancing our mission.

Like each of them, all of us at The Jackson Laboratory — more than 1,700 scientists and staff — are determined to work together as One JAX to achieve our vision. This entails creativity and collaboration, not just across multiple geographic locations, but also across focus areas: fundamental mammalian genetics, clinical genomics, education and the development of resources for the global biomedical research community.

As we look ahead, the future holds even more opportunities to envision the transformation in human health that our research will make possible. The new Precision Medicine initiative recently launched by the federal government is focusing attention and investment on genomic medicine. With our new JAX Genomic Medicine campus in Connecticut open and building momentum, we are poised to play a leading role in uncovering the full potential of precision medicine to prevent, treat and cure disease.

JAX researchers are embracing the new technologies that will be vital to advancing precision medicine, including CRISPR/cas gene editing technology. Wayne Frankel's work on epilepsy, for example, has been transformed by rapid advances in sequencing technology that have enabled him to identify myriad genes related to this complex condition.

At the same time, some of the creative solutions that move science forward are surprisingly low-tech: witness Elissa Chesler's use of LEGO® bricks as a tool for understanding the neurobehavioral underpinnings of addiction. Sometimes the basic building blocks of great science are just that: simple tools that unleash creativity, enabling us to envision unexpected solutions.

At JAX, we are proud to be visionaries, working together as One JAX to improve human health through scientific discovery. We could not build for the future without the generous support of the many donors and friends who share our commitment to a healthier future. We are grateful to all of you who make it possible for us not only to envision new possibilities, but to make them a reality.

Edison Liu, M.D.

President and CEO, The Jackson Laboratory

news&notes

GROWING OUR WORLD-CLASS TEAM

INTERNATIONAL MAMMALIAN GENETICS LEADER NADIA ROSENTHAL JOINS THE JACKSON LABORATORY AS SCIENTIFIC DIRECTOR

Nadia Rosenthal, Ph.D., F.Med.Sci., a world-renowned researcher and leader in mammalian molecular genetics, has joined The Jackson Laboratory as scientific director of the institution's Mammalian Genetics headquarters in Bar Harbor, Maine. Rosenthal comes to the newly created position after serving as founding director of the Australian Regenerative Medicine Institute of Monash University in Melbourne, and as director of science for the Harefield Heart Science Center and chair in cardiovascular science at Imperial College, London.

Read the full profile of Nadia Rosenthal that begins on page 12.

KENNETH FASMAN NAMED VICE PRESIDENT FOR STRATEGIC INITIATIVES

Kenneth Fasman, Ph.D., a biomedical researcher whose work in the academic, nonprofit and business sectors has made him a leader in scientific collaborative research management, has been named The Jackson Laboratory's vice president for strategic initiatives. Fasman joins the Laboratory from the Adelson Medical Research Foundation in Needham, Mass., where he has been vice president and chief scientific officer since 2008.

JAX RESEARCHERS NAMED TO CHAIRS IN GENOMICS, COMPUTATIONAL BIOLOGY

Jackson Laboratory Professors Gary Churchill, Ph.D., and Yijun Ruan, Ph.D., have been appointed to new chairs in genomics and computational biology, Churchill as the Karl Gunnar Johansson Chair and Ruan as the Florine Deschenes Roux Chair. Both professorships were established by a 2014 gift to JAX by David and Barbara Roux and are part of the Roux Family Center for Genomics and Computational Biology.

AURO NAIR PROMOTED TO GENERAL MANAGER, JAX® MICE, CLINICAL & RESEARCH SERVICES

The Jackson Laboratory has promoted Auro Nair, Ph.D., to general manager of JAX® Mice, Clinical & Research Services. Nair joined the Laboratory in 2007 as associate general manager of what was then known as JAX® Mice & Services. The institution added clinical services to its offerings and in 2011 Nair was named general manager of JAX® Clinical & Research Services, responsible for all clinical and scientific research services provided to internal researchers at The Jackson Laboratory and external researchers worldwide. With the new promotion, Nair is now also responsible for all mouse production and operations.

LEROY STEVENS, PH.D., 1920-2015

Leroy Stevens, Ph.D., a retired Jackson Laboratory scientist acknowledged as the pioneer of embryonic stem cell (ES cell) research, died on March 28.

In 1958, while examining a large testicular tumor on a mouse from the strain known as 129, Stevens noticed that it was composed of many kinds of tissue, including muscle, skin, bone and hair. In later studies, Stevens observed that the tumors, known as teratocarcinomas, produced not only the various kinds of tissues as expected, but also groups of undifferentiated cells with the capacity to grow into a wide range of tissue types. He dubbed these cells "pluripotent embryonic stem cells."

In 1981, Dr. Gail Martin of the University of California was the first to isolate mouse embryonic stem cells from normal embryos, a feat repeated shortly thereafter by Drs. Martin Evans and Matthew Kaufman in England. By the late 1990s, the first human ES cells were isolated. In 2004, on the occasion of The Jackson Laboratory's 75th anniversary, Martin commented, "Stevens' contributions to stem cell biology built the road that led to current knowledge about the properties and potential of human ES cells.

news&notes

PARTNERING TO ADVANCE HEALTH

THE JACKSON LABORATORY, AUSTRALIAN REGENERATIVE MEDICINE INSTITUTE ANNOUNCE COOPERATIVE AGREEMENT

Two international centers for mammalian genetics, The Jackson Laboratory and the Australian Regenerative Medicine at Monash University, have entered an agreement to establish several cooperative programs and activities. Under the agreement, the two institutions will explore opportunities for short- and long-term faculty and student exchanges, and partner together in new education, training and research initiatives.

ACCELERATING DISCOVERIES

CANCER'S PROTEOMIC INSTABILITY OFFERS A NEW TREATMENT APPROACH

Exploiting one characteristic of cancer — proteomic instability — could be a way of combating that very cancer, a Jackson Laboratory research team led by Chengkai Dai, M.D., Ph.D., reports. In a featured article in the journal *Cell*, Dai and colleagues show that the warped signaling pathway in tumors protects the tumor's protein stability and suppresses amyloid production. The findings suggest a potential therapeutic strategy in disrupting tumors' fragile proteome equilibrium and thereby promoting tumor-suppressing amyloid production.

NIH, JAX TEAM REVEALS LINK BETWEEN POWERFUL GENE REGULATORY ELEMENTS AND AUTOIMMUNE DISEASES

Investigators with the National Institutes of Health and The Jackson Laboratory have discovered the genomic switches of a blood cell key to regulating the human immune system. The findings, published in *Nature*, open the door to new research and development in drugs and personalized medicine to help those with autoimmune disorders such as inflammatory bowel disease or rheumatoid arthritis.

FUNDING MAKES OUR WORK POSSIBLE

FOUNDATIONS GRANT $175,000 FOR INNOVATIVE TEACHER EDUCATION PROGRAM

The Jackson Laboratory will receive $100,000 from The Arthur Vining Davis Foundations and $75,000 from Jane's Trust in support of "Teaching the Genome Generation," the Laboratory's professional development program for educators.

Launched last summer, "Teaching the Genome Generation" gives high school science and math teachers hands-on lab experience. This "teach the teachers" approach brings greater understanding of the basics of genomics — molecular biology techniques; use of genome databases; and social, ethical and legal issues — to public schools. Teachers can share the knowledge they gain in the course with their colleagues as well as their students.

$1.74 MILLION AWARD SUPPORTS THE JACKSON LABORATORY'S ELLSWORTH FACILITY

The Maine Technology Institute (MTI) has awarded $1,740,000 to The Jackson Laboratory from the Maine Technology Asset Fund (MTAF) to develop a next-generation vivarium, a facility to maintain research mouse models, at the institution's Ellsworth location. The MTAF award, which JAX will match, will enable JAX to launch a pilot phase to test and validate the concept and equipment — R&D innovation that could be commercialized in the future.

The award is one of eight, totaling $4.85 million, that MTI has made to Maine companies, nonprofit research institutions and the University of Maine to develop R&D capabilities in the state.

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

LIVING HISTORY

EIGHT DECADES OF GROUNDBREAKING RESEARCH AND RESOURCE DEVELOPMENT AT JAX

Jackson Laboratory Professor Emeritus Muriel Davisson, Ph.D., has been an eyewitness to more than half of JAX's 85-year history. In the last edition of *The Search*, she reviewed major milestones of the Laboratory's genetics research and discovery to date.

Now, also from her own unique perspective, Davisson recognizes JAX's award-winning faculty and highlights the groundbreaking contributions they and their peers have made to genetics research and resource development during the last eight decades.

Read her narrative and see historic photos on our new website, *www.jax.org/thesearch/85years*. You'll gain insight into how JAX scientists have improved our understanding of cancer, diabetes, obesity, glaucoma, neurological disease, tissue and organ transplantation, reproduction, development and many other facets of health, disease and medicine.

85 *YEARS OF* *DISCOVERY*

EPILEPSY

ELECTRICITY AND THE TOOLS OF GENOMIC DISCOVERY

STORY BY MARK WANNER
PHOTOGRAPHY BY MARIE CHAO
ILLUSTRATION BY KAREN DAVIS

Just a few years ago, epilepsy's mysteries made it appear intractable. But now, thanks to new data and new research methods, there's real hope for accelerated progress in finding its causes and identifying more effective therapies.

Jackson Laboratory researcher Wayne Frankel, Ph.D., is leading the way. His long-time epilepsy research efforts and promising future directions gained recognition in the fall of 2014, when he received the prestigious Javits Neuroscience Investigator Award from the National Institute of Neurological Disorders and Stroke. The Javits Award, made to distinguished investigators with "exceptional talent, imagination, and preeminent scientific achievement," will support Frankel's pioneering work to combine the insight of human patient data with the experimental power of precise mouse models.

EPILEPSY MYSTERIES

When Frankel began working on the genetics of epilepsy more than 20 years ago, it was regarded as a particularly puzzling and difficult condition to research — so much so that many scientists steered clear.

"I was a geneticist, not a neuroscientist," Frankel says, "but I worked with a lab that was investigating epilepsy. I found it very interesting — the disease susceptibility varied between different strains of mice — but so little was being done in the field that I saw opportunity as well as challenge."

Epilepsy is a complex neurological disorder with a common trait: seizures provoked by spikes of electrochemical activity in the brain. Beyond that, however, the underlying causes and observable symptoms, including seizure type and severity, are highly variable. About one third of cases arise from a known brain trauma, such as an accident or a tumor, but most cases are idiopathic, meaning that they arise without known cause. And while recent progress suggests that most of these cases are genetically based, they are not necessarily heritable in the classic parent-offspring manner, confounding traditional approaches to studying them.

> "PEOPLE THOUGHT THAT WAS KIND OF CRAZY"

When Frankel launched his program at JAX in 1992, he investigated mice with both spontaneous and induced mutations leading to seizures. It was painstaking research, years of identifying the underlying genetics in mice and teasing out the neural mechanisms affected by the mutations, but his progress was steady. Frankel identified mouse mutations that could be matched with ones found in human epilepsy patient populations. And his efforts provided insight into the mechanisms of different kinds of seizures and the roles of the proteins affected by the mutations. The complexity of the disease, however, continued to present obstacles.

"So far, spontaneous seizures have been identified with over 200 different genes after they were knocked out in mice, mostly for other purposes," says Frankel. "Surely there are hundreds more. When we were doing our early gene mapping studies, I estimated that there might be as many as 1,000 genes with a seizure phenotype. People thought that was kind of crazy, but it looks like the actual number will in fact be closer to 1,000 than 100."

Excitement ran high in the scientific community after the human genome was sequenced in 2003, but the early genomics research methods were not terribly effective for epilepsy. Despite all the genes identified in mice, association studies in humans yielded only a few genes with strong signals. Clearly, more precise methods were needed.

SEQUENCING HUMAN EPILEPSY

Over the past several years, genome sequencing has taken phenomenal leaps forward in speed and cost, making it feasible at last to closely investigate changes in patient genomes.

"Several notable groups published a paper a couple of years ago looking at the exomes (the sequences of all protein-coding genes) of children with severe seizures," says Frankel. "They screened in particular for *de novo* mutations, meaning mutations that arise in patients spontaneously during early development and are not inherited from their parents. They found 329 *de novo* mutations in different genes, emphasizing their prevalence in pediatric epilepsies."

Many of these genes are also implicated in autism spectrum and cognitive disorders. And as it turns out, the expanding knowledge of human genetics substantially benefits disease research.

BETTER DISEASE MODELS

While sequencing technology has improved rapidly, scientists' ability to actually change the genome has remained limited. In the past two years, however, new techniques that use specific RNA sequences to identify locations in the DNA have changed all that. The most promising of these, CRISPR — clustered regularly interspaced short palindromic repeats — is relatively easy, cheap and quick to implement; it allows for exact cuts and DNA alterations (read more about CRISPR technology on page 34). With CRISPR, scientists are able to precisely disrupt gene function, so creating mouse models based on human genetics discoveries is now much more straightforward.

In these conceptual drawings, electrical impulses travel along neural fibers in the brain. The panel on the left shows normal transmission; on the right, abnormal activity sparks the kind of electrochemical "storm" that leads to an epileptic seizure. *Illustrations by Karen Davis*

Wayne Frankel explains his epilepsy research.

To watch a narrated animation of an electrochemical storm in a neural network, visit: *www.jax.org/thesearch/frankel.*

"This makes collaborating with human geneticists very powerful," says Frankel. "Human genetics is finally at the point where it can provide insight into which gene variants are actually causal for the disease, so there's way less guesswork. And we can take those genes, quickly make mice to model the disease and then look at the molecular mechanisms behind it."

With tools that are so much faster, easier and more specifically connected with human patients, Frankel can now focus on disease pathways with unprecedented efficiency and effectiveness.

"We can dissect cells — and even parts of cells — to assess function and learn more detail about how neurons connect with other neurons," says Frankel. "We can compare gene activity and regulation in mutant cells and healthy cells and ask how are they different and what might be contributing to the disorder?"

THE BENCH-TO-BEDSIDE LOOP

Frankel's work shows how biomedical research's traditional bench-to-bedside approach is giving way to a faster, more effective process. Data and insight flow continually from lab to clinic and from clinic to lab, with computational analysis playing a large role on both ends. It makes the disease models more useful and relevant to the patient's biology, and it provides a closer relationship between experimental discovery and clinical impact.

Genomics methodologies have progressed so quickly, research that was quite simply impossible only a few years ago is becoming routine. The effect of this progress is not lost on Frankel.

"We can do so much more, and every week it changes and improves," he says. "It's really exciting stuff."

THE SEARCH FOR BETTER THERAPIES

It is indeed exciting stuff, and it provides reason for optimism that the mysteries surrounding epilepsy — and other complex neurological disorders — can finally start to be unraveled. In the end, of course, there is the ever-present goal: better outcomes for epilepsy patients, who comprise approximately one percent of the population.

"About 30 percent of epilepsy patients still can't be effectively treated," says Frankel. "Moving forward, we can work on novel mechanisms that haven't been well studied yet and identify new, previously unappreciated targets. Hopefully, some of those targets will yield the better therapies that we need."

And someday, perhaps, dedicated researchers like Frankel, armed with the tools of genomic technology, will solve all the intricate mysteries of epilepsy.

Big thinker

Renaissance woman Nadia Rosenthal, a distinguished scientist, mentor and leader, will oversee the scientific pursuits of JAX's Bar Harbor campus.

STORY BY NICOLE DAVIS
PHOTOGRAPHY BY MARIE CHAO
ILLUSTRATIONS BY NADIA ROSENTHAL

A superb scientist, a keen intellect, an outstanding teacher, a visionary leader — this is how others describe Nadia Rosenthal, who is taking on a newly created role to lead research at The Jackson Laboratory's mammalian genetics headquarters in Bar Harbor.

"The most impressive thing is that Nadia rolls all of these qualities into one. She integrates those characteristics so that the end result of any of her projects is not just a technical tour de force, but also something that elevates the entire scientific team to a higher level," says JAX President and CEO Edison Liu, M.D. "That's the hallmark of a visionary leader, and we are just very fortunate to have her join JAX."

In March, Rosenthal was named scientific director of JAX's Bar Harbor campus. As she begins her transition to JAX from her post as founding director of the Australian Regenerative Medicine Institute (ARMI) of Monash University in Melbourne, she brings with her a wealth of expertise and experience. Rosenthal is a world-renowned leader in mammalian genetics, with a particular focus on the mouse as a model organism. She has made fundamental contributions to multiple areas of biology throughout her career, including cloning and sequencing the insulin gene, unlocking the biology of muscle cell differentiation, discovering novel aspects of heart development and harnessing stem cells for regenerative medicine.

In addition to her diverse scientific talents and far-reaching knowledge, Rosenthal also has a knack for growing and leading scientific organizations. In 2001, she moved to Rome to build a mouse biology program for the European Molecular Biology Laboratory (EMBL), a highly distinguished research organization dedicated to molecular biology research. Recognizing the power of the EMBL model, particularly for attracting and cultivating young researchers, Rosenthal helped disseminate it to other parts of the world by establishing the first non-European EMBL outpost in Australia. By the end of this year, there will a dozen such groups across the continent. She also created ARMI at Monash University and served as its founding director. First launched in 2009, it is now a prominent institute for research on stem cell biology and regeneration.

"She really has a talent for inspiring others to collaborate toward a common goal. She knows what needs to be done and will work with people so that it's a win-win situation," Liu says.

Melding art and science

Although her achievements in science might suggest otherwise, Rosenthal began life with decidedly different proclivities. Her parents were classically trained musicians, and she spent her childhood surrounded by artists, poets, musicians and playwrights. As she grew up, the glamour and glitz of Hollywood and the bright lights of Broadway became familiar scenes.

Her own interests in art were wide-ranging. "I was insatiable — I sculpted, I drew, I painted," she recalls. She tried her hand at nearly every art form, from painting in the style of photorealism to modern sculpture to bookbinding. Art was more than just a broad passion, though. It was also a gateway to Rosenthal's scientific pursuits. Through her artwork, she became fascinated by the extraordinary patterns that exist in nature and sought to understand why things were the shape they were. In high school, an inspiring teacher gave a captivating tour of the biological world, teaching everything from hard-core biochemistry to plant and animal phylogeny.

Adam, 2008
Nadia Rosenthal
colored pencil on vellum

"I just lapped it up because of the way she taught it. She made it relevant," says Rosenthal. "And I became obsessed with the idea, with all of this detail she taught me, that I would be able to translate it into an understanding of pattern formation, which was the thing I was really interested in."

Although Rosenthal had studied science before and enjoyed it, that advanced biology class marked a real awakening, setting her on a path to study how form emerges — a central question in the field of developmental biology.

Globetrotter

As Rosenthal finished high school and contemplated her undergraduate studies, she was particularly drawn to the style of university education in the United Kingdom, which allowed students to focus, almost single-mindedly, on one area of study to the exclusion of other subjects. To Rosenthal, that seemed a perfect fit. Her education had been fairly liberal up until that point; as a rising undergrad, she felt ready to focus on science. So she enrolled at the University of North Wales in Bangor, U.K.

Soon, though, her wide-ranging interests and curiosity got the better of her, and she found herself gravitating toward courses in French literature and ancient Greek architecture. Rosenthal also realized that her scientific training was not heading in the direction of her true love: developmental biology. She eventually returned to the U.S., and landed at Harvard University, where she completed her undergraduate degree and also earned her Ph.D.

While the academic environment at Harvard proved challenging, even grueling at times, it was also deeply formative. The field of molecular biology was booming, and the ability to isolate and decode individual genes had just hit the scientific scene. "It was so powerful and so compelling, I felt that if I didn't learn it, I would lose the opportunity to apply all these molecular tools to the questions of development," Rosenthal recalls. She shelved her pursuit of developmental biology and fully dedicated her efforts to gene hunting. That meant shifting her work with her graduate advisor, Fotis Kafatos, to the laboratory of a nearby faculty member, Walter Gilbert, who pioneered one of the two pivotal DNA sequencing methods of the day. Gilbert's lab was engaged in an intense race to sequence the full genetic code of the insulin gene. Rosenthal recalls the experience as both intense and exhilarating. "We felt like we were the center of the universe, scientifically."

Although her work cloning genes may have seemed far-flung from development, it motivated her later efforts to study how genes are turned on and off — a key aspect of developmental processes. At the time, little was known about how genes were regulated in humans. As a postdoctoral fellow at the National Institutes of Health, she identified a key regulatory component — the first enhancer element in humans — using homology searching, a technique that fishes out similar stretches of DNA from even distantly related organisms, purely on the basis of shared genetic sequences. Her landmark discovery was published in *Science* in 1983.

In addition to catalyzing important scientific discoveries, Rosenthal's days at Harvard also instilled in her a deep sense of scientific community, particularly the importance of peers.

"It is really important to know whom you are traveling with in life," she says, "and scientists are some of the most interesting people out there. My best friends have invariably been scientists because we share that love of the embryo, or something we've seen down the microscope, or the thrill of the chase or the sense of wonder."

Committed to mentoring

While Rosenthal has earned many accolades throughout her career, she is particularly proud of the cohort of young scientists she has helped train. She has mentored over 60 graduate and post-graduate trainees over a span of more than 30 years. Not all have remained at the laboratory bench, but almost all have pursued a path in a science-related field. "That means a lot to me," she says, "because it means that I have managed to get people through some difficult times in their lives as students and postdocs, and steer them toward productive areas of science."

Rosenthal's teaching extends well beyond the laboratory. As a graduate student at Harvard Medical School, she taught biochemistry to medical students. In the classroom, she often drew upon her own artistic capabilities, arriving at lectures a half-hour early so she could illustrate complex metabolic

To see a video clip and a photo gallery of Nadia Rosenthal, visit *www.jax.org/thesearch/rosenthal*.

Nadia Rosenthal prepares to set up her lab at The Jackson Laboratory in Bar Harbor, Maine.

pathways in exquisite detail on the blackboard using multi-colored chalk. Her students would ask for photocopies, but she refused, insisting instead that they draw the diagrams for themselves with the colored pencils she provided to each student. "If you draw it yourself, it is in your hand. And your eye-hand connection somehow emblazons it in your brain and it is a lot easier to remember," she says.

She also authored a textbook on heart development. Enticed by the beautiful morphology of the embryonic heart, Rosenthal became deeply interested in the development of the heart and decided to co-write a book on it — now widely considered the definitive reference in the field.

A champion for mice

With JAX's rich legacy of innovation and discovery in mouse genetics, it is fitting that Rosenthal was lured to the organization by her own love of the mouse as a model organism. Like many scientists who choose the animal as their laboratory muse, Rosenthal has often worked with strains that are highly inbred — mice mated together over many generations, making them genetically homogeneous. Such genetic similarity is a boon for biological studies, enabling researchers to replicate results across multiple experiments and untangle the effects of genes from those of the environment.

But these advantages come at a cost. By minimizing genetic diversity in the mice they study, scientists may neglect the very features that can be helpful in understanding complex traits in humans, such as aging or susceptibility to diabetes.

"There is a lot of genetic diversity in the human population, so if you are trying to model a genetically diverse population with a basic inbred mouse, you are really coming up short," explains JAX Professor Gary Churchill, who has devoted the last decade to creating a vast repository of mouse strains, about 150 in total, that have been painstakingly bred to maximize their genetic variability. This resource, known as the Collaborative Cross, is proving to be a powerful tool for unlocking key aspects of human biology.

Rosenthal recently screened a portion of the mouse collection pioneered by Churchill, searching for differences in the ability to regenerate heart tissue following a heart attack. The results were astonishing. "I was stunned at what we got; the results were all over the map. Some animals recovered from heart attacks just like that and others repeatedly did not; in fact, they did terribly," she notes.

Others have unearthed surprises, too. A recent study published last fall in the journal *Science* shattered the long-held view that Ebola infection cannot be effectively studied in mice. The animals have been excluded from Ebola research because no one has been able to reproduce the hallmark symptoms of the viral infection. But using mice from the Collaborative Cross, a research team led by scientists at the University of Washington demonstrated a range of responses to Ebola in mice, from resistance to infection to hemorrhagic fever to systemic organ failure, mimicking what is seen in the human form of the disease.

Rosenthal sees these findings as just the tip of the iceberg, particularly when it comes to studying human disease. "This is a golden opportunity for JAX to really showcase all of the mice in the cupboard, not just the ones that people think they need," she says.

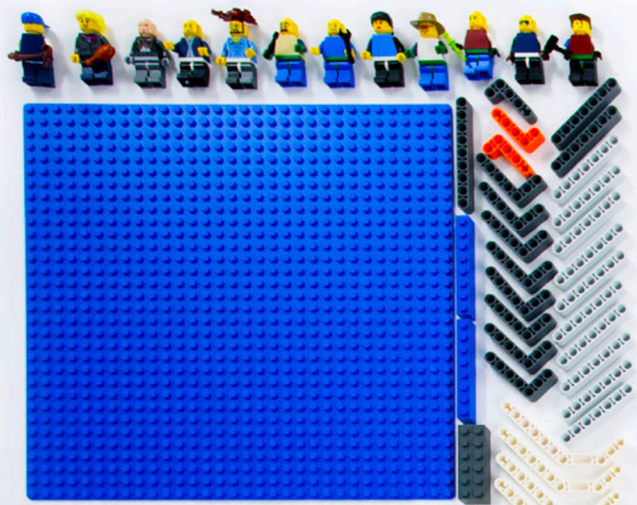
As Rosenthal takes the research helm in Bar Harbor, she will be championing this scientific approach and ensuring that JAX's scientific services are poised to fully realize the promise of a new era of mouse genetics. She will also serve as a mentor and advisor for JAX faculty in Bar Harbor, helping to shape their research and provide a cohesive vision that unifies their work.

And Rosenthal is no stranger to Bar Harbor and its surroundings. As a child, she spent summers in the area, so her appointment at JAX is a kind of homecoming. "I have a deep, deep affection for this part of the world," she says. "Like a sailor who has been around the world, you bring the world with you in your head."

And it is no surprise that she is embracing her new role with the same gusto as in her previous feats, undeterred by the risks and challenges that can accompany change.

"I am going to change my direction again by coming to JAX," she says. "I'm proud of the fact that I'm not scared of changing — it's the change that makes you learn."

Crest, 2010, Nadia Rosenthal, from the series Hearts on a Plate, marker pen on paper



STORY BY JOYCE PETERSON
PHOTOGRAPHY BY MARIE CHAO
& DANIELLE MEIER

THINKING OUTSIDE THE BLOCKS

Few people think more about mouse behavior than Jackson Laboratory Associate Professor Elissa Chesler, Ph.D. Maybe even fewer people have, like Chesler, decorated their homes with the World War II fighter aircraft and space shuttles they built from tiny interlocking plastic building blocks. So it's not surprising that Chesler thought up a unique assignment for her summer intern: build a conditioning chamber to test mouse behavior, and build it from bright-colored LEGO® bricks.

Chesler studies addiction behaviors. She and her team also develop technological tools for understanding the self-destructive and antisocial behaviors associated with alcohol and drug dependence and other forms of addiction.

"We know that laboratory mice manifest behaviors that resemble attributes of addiction disorders," she says. "And different mouse strains, which have different genetic backgrounds, show different behaviors. These include preference for alcohol and how quickly they acquire a reward behavior."

After years of exploring the biology of addiction, Chesler became convinced that it might hold the key to a new approach to helping young people avoid the dangerous pitfalls of drug and alcohol abuse.

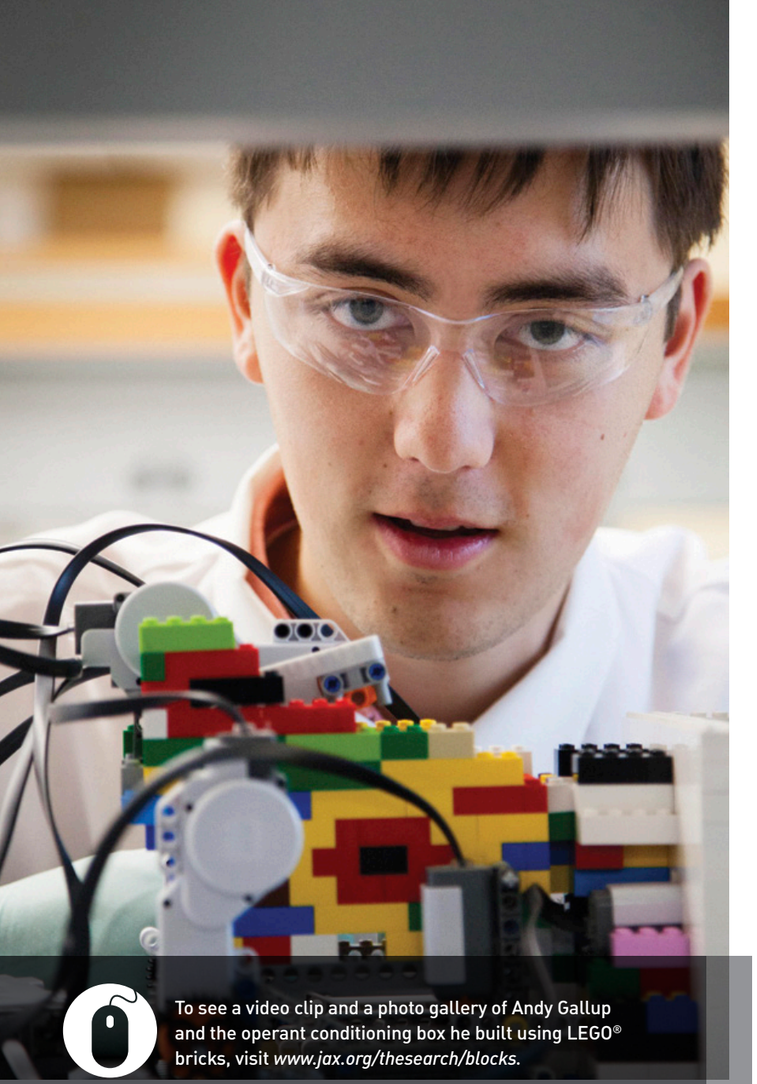
"A lot of education around substance abuse is about preventing that first use of drugs or alcohol," she says. "That mainly involves explaining to students what the drugs' effects are, and encouraging behaviors that help them to decline that first drink or cigarette or drug — the 'Just Say No' approach.

"But the fact of the matter is that many, many adolescents use drugs anyway. And what we want to teach these students is what it means to be addicted. What is the behavior process of reinforcement learning, compulsive behavior, impulse control — what are the behaviors associated with addiction? And how do you recognize early in the process that an addiction is setting in?

"Prevention is important, but the real core of addiction is this reinforcement behavior, and that's something we could be bringing to the classroom."

The classic way to test laboratory mouse behavior is through a conditioning chamber in which an animal receives a reward when it successfully learns a new behavior, such as pressing a lever in response to a light or sound signal. Chesler's lab uses a sophisticated new version of the chamber, which allows the mouse to self-administer a drug dose and transmits

Over 900 LEGO® pieces made this story possible.



To see a video clip and a photo gallery of Andy Gallup and the operant conditioning box he built using LEGO® bricks, visit *www.jax.org/thesearch/blocks*.

Addiction and its related behaviors can develop in response to many kinds of stimuli, including food. Here, JAX Associate Professor Elissa Chesler considers a cheeseburger.

a record of every movement the mouse makes to a computer database for later analysis.

The Jackson Laboratory has an extensive suite of such testing tools in a new neuroscience biometrics suite, thanks to a gift from the Connie B. Rossi Foundation. But the tools are expensive to buy and require a team of experts to operate and maintain, and thus are not feasible for use in a high school or junior high classroom.

Enter the simple plastic LEGO® brick.

Chesler grew up with them, from the basic rectangular blocks ("you had to use a lot of imagination") to the Legoland® Space sets to the LEGO® Logo line, programmable components that could be configured to set up science experiments.

"When I first heard about the LEGO® Robotics system," she recalls, "back when I was setting up my lab and researching a lot of the equipment I would buy, the thought crossed my mind that it might be possible to build some of these complex testing apparati, even the most sophisticated ones, out of LEGO® blocks."

The opportunity to put this bold idea to the test came in the spring of 2013. Andy Gallup, a student at Mount Desert Island Regional High School, about seven miles from The Jackson Laboratory's Bar Harbor, Maine, campus, was applying for a slot in the Laboratory's prestigious Summer Student Program. Gallup is the son of JAX Senior Research Scientist Kyuson Yun and David Gallup, coach of Bar Harbor's highly successful student robotics team.

"I knew Andy was on the robotics team," Chesler says, "and someone had mentioned to me that he was a crack LEGO® programmer and engineer. And so when I met with Andy to discuss what his summer project would be, and asked if he would consider a project involving the LEGO® system, I think his eyes bugged out!"

Gallup says, "I was kind of surprised, and even a little hesitant, because I wasn't sure what I was getting myself into. But at the same time, hey, it's LEGO®, so I was also really excited."

Gallup, already an outstanding science and math student with a year of computer science and a lifetime of LEGO® under his belt, undertook the challenge of designing, testing and documenting an operant conditioning chamber using only off-the-shelf components.

"THE THOUGHT CROSSED MY MIND THAT IT MIGHT BE POSSIBLE TO BUILD THESE COMPLEX TESTING APPARATI OUT OF LEGO® BLOCKS."

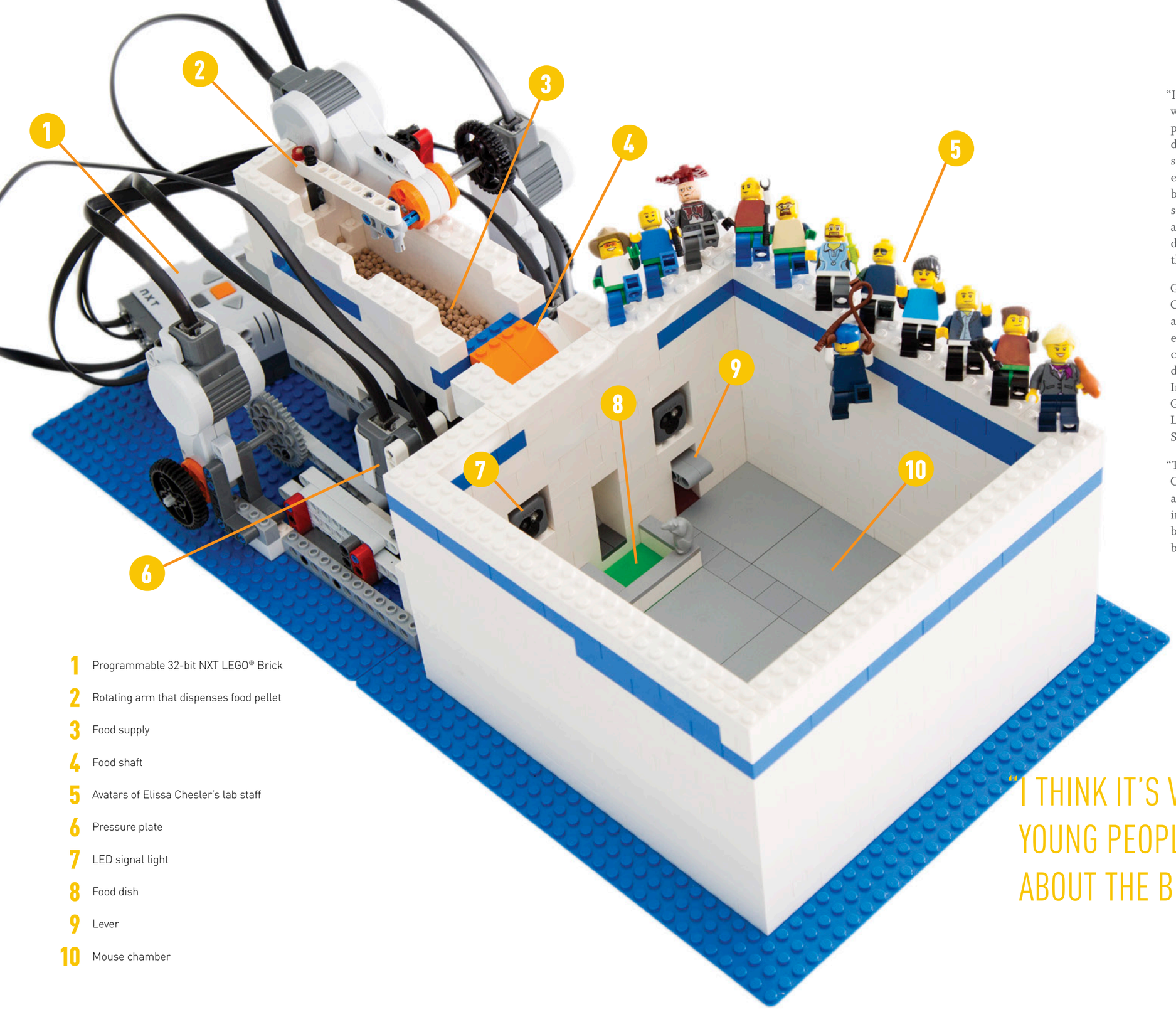
— Elissa Chesler, Ph.D.

"The prospect of inventing something new is very exciting," he says, "but it's also intimidating, because you're not sure what you're doing is right. You could just be wasting your time and resources. But it was really fun working in the Chesler lab. They were very welcoming and they always took time out of their day to help me when I needed it."

By the end of that summer, Gallup had built his conditioning box, complete with levers that activate miniature catapults that fling a single tiny food pellet into the chamber. It looks like a toy any kid would want to play with and an instrument any scientist would want to use.

Gallup continued working on the project throughout his senior year, testing mice and accumulating data, and into the following summer, writing the software documentation and creating an instruction manual with step-by-step photographs showing how to build and operate the unit.

Chesler says Gallup made even more of the educational experience than she had anticipated.



1 Programmable 32-bit NXT LEGO® Brick
2 Rotating arm that dispenses food pellet
3 Food supply
4 Food shaft
5 Avatars of Elissa Chesler's lab staff
6 Pressure plate
7 LED signal light
8 Food dish
9 Lever
10 Mouse chamber

"I was impressed by how he worked, rapidly moving through prototypes and taking many different approaches," she says. "He went from mechanical engineering to computer science, biostatistics and behavioral science, and built that all into a well-documented system, and did the mouse testing to validate that his instrument worked."

Gallup, who is returning to the Chesler lab this summer, took a gap year before college to explore Nepal, India and other countries, an experience he describes as "incredibly valuable." In November, Chesler presented Gallup's poster describing the LEGO® conditioning box at the Society for Neuroscience meeting.

"That poster got a lot of attention," Chesler says. "*Science News* wrote an article, and we had interest from instrument vendors, addiction biologists and people who do brain-awareness outreach."

She hopes to collaborate with educators to bring the project into the classroom. "I know there is increasing pressure on teacher time. But you could envision a short project with high school students collaborating with a university behavioral science lab." The kids build the device, she explains, and bring it to the lab to do the testing with mice, and the university handles all the safety, animal welfare and other laboratory compliance issues.

"The more I work on this the more I realize the importance of what we're doing," Chesler comments. "Behavioral disorders are pervasive, they are phenomenally widespread and there's a lot of social stigma associated with having them. We have an area of research that's becoming increasingly recognized as fundamentally important to human health and the cost of health care.

"I think it's vitally important for young people to learn basic concepts about the biology of behavior. I hope this project can help promote greater understanding of addiction and other behavioral disorders."

"I THINK IT'S VITALLY IMPORTANT FOR YOUNG PEOPLE TO LEARN BASIC CONCEPTS ABOUT THE BIOLOGY OF BEHAVIOR."

— Elissa Chesler, Ph.D.

Navigating change

STORY BY BARRY TEATER
PHOTOGRAPHY BY CLEM MURRAY,
JENNIFER TORRANCE & ROGIER VAN BAKEL

When people ask Leo Holt what he does for a living, he tells them, "I load and unload ships."

If only it were that simple.

His family-owned company, Holt Logistics Corp. of Gloucester City, N.J., receives, stores and distributes mountains of imported commodities and consumer products from every continent. "The map of the world is very much in our DNA," Holt says.

If you live in the eastern half of the United States and have bought a Del Monte banana, a Hyundai car or an Ikea sofa, it's likely that Holt Logistics touched these products before you did, at one of its four massive warehouse complexes along the Pennsylvania and New Jersey waterfronts of the Delaware River.

Holt is named for his grandfather, who started the transport company with one pickup truck in 1926. Along with his brothers, Holt started working for the business as a teenager; today, at 51, he is president of its management and consulting arm. Holt Logistics boasts nearly 2,000 employees; hundreds of forklifts, 1,000-ton cranes, stackers, trucks and other equipment; 1.7 million cubic feet of refrigerated storage; and complex tracking systems — all devoted to the safe and efficient handling of perishable and nonperishable products on a large scale.

Despite shouldering these company responsibilities and raising two toddlers with his wife, MeLinda DeNofa, Holt has managed to carve out time to support The Jackson Laboratory for more than a decade. He has served on the Board of Trustees since 2007 and as chair since 2011.

"The Lab represents my family's deepest level of commitment so far to a philanthropic organization," he says. "It touches so many people in so many ways. In terms of bang for your buck, there's no place like The Jackson Laboratory in the world where you can make a bigger impact by giving support."

Stephen Harmelin, a Philadelphia attorney who has known Holt for 20 years and has represented the family's business in financial transactions, says the Laboratory is fortunate to have engaged Holt's support.

"He talks with passion about the day when so many of the Laboratory's initiatives will find their way into treatments that improve the quality of life and chances for a cure," Harmelin says. "That dream is the source of his commitment to the Laboratory and fuels his hopes for its future growth and prosperity."

Holt is known among the Laboratory's development staff for consistently promoting the Laboratory and its "search for tomorrow's cures" to perfect strangers he meets on airplanes, at industry meetings or on the street — conversations that he finds surprisingly easy to start.

"By far the most common thread that one can pull from the jacket of humanity is what hurts, what worries you, what troubles you, what causes your family grief," he says. "How could you not talk about it?"

Holt was introduced to the Laboratory in 2003 by Edwin Johnson, a friend, mentor and fellow Pennsylvanian who was CEO of The Johnson Companies, an employee benefits consulting firm known for designing and establishing the first 401(k) savings plan. Johnson, along with his wife Cindy, was a loyal Laboratory supporter until his death in 2012.

"Ed provided a stellar example of what any organization's most valued trustees are," says Holt. "He was a true example of a servant leader."

Holt has chaired the Laboratory's Board of Trustees during the most transformative time in the organization's 86-year history. Under his guidance, the Laboratory hired Edison Liu, M.D., as president and CEO, shifted its research focus to genomic medicine, built a $135 million genomics research center in partnership with the state of Connecticut, successfully recruited new faculty, expanded its California facility, forged new research and clinical partnerships, and began educating doctors in the practice of genomic medicine.

Holt modestly deflects any credit for these advances. "My contributions have been so small that history won't be able to find me in the footnotes," he says, "but it's been an absolute delight that when someone needed a boost to be able to give it to them, and when someone needed to get a hug that they got it, and also to give this incredible team the field room that they needed to run. I'm happy to cheerlead."

> "A decade from now people will look back and recognize the monumental importance of answering this call to come up with cures for some of the worst diseases we encounter."

Leo Holt attends the opening of The Jackson Laboratory for Genomic Medicine in Farmington, Conn.

Holt's family provided a $1 million gift to the Laboratory in memory of their patriarch, Tom Holt. The elder Holt died of prostate cancer in 2011 at age 74, after building the family business into what it is today with the help of his brother, who is also named Leo. The gift established the Tom Holt Cancer Research Endowment, which funds research into prostate cancer.

"In a tightly knit Philadelphia-style family, your parents are everything," says Holt, who relished the opportunity to work closely with his father and fondly remembers traveling with him as a teenager on business trips — "not snapping photos, but hustling freight" — to such far-flung destinations as Japan, China, Kuwait and Macau.

"My father was very much a dynamic, roll-up-your-sleeves, do-it-on-your-own kind of person," he says. "At the same time, empowering a team and leading from the front were very much part of his personality. So we all felt that it was very appropriate and impactful to team up with the Lab. We are proud to support its really seminal work in tumor treatment and the concept of personalized medicine, as well as the emergence of PDX." Patient-derived xenografts (PDX) are human cancer tumors implanted into mice and used to pinpoint effective treatments.

"It's not so much about glum memorials as it is about raining enthusiasm," Holt says of his family's gift to The Jackson Laboratory. "There's an implicit and explicit trust and faith in the Lab to deploy the resources that families like ours give, in ways that align with our interests but that move the Lab forward. A specific interest can be the booster rocket that takes you to the next level."

According to Liu, Holt himself has been a dynamic force propelling the Laboratory to new heights. "Leo's enthusiasm for JAX and his commitment to us have been absolutely vital to the Laboratory's success and growth in recent years," says Liu. "Without his leadership, friendship and sage advice, we would not be where we are today. I am personally indebted to him."

As he prepares to step down as board chair this summer, Holt is confident of the Laboratory's growing capacity to lead the development and application of genomic medicine.

"A decade from now people will look back and recognize the monumental importance of answering this call to come up with cures for some of the worst diseases we encounter," he says. "I think just a walk through the halls of any Jackson Lab facility gives you confidence there are people who are dedicated, energetic and excited about what they do every single day. You don't see that in many organizations. And they are working together with a collegiality that is to be envied in any organization. I think all of that spells continued success."

The Holt brothers are pictured (from left): Michael, Thomas Jr. and Leo at the Packer Avenue Marine Terminal on the Delaware River in South Philadelphia.

Staff photo by Clem Murray. Used with permission of Philadelphia Inquirer. Copyright© 2015. All rights reserved.

Leo Holt and his mother, Joan Holt, tour JAX's Bar Harbor campus in 2009.

"Living my dream"

Donna King parlayed a JAX summer experience as a high school student 40 years ago into a rewarding biomedical career. Now, she's repaying the institution that inspired it all.

STORY BY BARRY TEATER
PHOTOGRAPHY BY JIM GRAHAM

As the daughter of high school math and science teachers, Donna King was accustomed to learning everywhere she went while growing up near Philadelphia.

"For me, curiosity was always encouraged," she recalls. "Learning was always fun, and that's how I grew up. Our family vacations — and there were many, far and wide — always had an educational component."

One summer vacation would prove more educational than all the others combined. During a camping trip to Maine's Acadia National Park in the early 1970s, her parents, Ken and Mary, took Donna and her two younger sisters to The Jackson Laboratory in Bar Harbor for a tour one rainy day.

"That tour set me on the path to becoming a scientist, sparking a fascination with biomedical research," she says.

Her father joined JAX's mailing list that day, and when he read about the Laboratory's Summer Student Program, he shared the information with Donna. She applied to the program and was accepted.

As a 16-year-old rising senior in high school, King spent the summer of 1975 at Highseas, the Laboratory's seaside mansion, living and learning with some of the nation's brightest students.

"I was only there for one summer," she says, "but it was a very important summer."

King and another student were paired with a JAX mentor, Edwin Les, the Laboratory's director of animal health. Together, they embarked on a "very labor-intensive project" to test the effects of regular, high-fat and high-fiber diets in mice.

"I didn't change the world with that little project," King says, "but it changed me. It was really my summer at The Jackson Laboratory that absolutely convinced me that I was going into science as a researcher."

She majored in biochemistry at Pennsylvania State University. And when the going got tough and many of her classmates began changing their majors, "I had the memory of my research experience at The Jackson Laboratory to fall back on, and I stuck it out," she says.

King earned a Ph.D. in developmental biology at the University of Cincinnati and then did postdoctoral research in animal reproduction at the U.S. Department of Agriculture outside Washington, D.C., where she helped developed transgenic mice and livestock.

She then led her own mouse-based research labs, first at Rosalind Franklin University of Medicine and Science, and later at Northeast Ohio Medical University, while also mentoring graduate students and teaching biochemistry and molecular pathology to medical students.

> *"It was really my summer at The Jackson Laboratory that absolutely convinced me that I was going into science as a researcher."*
>
> — Donna King, Ph.D.

"I was living my dream from the summer of 1975 of doing medically relevant research," she says.

Her research focused on the effects of growth hormone on bones and connective tissue in mice. She not only used JAX® Mice to study osteogenesis imperfecta, a rare bone deficiency, but also donated to JAX a mouse model for acromegaly, a syndrome caused by excess production of growth hormone.

Along the way she published the first paper demonstrating the use of polymerase chain reaction (PCR) technology for genotyping

Donna King enjoys her 15-year-old Meyer's parrot, Shaler.

pre-implantation embryos, and she later gained a patent for a method to express therapeutic genes in marrow cells for the treatment of bone diseases.

In 2007, rather than continuing as a "good but not great" basic research scientist whose ideas might never be translated into clinical applications, King decided to leave academic research for a job in the pharmaceutical industry. She wanted a more direct role in helping patients.

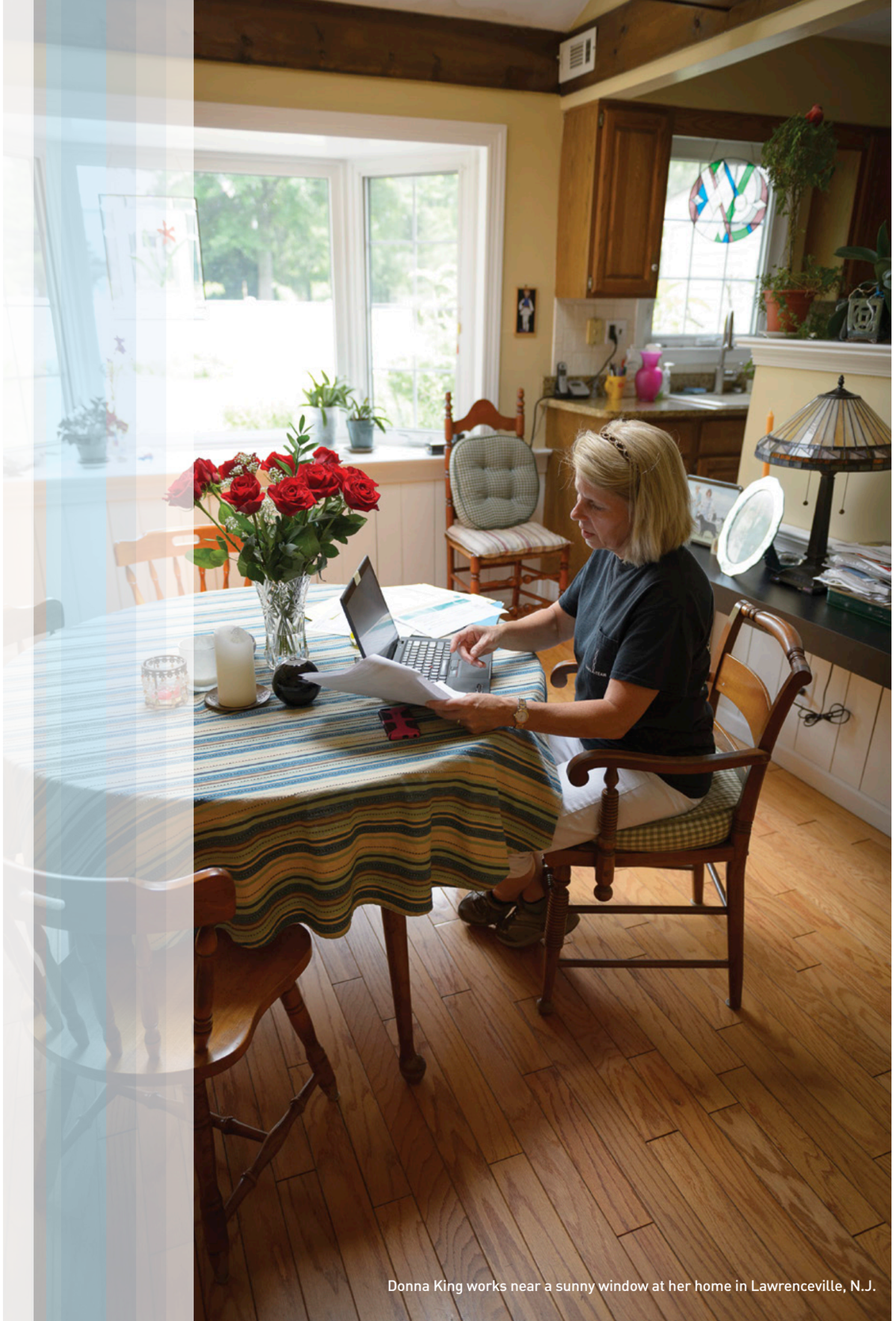
"I realized I could have a bigger impact facilitating other people's ideas," she says.

Today, at 56, King works in New Jersey as a medical science liaison for a multinational drug company. She interacts with scientists, doctors, insurers and thought leaders to gain and share constructive ideas for the safe and effective use of the company's smoking-cessation and endocrine-care drugs.

She is glad for the opportunity to help smokers break their tobacco habit. "There are so many people who have difficulty quitting, or think they'll do it tomorrow," she says. "It's a very important health problem. If we had to have a message about quitting smoking, it would be, 'Don't assume you can do it alone; get help.' There are counseling services, quit lines and pharmaceutical aids that can help break the addiction to nicotine."

Helping patients is not only personally satisfying but also enables King financially to support a nonprofit institution that also helps patients, by translating basic research into precise genomic solutions for disease.

"The Jackson Laboratory is my major philanthropic interest," King says. "I'm no longer at the research bench myself, but with my corporate salary, and maximizing my company's generous match, I'm able to support this medical revolution through my donations. While I regularly support several local charities and one rare disease charity, I like the ripple effect that my support of The Jackson Laboratory has the potential to generate."



Donna King works near a sunny window at her home in Lawrenceville, N.J.

Her ardent support of JAX doesn't surprise Kathleen Sartoris, Pharm.D., King's former corporate colleague and supervisor. "Donna believes in good science, and I think she feels that she can recognize it," Sartoris says. "She's a long-term thinker about where ideas can go, and she likes to match that with people she thinks can make that happen."

King serves on JAX's Annual Fund Leadership Gifts Committee, encouraging others to give $1,000 or more. The Annual Fund aims to raise $2 million in 2015 to support research, the recruitment of world-class faculty and educational programs for emerging scientists — and she would like to aim higher next year.

"I'm in love with The Jackson Laboratory — that's my nearest and dearest educational affiliation," King says. "It's a national treasure."

Edison Liu, M.D., JAX's president and CEO, couldn't agree more.

"Donna's story illustrates the power JAX has to shape the careers of aspiring scientists and our commitment to make a difference in the lives of each of our student colleagues," says Liu. "We are most grateful for Donna's passion in giving back to JAX, as these resources are precisely what we need to fuel innovation in research and in education. She inspires me, so I know she will inspire others."

5 questions

PHOTO BY MARIE CHAO

Emily Edelman

Associate Director, Clinical and Continuing Education Program

In 2013, The Jackson Laboratory signed an agreement with the National Coalition for Health Professional Education in Genetics (NCHPEG) to acquire that organization's extensive educational programs and hire three core employees. With this agreement, The Jackson Laboratory leverages 17 years of expertise, education and resources in genetic and genomic education for diverse clinical audiences. Emily Edelman is the associate director of the program, now known as the Clinical and Continuing Education Program.

Q Why is JAX providing clinician training in genetic risk assessment?

With the opening of The Jackson Laboratory for Genomic Medicine, the Laboratory's mission expanded to include translational research to improve clinical medicine. One of the barriers to realizing this mission is a health professional workforce that is not prepared to use genomic applications in patient care. The Clinical and Continuing Education Program (CCEP) is trying to close that gap by developing education and training programs that help clinicians build skills to improve their genetic risk assessment practice.

Q What is the role of primary care providers in performing genetic risk assessment?

While most genetic testing happens in specialty clinics, primary care providers are the front-line clinicians who identify individuals at increased risk for disease. They also refer patients to genetic experts for further evaluation and incorporate family history and genetic test results into personalized management plans for their patients.

Q What is the most popular clinical course offered by CCEP?

The most popular online course is called "Collecting Family History with Sufficient Detail." In this course, clinicians learn what kind of family history data is useful for hereditary cancer risk assessment. Participants watch a demonstration video of a physician asking targeted questions to investigate a family history of cancer, then apply these skills using interactive practice cases. Family history collection is widely applicable across provider types and practice settings; this course is a great way to advance competency in this area.

Q What's your most recent offering? What's coming next?

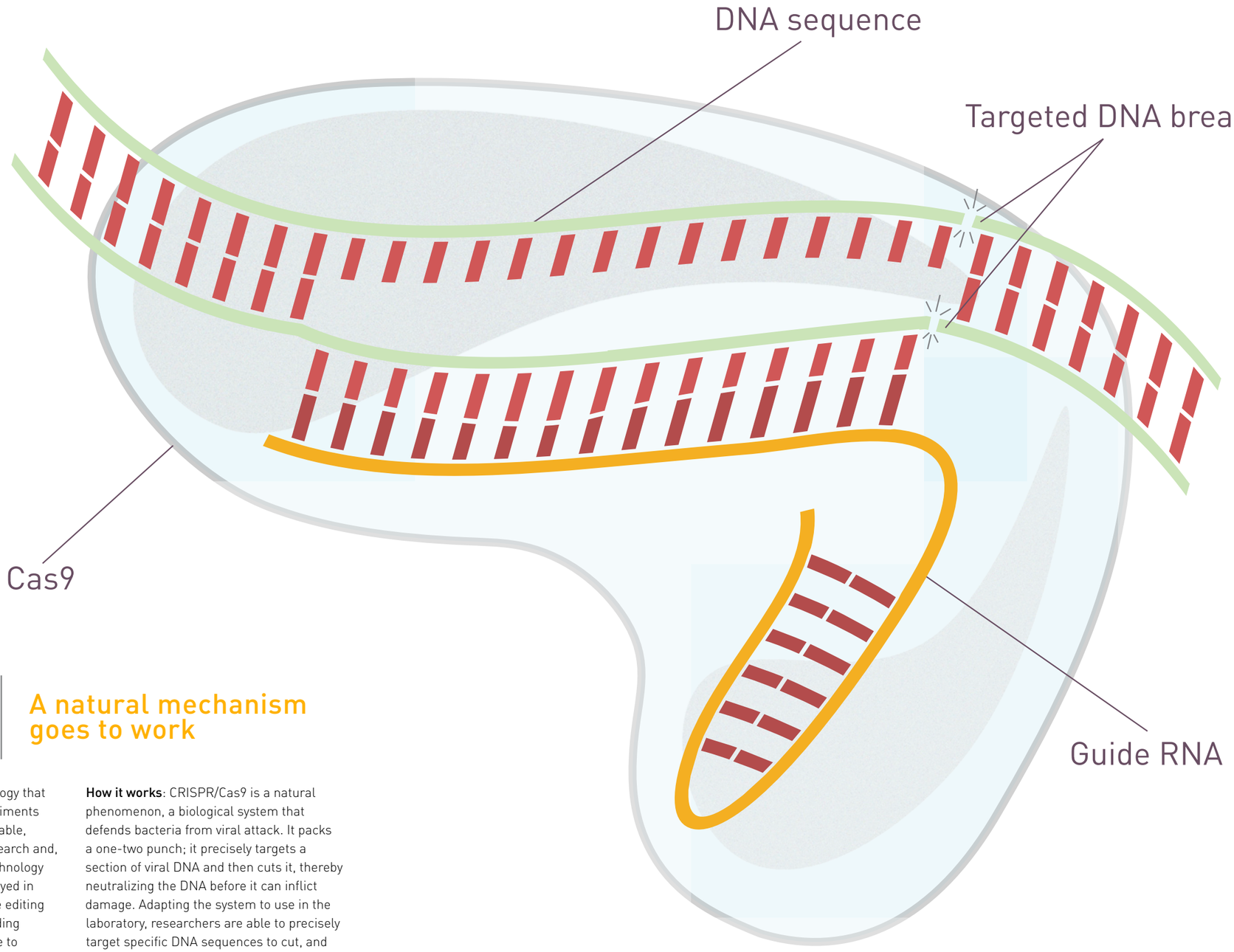
In June, we released an online module that focuses on genetic testing for hereditary breast cancer. It addresses topics such as talking with average risk patients about BRCA1/BRCA2 testing and when to order a multi-gene panel for breast cancer risk.

We are also developing "blended learning" opportunities for clinicians, which involve holding an in-person workshop and then providing online resources to help use the information with their patients. Our first program of this type was in Connecticut last November and we are taking that program on the road to new groups of providers in New England and across the country.

Q What is the future of genetic screening as a routine part of preventive care in the U.S.?

In many areas of medicine, genetic screening is already a routine part of care. Family health history risk assessment has long been recognized as standard of care in preventative medicine, and is a useful tool for identifying risks of common diseases such as diabetes and cardiovascular disease, in addition to hereditary risks. Newborn screening is a nationwide genetic screening program that identifies babies with genetic diseases who could benefit from early medical intervention. Additionally, screening for conditions such as Down syndrome, cystic fibrosis and sickle cell disease is also a routine offering in prenatal care.

As we learn more about the clinical validity and utility of using genetic screening with expanded patient populations, we can expect to see it become a more familiar tool in the hands of primary and preventive care providers.



CRISPR/Cas9

A natural mechanism goes to work

BY MARK WANNER
ILLUSTRATION BY
DANIELLE MEIER &
ZOË REIFSNYDER

CRISPR/Cas9 is revolutionary technology that has made genome engineering experiments possible that were previously unthinkable, opening new avenues for disease research and, potentially, clinical therapies. The technology has recently been adapted and employed in research as a highly effective genome editing technique in model organisms, including mammals. With CRISPR, it is possible to delete genes; modify genes in ways that mirror disease variants in humans; and even "fix" genes by cutting out a mutated sequence and inserting a functional one.

How it works: CRISPR/Cas9 is a natural phenomenon, a biological system that defends bacteria from viral attack. It packs a one-two punch; it precisely targets a section of viral DNA and then cuts it, thereby neutralizing the DNA before it can inflict damage. Adapting the system to use in the laboratory, researchers are able to precisely target specific DNA sequences to cut, and they can delete or correct mutations at the targeted site.

The Jackson Laboratory

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Bar Harbor, ME 04609-1523

Return Service Requested

High school students from across the state participated in the 2015 Maine State Science Fair, organized by The Jackson Laboratory and the Maine Mathematics and Science Alliance. Winners traveled to the Intel International Science and Engineering Fair in Pittsburgh. Pictured here, left to right, are participants Marcy Kittredge, Vishva Nalamalapu, Kaici Aloupis and Emma England, all of Falmouth High School.
Photograph by Aaron Boothroyd