SEARCH

USING BIG DATA TO MODEL ALZHEIMER'S

LIVING WITH ALZHEIMER'S • TACKLING BREAST CANCER • FIGHTING RARE DISEASE

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SEARCH

ON THE COVER

Alzheimer's disease is still poorly understood despite its huge costs and burden. Associate Professor Greg Carter, Ph.D., is working at the intersection of patient and mouse research, using new technology to create accurate disease models and develop effective therapies. Inside cover: an illustration of "fluorescence *in situ* hybridization" (FISH), a technique used to localize DNA sequences on chromosomes.

The Jackson Laboratory
Leading the search for tomorrow's cures

COVER AND INSIDE COVER ILLUSTRATIONS BY KAREN DAVIS

FEATURES

10 **Forget me not: Living with Alzheimer's**

14 **Using big data to model Alzheimer's disease**

18 **New strategies for tackling triple-negative breast cancer**

24 **Families are catalysts for rare disease discovery**

DEPARTMENTS

6 Community

8 Spotlight

20 Connections
JAX network: Poland

22 Voices
On human "knockouts"

26 Beyond the news
What is epigenetics?

from the President

THE POWER TO LEAD DISCOVERY

Every day at The Jackson Laboratory (JAX) brings new discoveries and insights that lead us closer to cures for devastating diseases. Like how the waters of a river come from many tributaries, each discovery is fueled by initiatives from many sources.

The mouse model has long been the engine powering JAX science. In my own lab, a combination of special mouse models and technologies — specifically, the patient-derived xenograft, or PDX — has led to breakthroughs in understanding how to treat triple-negative breast cancer, an especially deadly form of the disease.

New technologies, and particularly the power of computation and big data, enable scientists at JAX to analyze the mechanisms of disease and identify potential targets for therapy. These computational approaches allow us to model disease mathematically. In this issue of *Search*, we take a closer look at the power of big data to create better models of Alzheimer's disease. The work that JAX scientists Greg Carter, Ph.D., Gareth Howell, Ph.D., and their collaborators are doing would not be possible without vast computational power — nor without the brilliance, multidisciplinary expertise and collaborative spirit of these researchers.

Ultimately, it is people who power discovery — and not only the talented scientists working in labs. Others who share our vision for a healthier future champion our work. Nowhere is this more evident than among families of those affected by disease, from caregivers for patients suffering from Alzheimer's to the parents of children with rare diseases. Patients' families are determined to find cures, and as you will read, they are unstoppable catalysts for discovery. Not only do they support us, but more importantly, they give us the motivation — a purpose — for our work.

People from all walks of life advance science through their advocacy and generosity. Philanthropy can create a launching pad for new ideas and fuel creative research.

Gifts to JAX's Innovation Fund helped to jump start the early work of Alzheimer's researchers Carter and Howell, and earlier this year, an extraordinary gift from JAX Trustee Anthony Evnin and his wife Judith Evnin established an endowed chair for Alzheimer's research at JAX, held by Catherine Kaczorowski, Ph.D., whose work is highlighted here. Every gift to JAX makes the light of scientific progress — and hope for cures — burn brighter.

Each of us holds the power to lead discovery. Together, we are unstoppable.

Thank you, as always, for your support of our mission.

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

did you know?

Today, more than 125,000 organs are transplanted around the world. The kidney is the most commonly transplanted organ in the United States, followed by the liver, heart, lungs, pancreas and intestines.

This success would not be possible without the work of mouse geneticist and transplant immunologist Dr. George Snell of The Jackson Laboratory.

Snell won the 1980 Nobel Prize in Physiology or Medicine for providing an in-depth understanding of the immune system's major histocompatibility complex, making organ transplants possible.

Snell's work helped doctors do what was once thought to be unachievable. Learn how you can help forge a revolution in genomic medicine. Visit *www.jax.org/give* today.

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PHOTOGRAPHY BY TIFFANY LAUFER

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VOLUNTEERING TO HELP FAMILIES IMPACTED BY ALZHEIMER'S

For two days this spring, more than 100 JAX employees volunteered to complete projects to help families impacted by Alzheimer's disease in Maine, Connecticut and California. Alzheimer's disease, which affects approximately five million Americans, is one of the focus areas for the nonprofit biomedical research institution.

In Maine, 60 volunteers created care packages to help make Alzheimer's caregivers — who often spend much of their daily lives focused on helping their family members — feel pampered. Volunteers also helped with spring cleanup projects in Bangor and Ellsworth.

In Connecticut and California, 34 volunteers and 36 volunteers, respectively, spearheaded statewide spring cleanups for caregiver families. They raked yards, prepared soil for spring gardens, cleaned windows and did a variety of other outdoor chores, allowing caregivers to take these tasks off their "to do" lists.

"Alzheimer's disease impacts so many more people than just the one diagnosed. Spouses become full-time caregivers; children become medical advocates. This truly is a family disease, and we are honored to have the chance to help our friends and neighbors in this way," says Clare Tully, senior director, HR, Health & Safety at JAX.

In collaboration with the Alzheimer's Association Maine, Connecticut and Northern California chapters, the JAX team is building upon its promising research to reach another population impacted by Alzheimer's disease: caregivers.

JAXTAPOSITION: CURES CAN'T WAIT

JAX recently kicked off its new event series, JAXtaposition, at the Cumberland Club in Portland, Maine.

In a TED-style talk, Executive Vice President Charles E. Hewett, Ph.D., showed the audience how cutting-edge genomic testing is giving physicians access to the most advanced precision cancer care for their patients. JAX scientist Francesca Menghi, Ph.D., also shared how the Laboratory is tackling one of the deadliest forms of breast cancer.

Keep an eye out for a JAXtaposition event near you. Visit *www.jax.org/jaxtaposition* for more information.

SHARING RESEARCH AND HOPE FOR ALZHEIMER'S DISEASE

Alzheimer's disease is a debilitating, degenerative brain disease, causing short-term memory loss and, as it progresses, motor function and long-term memory loss.

In February, The Jackson Laboratory and the Alzheimer's Association, Maine Chapter co-hosted a discussion about the complexities of Alzheimer's disease, to share the latest research and bring together a community of scientists and those whose lives are affected by Alzheimer's.

The discussion was moderated by JAX President and CEO Edison T. Liu, M.D., and included U.S. Senator Susan Collins (R-ME); JAX Alzheimer's researcher Gareth Howell, Ph.D.; Executive Director of the Alzheimer's Association, Maine Chapter Laurie Trenholm; and Alzheimer's advocate Robert O'Keefe.

Learn how you can support Alzheimer's research at JAX. Visit *www.jax.org/endalz* today.

PHOTOGRAPHY BY AARON BOOTHROYD, ANDREW HUIE, TIFFANY LAUFER & BRIAN FITZGERALD

Honey Reddi is a WOMAN OF INNOVATION

BY SARAH LASKOWSKI | PHOTOGRAPHY BY ALEX SYPHERS

Honey Reddi, Ph.D., FACMG, clinical laboratory director at The Jackson Laboratory, was among the winners at the annual Connecticut Technology Council Women of Innovation® Awards presentation in March.

Reddi, a molecular geneticist, won in the Large Business Innovation and Leadership Category and was one of 50 Connecticut women nominated in nine categories. The awards celebrate and foster a growing network of Connecticut women in science, technology, engineering and math.

At JAX, Reddi is focused on developing sophisticated clinical genomics testing for cancers and other diseases.

"I'm honored to receive this award — it's a reflection of the innovative work we do at JAX and our CLIA laboratory where science becomes precision medicine. The opportunity to translate research more rapidly into genomic tests that enable physicians to diagnose and treat their patients more precisely and effectively is making a real difference to the health of people right here in Connecticut, and around the country," Reddi says.

Reddi joined JAX in 2016 from Transgenomic Inc., where she held the role of vice president for clinical operations and clinical lab director. She earned her Ph.D. in biotechnology from the International Centre for Genetic Engineering and Biotechnology and Jamia Hamdard University (New Delhi, India), and completed a fellowship with the Mayo Clinic (Rochester, Minn.) in clinical molecular genetics. Reddi sits on the advisory board for the University of Connecticut's Professional Science Master's program in applied genomics and has an assistant professorship position at UConn Health.

Award winner Honey Reddi speaks to the crowd after winning the Large Business Innovation and Leadership award during the 2018 Women of Innovation Awards hosted by the Connecticut Technology Council.

Honey Reddi, in her laboratory at JAX Genomic Medicine in Connecticut.

Forget me not

Living with early-onset Alzheimer's

BY GRACE NIEWIJK | PHOTOGRAPHY BY TIFFANY LAUFER

Jackie Frisk can no longer recall how many children she has, but she can still play the piano beautifully.

This strange juxtaposition is one of many changes that have come with the progression of her Alzheimer's disease.

She has spent much of her life making music and sharing it with others. She was in many handbell choirs, which she says she still remembers, and ran music workshops all across New England. She taught music in Bangor elementary schools for more than 20 years. But nine years ago, Jackie started experiencing uncharacteristic confusion. A principal at one of the schools expressed concern that she was having trouble finding her classrooms.

Thom Frisk, Jackie's husband, started seeking answers from medical professionals. At first, they thought Thom's worries might be unfounded — that he might have unrealistic expectations of his wife. Eventually, the Frisks got a referral to a neurologist, who in turn referred them to a neuropsychologist. Each referral came with an agonizing six- to 10-month waiting period. As they waited, her mental condition only worsened.

"I'm at school one night, and I get a phone call from Jackie," Thom recalls sadly. "She can't find her way home from the high school. And she had been going there for various music activities for 25 years."

Most people associate Alzheimer's disease with the elderly. Jackie, however, finally received her diagnosis when she was only 51 years old. This form of Alzheimer's, called early-onset or younger-onset, is rare, accounting for just five percent of all Alzheimer's cases. Unfortunately, delayed diagnoses like hers can allow the disease to progress beyond the reach of the most effective early-stage interventions.

> “I don't feel helpless with this disease anymore, and I can communicate that optimism.”
>
> – Dr. Cliff Singer

“The most frustrating part was not getting the help that she needed early on,” says Thom, “and trying to convince the doctor that this was the problem. And the long wait between each referral.”

Shortly after confirming Jackie’s diagnosis, a neurologist referred the family to the office of Dr. Cliff Singer, chief of geriatrics at Bangor’s Acadia Hospital. According to Singer’s recommendations, the Frisks are doing all the right things to slow the remaining progression of her disease, though she is already into the middle stages. The couple far exceeds the suggested 150 minutes of exercise per week, walking at least three miles most days. Thom holds his wife’s hand gently as they walk, pointing out landmarks along the path.

Even though the Frisks don’t expect a treatment for Jackie to appear, they’re contributing to research that will help others with the disease. Singer has been running a clinical Alzheimer’s research program since 2013, and Jackie has already participated in three clinical trials.

“We've basically been doing the trials, realizing that there's not a whole lot of hope at the present time, but for the next generation,” Thom explains. “If this is something that's genetically passed on, hopefully there will be some treatment for our children if they happen to have it.”

In the 30 years since Singer diagnosed his first Alzheimer’s patient, scientific knowledge and his own skill set have grown immensely. He can now offer practical steps for patients, especially those who are in the early stages of the disease.

“I don't feel helpless with this disease anymore, and I can communicate that optimism,” he says.

He hopes to find interventions that can completely halt the disease in the early stages, limiting the effects to mild impairments such as memory loss for recent events, as opposed to more severe symptoms like full-blown dementia, personality changes or an inability to express oneself. Having the ability to prevent these severe symptoms could make an Alzheimer’s diagnosis in the future a lot less scary.

Singer sees translational Alzheimer’s research as a cohesive spectrum, with his clinical work anchoring one end and basic scientists — like those at The Jackson Laboratory — at the other end.

“The best hope for finding real effective therapies, maybe even cures, for Alzheimer's disease lies in the interactions and collaboration between the basic scientist and clinical scientist and clinicians,” he says.

The process starts with basic scientific discoveries; those discoveries and ideas can move forward and develop into clinical protocols, which clinical researchers like Singer can test with patients in rigorous trials.

JAX has multiple groups of scientists working to understand and treat Alzheimer’s, including the laboratory of Associate Professor Catherine Kaczorowski. Her team is focused on a population that has confused doctors and scientists for years: people who should have Alzheimer’s due to specific genetic predispositions but show no signs of the disease.

“Our hypothesis is that they are harboring factors that are protecting their brains,” she says. “That is resilience.” Once Kaczorowski and her team determine what those protective factors are, they’ll be able to work with clinicians like Singer to develop treatments that incorporate this powerful resilience.

Judith and Anthony Evnin, Ph.D., recently gave JAX $1.5 million to establish the Evnin Family Endowed Chair in Alzheimer’s Research, for which Kaczorowski is the chairholder.

“Dr. Kaczorowski is approaching Alzheimer’s from a novel perspective and one that we believe might eventually lead to prevention of or treatments for the disease,” says Dr. Evnin, who is also a member of the Laboratory’s board of trustees. “We are thrilled to support the innovative Alzheimer’s research under way in her laboratory.”

JAX® Mice are crucial to Kaczorowski’s ability to study resilience. Without scanning the whole human population, it’s very difficult to discover enough resilient people to study.

Kaczorowski says her interactions with Alzheimer’s patients have helped give her work meaning and purpose. “They don't come into the clinic because they're doing really well,” she explains. Working with a mouse population that mirrors the genetic diversity of humans will help Kaczorowski identify and study different forms of resilience.

Singer emphasizes the importance of helping everyone involved understand the human impact of translational research.

“This communication between basic scientists and clinical people is critical for the success of any scientific enterprise, particularly with this disease, which can be very difficult to understand in the abstract until you actually sit down face-to-face with the patients and the families who are trying to cope with this condition,” Singer says.

As for the Frisks, they are coping with the condition by spending time together and enjoying life each day. They take trips, visit art museums and see concerts. When Jackie Frisk smiles, her face loses all confusion or blankness.

Thom offers advice to friends and family of other Alzheimer’s patients. “Drop in and see them, you know. It doesn't have to be for very long,” he says. “Jackie loves to get cards in the mail. I have baskets of cards around the house that she'll go through for the first time, multiple times.”

I think the point that is driven home with me on this whole diagnosis is that life is short,” he says. “Right now, our goal is just to be happy.”

Learn more at www.jax.org/endalz.

The Frisks visit with Dr. Cliff Singer (right) at Acadia Hospital in Bangor, Maine.

Associate Professor Greg Carter

Using big data to model Alzheimer's disease

BY MARK WANNER | PHOTOGRAPHY BY MARIE CHAO

Alzheimer's disease is still poorly understood despite its huge costs and burden.

Associate Professor Greg Carter, Ph.D., is working with patient and mouse research to develop accurate disease models and effective therapies.

Think about all the variables associated with a disease that affects older people, such as late-onset Alzheimer's.

There are baseline genetics that help determine who is susceptible and who is less so. There's environment, which usually changes many times over the years. And there are behaviors, such as diet and exercise. Over time, it all adds up to neurodegeneration and disease. Or it doesn't.

Now, think about assembling enough of this information to effectively model all of it experimentally. That's what Carter is trying to do.

Reconstructing disease states

As a computational biologist, Carter can work in any disease area, and he has research interests in cancer and autoimmune disorders such as lupus. But as his program has grown and evolved, it has formed an intersection in which information from human clinical research is integrated with research using mice to push biomedical research forward. And his primary focus is now Alzheimer's.

Carter's approach has grown from his background in particle physics, his original field of study. It applies computational expertise and mathematical precision to see through the messiness of biology and find the important patterns and signals. It was a somewhat unusual perspective in biology not long ago, but it is becoming essential as the field explodes with data that yield insights only grudgingly.

"When you collide two gold nuclei in a particle accelerator, they'll break into 5,000 different particles," he says, alluding to his physics past. "I would try to reconstruct what really happened by tracking back to the moment of the collision. In biology, there are multiple levels of data, such as genetic, proteomic, metabolomic and many, many more, all interacting to produce the state of the organism. So how do they combine to produce that outcome, which might involve a disease like Alzheimer's? And how can we construct a model that not only includes all these data but also predicts what will happen if we add another variable?"

Clinical problems, philanthropic solutions

Alzheimer's disease is a progressive, fatal neurodegenerative disease. Its burden is already massive — the direct costs of caring for those with it and other dementias totaled an estimated $259 billion in 2017 alone — and will rise steeply as the population ages. Efforts to cure, slow or prevent it have usually focused on reducing Alzheimer's physiological hallmarks: buildups of beta-amyloid plaques or tau protein tangles in the brain. Unfortunately, so far nothing has succeeded in affecting disease progression.

Progress is being made, however. Researchers are using advanced techniques to investigate the differences between disease and healthy states in unprecedented detail. The work has yielded tantalizing clues, but no clear diagnostic markers. Yet.

An important part of the change vanguard is the MODEL-AD Center, a collaborative effort between JAX and Indiana University (IU). Carter is a co-principal investigator of the Center with JAX Associate Professor Gareth Howell, Ph.D., plus IU's Bruce Lamb, Ph.D., and Paul Territo, Ph.D. Although the NIH provides the funding for the MODEL-AD Center, the catalyst for it at JAX was support from the President's Innovation Fund. Supported in part by philanthropic gifts to JAX, the Fund made possible Carter and Howell's early collaborative research and, subsequently, the successful launch of the Center.

The scope of the data with which the Center works is massive. That's where Carter comes in.

Information overload

"There are multiple data types we need to integrate," he says. "All the data sets have different formats and structures. But only by combining them can you see the whole picture and begin to figure out their measurable effects on the patient."

The Center's goal is to bring the human data to bear on developing better Alzheimer's research tools, namely mice. Historically, late-onset Alzheimer's has been very difficult to model in mice, in part because of the time frames involved — in humans it usually takes decades to manifest, whereas mice seldom live more than three years — and in part because it wasn't understood well enough in humans to model it accurately. With new research capabilities and human data in hand that is growing all the time, however, the Center is able to generate an entirely different kind of Alzheimer's mouse model.

With the advanced technologies now available in sequencing and genetic engineering (e.g., gene-editing technologies like CRISPR), the mice can now carry the same genetic changes as humans, down to the individual genetic unit. They can have the same biological pathways disrupted as patients, down to the molecular level. They can carry any combination of these disruptions to see if two or more are needed for disease to manifest. And they can mimic behavior patterns such as diet and exercise and can be monitored around the clock for changes in motion and response.

"Alzheimer's disease is exceptionally complex, and it's becoming clear that humans develop different subtypes, so the question is how to define it in the mice," says Carter. "What biological disruptions or combinations of disruptions can we model? What are the effects of targeting these pathways? The mice provide a very powerful system for understanding the fundamental biology and pathology underlying the disease."

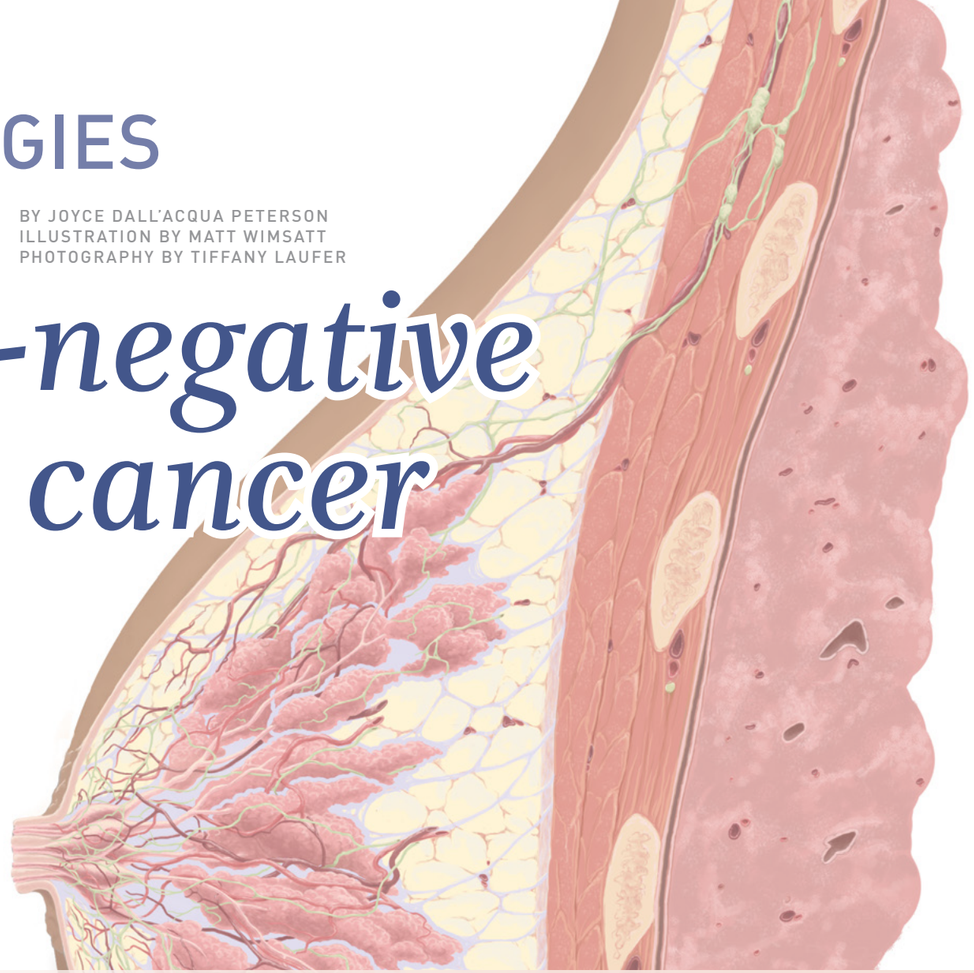
The ultimate goal

In addition to developing the mice, the Center will make its data and at least 40 new mouse models available to the Alzheimer's research community. Research groups around the globe will therefore benefit from its work and Carter's ability to translate what happens in human patients to what will happen in the mice. Of course, the work that the Center and its research colleagues do has but one ultimate goal.

"With the mice, we can target the most important mechanisms to see what is going wrong," says Carter. "Once we find accurate biomarkers, we can test what happens when we intervene very early and stop disease progression before any symptoms occur. The goal is to develop effective therapeutics and bring them back to the patients to prevent or cure the disease."

NEW STRATEGIES FOR TACKLING *triple-negative breast cancer*

BY JOYCE DALL'ACQUA PETERSON
ILLUSTRATION BY MATT WIMSATT
PHOTOGRAPHY BY TIFFANY LAUFER



Research at JAX has uncovered a molecular "fingerprint" that could lead to better outcomes for TNBC patients.

Researchers at The Jackson Laboratory are on a fast track to identifying better treatments for patients diagnosed with a particularly deadly type of breast cancer.

Triple-negative breast cancer (TNBC) does not respond well to hormonal therapy, and patients face a lack of tailored treatment options.

"It's the worst breast cancer to have today, the fastest-growing, the most metastatic," says JAX President and CEO Edison Liu, M.D., whose lab is focused on TNBC.

To this end, the Liu lab is pursuing three main objectives: establishing a cohort of genomically and clinically characterized TNBC samples; determining TNBC-specific drug responses; and understanding the exact mechanisms leading to the emergence and tumor formation of this cancer.

A gift from the Scott R. MacKenzie Foundation is funding the ongoing work of Liu's lab in this area, with the ultimate goal of identifying a potentially curative regimen for the cancer.

Last year Liu announced the discovery of a molecular "fingerprint" that is characteristic of TNBC as well as other deadly cancers of women, including serous ovarian cancer and endometrial carcinomas.

This configuration, which they call a "tandem duplicator phenotype," is the result of mutations that cause faulty DNA replication during cell division.

Liu and his team showed that TNBC and other cancers with the tandem duplicator phenotype respond to a specific chemotherapy, cisplatin. The researchers observed strong responses in both cell culture and in patient-derived tumors implanted in mice, with some of the mice showing no detectable cancer whatsoever after treatment.

None of the tumors without the trait showed any response to cisplatin.

The findings, Liu says, "provide the possibility for characterizing approximately 40 percent of these tumors by a genome-based tandem duplicator score and treating them with the best drug possible, providing more precision and effectiveness."

Francesca Menghi, Ph.D., an associate research scientist in Liu's lab who collaborated in the tandem duplicator phenotype research, wants oncologists to have a much larger array of therapies available for their TNBC patients.

Based on the genomic configurations and defects of specific tumors, and the lines of therapy of interest to the clinician-oncologists with whom she collaborates, Menghi says they have compiled a list of about 20 single agents or combinations — all of which are already approved by the Federal Drug Administration — to test for effectiveness.

"Our preliminary data in the lab would suggest that certain tumors with specific genomic profiles will be more responsive to certain drugs," Menghi says.

Not only will the resulting study reveal which drugs and combinations work best on individual tumors, she says, "but also, when we find treatments that work well, we will go back in and figure out why — what the mechanisms are."

These studies in the Liu lab are possible thanks to the advent of patient-derived xenograft (PDX) trials in special mice that can host (and not reject) human tumors. Fragments of a patient's tumor can be reproduced in these mice, and researchers can use the models to explore the basic biology of any cancer.

Moreover, PDX models are ideal for testing multiple cancer drugs simultaneously, both by themselves and in combination, and for gleaning insight into chemotherapy responses. PDX drug trials offer a clinical-trial roadmap for piloting treatments for patients with similar tumors or molecular profiles. They are also a powerful system for understanding the mechanisms of treatment resistance — one of the most serious obstacles to successful chemotherapy — and for devising strategies for overcoming that resistance.

The PDX approach has gained significant traction in the cancer research community due to its increased precision in measuring drug response.

"Better combination therapies mean we could turn triple-negative breast cancer from a death sentence into a chronic but manageable disease," says JAX Professor Carol Bult, Ph.D., the scientific director of the JAX PDX program.

For a patient facing a TNBC diagnosis, she says, "That would be everything."

JAX Associate Research Scientist Francesca Menghi wants oncologists to have a much larger array of therapies available for their triple-negative breast cancer patients.

JAX network: Poland

BY JOYCE DALL'ACQUA PETERSON | ILLUSTRATION BY REBECCA HOPE WOODS
PHOTOGRAPHY BY TIFFANY LAUFER, MARIE CHAO & JANINE GELINEAU

Poland has about 38 million inhabitants, about a tenth of the U.S. population, but the Eastern European country has a significant and growing presence in the world of science, including at JAX.

JAX Professor Yijun Ruan, Ph.D., collaborates on several research projects with Grzegorz Wilczyński, M.D., Ph.D., of the Laboratory of Molecular and Systemic Neuromorphology at the Nencki Institute of Experimental Biology in Warsaw, Poland. In one project, funded by the international Human Frontier Science Program, researchers explore the role of the 3-D genome in the complex mechanisms involved in memory, learning and epilepsy.

JAX Professor Karolina Palucka, M.D., Ph.D., is an internationally recognized clinical oncologist and cancer immunologist. She conducts research to understand how vaccines work and to define precisely the immune mechanisms that underlie vaccination, with a focus on cancer immunotherapies. Palucka earned her undergraduate and M.D. degrees in Poland but moved to Sweden to obtain her Ph.D. in hematology and immunology at the Karolinska Institutet in Stockholm, followed by a postdoctoral fellowship in Paris. She came to the U.S. to join the Baylor Institute for Immunology Research before joining the JAX faculty in 2014.

Palucka is one of three members of the JAX research faculty who were born in Poland and received their primary and secondary schooling in the rigorous public education system there. "You had to pass a difficult entrance exam to get into your chosen high school or university," says Assistant Professor Ewelina Bolcun-Filas, Ph.D. "And students coming out of the top high schools were often at the level of a four-year college student in the U.S."

Bolcun-Filas left Poland to earn her Ph.D. at the Institute for Human Genetics Georg-August-Universität Göttingen, Germany, followed by postdoctoral work at the MRC Human Genetics Unit in Edinburgh, Scotland, and Cornell University in Ithaca, N.Y. She studies the mechanisms of DNA damage detection and repair in developing germ cells, which could hold clues for ways to protect the fertility of female cancer patients undergoing radiation or chemotherapy treatments that could damage the finite egg reserve in the ovary.

Like Bolcun-Filas, Assistant Professor Olga Anczuków, Ph.D., continued her education outside her native country, earning her undergraduate and graduate degrees in Lyon, France, at the École Normale Supérieure de Lyon and Université Claude Bernard. At JAX, Anczuków investigates how RNA splicing contributes to breast and ovarian cancer progression, metastasis and drug resistance.

Anczuków and Bolcun-Filas pursued their scientific training in the era following the fall of communism when there were few academic research positions for the country's many well-trained scientists.

However, a recent article in the journal *Nature*, "Into the Light," depicts Poland as a nation that is building its research infrastructure and growing in scientific influence, doubling the percentage of gross domestic product spent on science between 2005 and 2015. "Poland is already taking the lion's share of scientific publications produced in Eastern Europe," the article notes.

Polish-born Wojciech Rosikiewicz, Ph.D., a postdoctoral associate in the laboratory of JAX Assistant Professor Sheng Li, Ph.D., notes, "There are currently so many funding opportunities available in Poland that a scientist with a good idea will always find a way to fund his or her research." He also points to grant programs that enable students to continue their education in other European Union countries and to establish labs back in Poland once their education is complete.

These indications of a thriving Polish scientific community should ensure that collaborations and partnerships with JAX continue well into the future.

On human "knockouts"

BY MARK WANNER
ILLUSTRATION BY KAREN DAVIS

What if I told you that almost all of us have a rare genetic condition?

Of course, natural genetic variation occurs in millions of places throughout everyone's genome, creating the small person-by-person differences that make us unique. But it turns out that most, if not all, of us also have the sort of genetic mutations that cause rare genetic diseases.

In essence, people exist on a mutation spectrum. Most mutations go unnoticed, with little to no impact on our day-to-day lives, but some do affect health and manifest in ways that are mild to quite severe.

Why does this happen?

Sometimes the answer is easy. We carry two copies of each gene, so when one copy of a gene is lost or mutated, the other is often sufficient for full function. These are known as recessive disease genes, and people with such mutations are known as carriers. If they have children with another carrier, there's a one in four chance for each child to have no functional copies of the gene, and a genetic disease will likely result. When the mutation is on an X chromosome, the probability jumps in boys.

But sometimes the answer is more complicated. A study analyzing 185 human genome sequences turned up a surprising number of loss-of-function mutations in outwardly healthy people. At that time, the authors estimated that the average healthy person walks around with 100 loss-of-function gene variants, including 20 genes that are completely inactivated. It's a mix of evolution and good fortune that they occur in genes known as "loss-of-function tolerant."

Rare genetic diseases, on the other hand, usually arise from mutations in important genes that don't have robust backup systems, or in other genomic regions that regulate these genes.

Another study looked at a larger number of genomes — more than 10,500 — from a study based in Pakistan. First cousins often marry in Pakistan, leading to a higher incidence of homozygous (affecting both copies of a gene) mutations. In this population, they found 49,138 rare loss-of-function mutations affecting 1,317 genes, seven of which were knocked out in more than one person.

Interestingly, some of them actually appear to provide benefits instead of disease. For example, a family lacking one gene, APOC3, appeared perfectly healthy, but when they consumed fat, such as a fat-laden milkshake, their blood fat levels barely rose at all.

Finally, a third study of human knockouts revealed yet another aspect of these mutations. Sometimes those thought to have adverse health effects don't have the expected impact. In this case, the researchers identified a woman with a loss-of-function mutation in a gene known as PRDM9, thought to be essential for recombination and reproduction. In addition to being healthy, however, the woman had three healthy children, much to the scientists' surprise. The exact mechanism through which she was still able to have children is not readily clear.

Because of these complications, it's essential to systematically investigate the biological mechanisms of knockout mutations.

JAX is one of the leaders of the mouse-based KOMP (Knock-Out Mouse Project) study, which is knocking out thousands of genes one by one and seeing which genes are essential, what happens to the mouse's physical traits without each gene and what mechanisms are involved.

KOMP is now progressing quite rapidly, and it has already begun to provide terrific insight into the nature of such knockouts in humans. It's important work because as the recent research shows, even "simple" single-gene mutations can be far from simple.

families
are catalysts for rare disease discovery

BY JOYCE DALL'ACQUA PETERSON | PHOTOGRAPHY BY AARON BOOTHROYD & JON SHAPLEY

Caroline Fletcher and family

Help us find a cure for Caroline and others suffering from rare diseases by visiting *www.jax.org/give* today.

It's just not fair. One measly gene out of more than 20,000 goes wrong, and a newborn baby faces a future with a disease that could hamper its mobility, make breathing a struggle or even end its life. And it doesn't help that a given genetic disease may be so rare there are only a handful of cases in the world.

Because of the small population afflicted by any one illness, funding to investigate causes and treatments tends to be limited, slowing the discovery of potential therapies. Yet with over 7,000 recognized rare diseases, an estimated 350 million people worldwide are affected at any given time.

Fortunately, teams of scientists and clinicians, armed with technologies that use laboratory mice to fast-track drug discovery and testing, are coming to the rescue.

The Jackson Laboratory may be the only "hit" patient families get when they search online for research programs in a specific rare genetic condition. That's because the chances are great that the culprit mutation is in a JAX mouse model.

"No institution in the world can match the genetic diversity of the JAX mouse population, or the expertise in mouse model development, for diseases including rare and orphan diseases," says JAX Associate Professor Greg Cox, Ph.D. Cox studies neuromuscular diseases with a focus on spinal muscular atrophy (SMA) and its very rare variant, spinal muscular atrophy with respiratory distress (SMARD).

"Mice that develop the same disease symptoms as patients, and that carry mutations in the same genes, enable researchers to test many different therapeutic strategies in a relatively short time," Cox explains.

But before the mouse model development, before the Federal Drug Administration approval, before the clinical trials, new therapies for rare diseases often start with the people who have the strongest motivation to find a cure: patients' families.

Eric Sims, a University of Notre Dame associate professor, and his wife, Jill, are the parents of two children born with SMARD. One of Sims' students organized a fundraiser to raise money for SMARD research after identifying the Cox lab online. Sims' parents, Grant and Patty, then connected with Cox to learn more about his SMARD research program, and subsequently established the Sims Family Fund for SMARD Research at JAX.

Caroline Fletcher was diagnosed at age 6 with a hereditary degenerative nerve disorder designated CMT2D, a rare variant of Charcot-Marie-Tooth (CMT) disease. Fletcher's grandparents contacted JAX, and now Professor Rob Burgess, Ph.D., director of the JAX Center for Precision Genetics, is pursuing a promising drug target, following successful experiments in a JAX-developed mouse model of CMT2D.

Just as the Fletchers' determination to find hope for Caroline sparked this collaboration, their philanthropic support has fueled its growth. The Fletchers' gifts to support Burgess' research (as well as the work of other scientists studying CMT) illustrate the power of philanthropy to accelerate scientific research and, in particular, to serve as a catalyst for innovative research projects that might otherwise not get off the ground.

Cat Lutz, Ph.D., is the director of the Rare and Orphan Disease Center at JAX. Her team is developing a system of resources that patients and their families can plug into to help lessen the burden of families pushing for a cure for rare diseases.

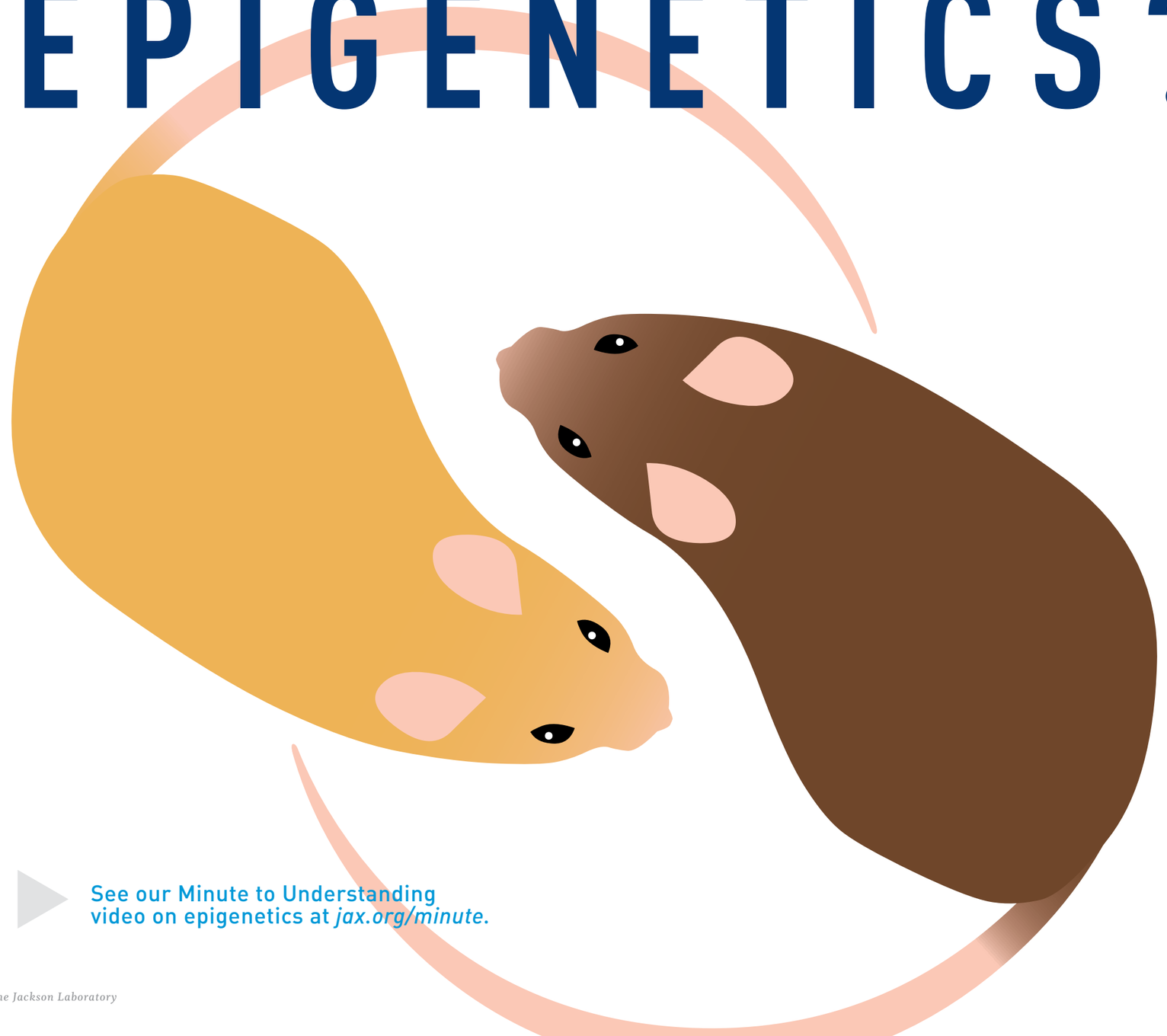
"A colleague once asked me why I was working so hard on a rare disease like SMA to benefit so few patients," Lutz recounts. "The fact is, all the things we learn from these rare and orphan diseases will be applicable to others with bigger patient populations.

"And when you see kids with SMA actually walking and playing, who without treatment probably would not even be alive, that's why we work so hard," she says.

Senior Research Scientist Cat Lutz and assistants

What is EPIGENETICS?

BY DAYANA KRAWCHUK, PH.D. | ILLUSTRATION BY ZOË REIFSNYDER



See our Minute to Understanding video on epigenetics at *jax.org/minute*.

Genetics is your genes. And each gene has a unique sequence that makes a protein that does something in your body.

A genetic mutation is a hardcopy change in one or more parts of that sequence.

This could just make you, *you*. Or it could contribute to a genetic disease.

An epigenetic change also changes a gene's DNA — but not at the sequence level.

Instead, special marks are added or removed to change how a protein works in the body. How these marks appear is a hot research topic. Some causes may be diet, stressors or environmental pollutants.

What's important about epigenetics is that it offers a different approach to treating disease. Whereas a hardcopy genetic mutation is difficult to fix, finding ways to remove a bad epigenetic mark, or add a good one, could be an easier solution.

How can two mice with the same DNA sequence have different coat colors? Epigenetics! In this particular yellow mouse strain, when a mother is given a diet enriched in folic acid (a good source for epigenetic "methylation" of DNA), a gene controlling coat color is methylated resulting in more brown pups being born than yellow. This is an example of how diet can cause epigenetic changes to affect an individual — without physically changing their DNA sequence.

The Jackson Laboratory

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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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