SEARCH

INTRODUCING THE CHARLES E. HEWETT CENTER

CONNECTING DOCTORS WITH CANCER DATA

TUNING IN TO THE INNER EAR • FAST-TRACKING ALZHEIMER'S RESEARCH

FALL 2018 • VOL. 11 • NO. 3 • **THE JACKSON LABORATORY**

SEARCH

ON THE COVER

Executive Vice President Charles E. Hewett gives a thumbs up during the ribbon-cutting ceremony for the new, state-of-the-art vivarium in Ellsworth, Maine, that bears his name. The center is enabling wider access to JAX® Mice that advance genomic medicine. Inside cover: Assistant Professor Basile Tarchini (right) works with mice to understand how tiny hair cells in the inner ear allow us to hear sound, like the jazz music he performs with JAX President Edison Liu.

The Jackson Laboratory
Leading the search for tomorrow's cures

COVER PHOTOGRAPHY BY AARON BOOTHROYD
INSIDE COVER BY KAYLA CHAGNON

FEATURES

DEPARTMENTS

from the President

OF MICE AND MAINE

A few months ago, we celebrated the opening of JAX's newest campus: the Charles E. Hewett Center in Ellsworth, Maine. This state-of-the-art facility will expand our capacity for producing the mouse models for which JAX is famous and which are so vital to the work of the global scientific community. At the same time, the Hewett Center also underscores our commitment to Maine, generating hundreds of good jobs and a significant positive ripple effect in the local and state economy.

The new center is named in honor of Chuck Hewett, who retired as JAX's chief operating officer earlier this year — a role he'd filled for a decade and a half. No one has done more than Chuck to put the Laboratory on a solid footing and growth trajectory, to build our reputation for quality and expand the vision for our science, and to raise the bar of what is possible for JAX.

This issue of *Search* magazine highlights some of the extraordinary research JAX® Mice make possible for scientists on our Bar Harbor campus: faculty like Basile Tarchini, whose work with mouse models explores the fundamental physiology of the ear and the regenerative processes that may hold clues to restoring hearing loss.

Centered in Bar Harbor, our extraordinary team of Alzheimer's researchers — which includes two of our endowed faculty chair holders, Catherine Kaczorowski and Gareth Howell — works with mouse models to identify genetic risks for dementia as well as genes associated with resilience, and to explore the interplay of genetic, behavioral and environmental factors such as diet and exercise in Alzheimer's disease and related dementias. In addition, the JAX-led MODEL-AD Center is developing new, more effective mouse models of Alzheimer's disease that scientists everywhere can use to conduct research and test new therapies.

Maine will always be at the heart of JAX, but our vision and reach are global — and not only because of our mice. Developed at our genomic medicine campus in Farmington, Conn., the JAX-Clinical Knowledgebase uses advanced computational tools and machine learning to help clinicians around the world select and deploy the best personalized treatment approaches for cancer patients.

Across all our locations, JAX is harnessing the power of mouse models and innovative technologies to create a healthier future — and the support of friends like you makes all of this possible. Thank you.

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

did you know?

Medicine today is built on a foundation of mice as models of human disease. This is because mice are biologically similar to us, get most of the same diseases with the same genetic susceptibilities and can be genetically manipulated to mimic most human diseases and conditions.

JAX pioneered the use of mice in disease research, and its mice and research programs have contributed to important medical breakthroughs ever since.

Working with mice in research is a privilege, and we are proud that JAX is considered the international gold standard for animal care and use, and meets or exceeds all regulatory guidelines and the voluntary standards of the Association for the Assessment and Accreditation of Laboratory Animal Care International.

Learn more at www.*jax.org/medicalprogress*.

connect with us

PHOTOGRAPHY BY TIFFANY LAUFER

GET THE LATEST NEWS AND INSIGHTS
Visit *www.jax.org/news*.

JAXTAPOSITION EVENT SERIES: CURES CAN'T WAIT

The Jackson Laboratory for Genomic Medicine in Farmington, Conn., was the host of our recent JAXtaposition event about JAX research on chronic fatigue syndrome (ME/CFS). ME/CFS is highly debilitating, poorly understood and difficult to diagnose.

In a TED-style talk, Derya Unutmaz, M.D., JAX immunologist and renowned expert on HIV, shared how he and his team are working toward a world in which patients can have their blood samples screened for potential immunological biomarkers of ME/CFS. This smart diagnostic tool can lead to personalized treatments for the disease.

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

SHARING THE POWER OF GENOMICS

JAX geneticist Steve Munger, Ph.D., highlighted the bright future of genomics during a lecture in Bar Harbor as part of the 2018 Primary Sources Speaker Series — a collaboration between JAX and the Jesup Memorial Library to inform and engage the community about genetics and science policy.

In his talk, Munger took the audience behind the scenes to explore how genetic data is analyzed and to better understand popular buzzwords like "big data" and "the cloud." He introduced the human genome and described experimental and analytical methods used to construct a genome using current "short read" sequencing technologies. Munger also demonstrated the power of having tens of thousands of individual genome sequences for discovering DNA variants associated with common diseases. He said sequencing technologies are rapidly improving and miniaturizing, and DNA itself may one day be used to store data more efficiently than current hard disks and flash drives.

MAKING BAR HARBOR DEMENTIA-FRIENDLY

On June 21, a team of 36 employees from The Jackson Laboratory donned purple shirts and visited Bar Harbor's downtown restaurants, stores and businesses to kick off an initiative to help make the island dementia-friendly. The project was part of the Alzheimer's Association's The Longest Day® event to help raise awareness for Alzheimer's care and support, and advance research.

JAX's "ADventures" team is composed of scientists and staff from Alzheimer's disease-focused labs including the Kaczorowski Lab, the Howell Lab, the O'Connell Lab, the Carter Lab and others. They took a break from their daily research to bring awareness to dementia while hiking, biking, swimming, kayaking and doing mental activities that are beneficial for the brain.

The day marked the start of the JAX ADventures team's efforts to help educate restaurant and store owners and staff about Alzheimer's with the longer-term goal to make Bar Harbor a dementia-friendly community. By helping educate the town, the team hopes to ensure people with dementia can live independently for as long as possible, and are able to engage in a variety of activities in their hometown in a supportive environment.

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

PHOTOGRAPHY BY CHARLES CAMARDA, STEVE MUNGER & TIFFANY LAUFER

Introducing the Charles E. Hewett Center

PHOTOGRAPHY BY AARON BOOTHROYD, TIFFANY LAUFER & JENNIFER TORRANCE

In August, The Jackson Laboratory celebrated the ribbon cutting of its state-of-the-art vivarium in Ellsworth, Maine, which will enable wider access to vital JAX mouse resources for the worldwide biomedical research community. The Charles E. Hewett Center represents the culmination of nine decades of unmatched experience and leadership in breeding and caring for laboratory mice.

The center is named in honor of The Jackson Laboratory's transformational Executive Vice President and former Chief Operating Officer Charles E. Hewett, Ph.D. Since joining JAX in 2004, Dr. Hewett's accomplishments include launching numerous research products and services; completing new research laboratories in Bar Harbor; expanding and relocating the Laboratory's California operations; conceiving and leading the development of The Jackson Laboratory for Genomic Medicine in Farmington, Conn.; and establishing the vision for the new mouse production facility in Ellsworth.

Dr. Hewett has been a champion for JAX employees and has worked tirelessly for their fitness and health, outstanding benefits and competitive salaries and wages.

"We are proud to be headquartered in Maine, where we are one of our state's largest private employers, bringing in more than $800 million in economic activity each year and providing more than 1,500 jobs," Hewett says. "We look forward to partnering with the Ellsworth community to advance vital biomedical research around the world."

The Charles E. Hewett, Ph.D., Leadership Excellence Endowment was established to continue and build upon Hewett's commitment to developing talent, cultivating leaders and ensuring that every employee at JAX is on a path to success. You can join us in continuing Hewett's legacy and empowering the next generation of JAX leaders by making a gift at *www.jax.org/chuck-hewett-fund*.

How do cancer cells achieve IMMORTALITY?

BY CARRIE COWAN, PH.D. | PHOTOGRAPHY BY JARED SKOLNICK | ILLUSTRATION BY ZOË REIFSNYDER

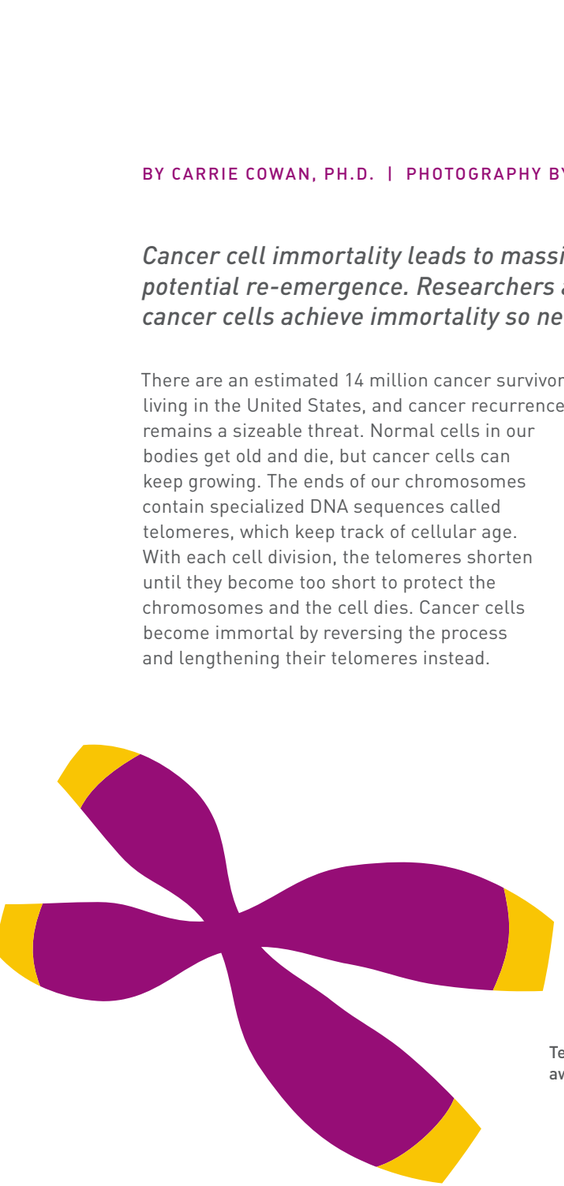
Cancer cell immortality leads to massive tumors, metastatic spread and potential re-emergence. Researchers are working to determine how cancer cells achieve immortality so new therapies can be developed.

There are an estimated 14 million cancer survivors living in the United States, and cancer recurrence remains a sizeable threat. Normal cells in our bodies get old and die, but cancer cells can keep growing. The ends of our chromosomes contain specialized DNA sequences called telomeres, which keep track of cellular age. With each cell division, the telomeres shorten until they become too short to protect the chromosomes and the cell dies. Cancer cells become immortal by reversing the process and lengthening their telomeres instead.

JAX Postdoctoral Associate Floris Barthel, Ph.D., who works with Professor Roel Verhaak, Ph.D., recently received funding from the National Cancer Institute to determine how cancer cells co-opt the cellular processes that control telomere length. Telomerase is the protein that maintains the telomeres on chromosomes. This mechanism is usually turned off, but cancer cells re-activate it.

"Therapies that target telomerase directly were found to be toxic to non-cancer cells, and understanding precisely how telomerase is turned on in cancer may allow us to circumvent that," says Barthel. "Ultimately, I hope that I can contribute to developing new cancer therapies that reduce or eliminate telomerase activity without affecting non-cancer cells."

Learn more about the Verhaak Lab and JAX cancer research at ***www.jax.org/cancer-research***.



Telomeres on a normal chromosome wear away as cells divide and the body ages.

Telomeres in cancerous cells continually replenish themselves, leading to cell immortality — and tumors.

Postdoctoral Associate Floris Barthel

CONNECTING DOCTORS WITH CANCER DATA

BY MICHELLE NG

Just as a size 9 shoe fits only a certain number of feet, the standard "one-size-fits-all" cancer treatment approach doesn't work for all patients. In fact, sometimes it actually does more harm than good.

A profound change in cancer care is under way, however. More precise and targeted therapeutic strategies based on new computational tools and machine learning are beginning to emerge, offering the potential to greatly improve care for cancer patients. And The Jackson Laboratory, through this innovative new data resource, is leading the way.

This resource is connecting doctors with scientists, giving clinical teams around the world access to detailed information that can result in more targeted treatments for patients and less trial and error. In other words, the JAX Clinical Knowledgebase (JAX-CKB) is helping oncologists find the most effective treatments for each of their patients, and it's helping them find the information fast.

An incomplete picture

Oncologists today have access to thousands of cancer drugs, but have little guidance as to which one, or which combination, is the best fit for a given cancer patient.

While some oncologists still examine tumors on slides to determine a patient's type and stage of cancer, recent advances like new tumor DNA sequencing technologies provide insight into the specific genomic mutations driving a patient's cancer. This growing wealth of knowledge speaks to exciting advances in the field, while also adding new levels of complexity to the search for the right treatments.

For example, an oncologist might have to parse through thousands of papers to distinguish between clinically significant genomic mutations in a tumor and those that do not contribute to cancer onset and growth. Then there are thousands more papers that may help determine what targeted therapies might treat

The JAX Clinical Knowledgebase is helping oncologists find the most effective treatments for each of their patients, and it's helping them find the information fast. Think of it as the Google of cancer data.

IMAGES BY VITANOVSKI/ISTOCK/THINKSTOCK

a patient's driver mutations. This already arduous process is complicated by the fact that different papers often refer to the same genes by different names.

This plethora of disorganized information can make it difficult to come away with the full picture, and limits oncologists' ability to prescribe the most personalized, targeted therapies that have the highest likelihood of success. It also prevents tumor boards — specialized teams that design treatment plans for patients — from reviewing more than a few patients each week, despite the needs of many more.

Capturing knowledge

JAX is streamlining this process with the JAX-CKB, a new translational medicine platform that connects clinicians with researchers in real time. The platform allows doctors and researchers to spend their time and energy more productively in order to help patients more quickly and effectively.

Susan Mockus, Ph.D., associate director, clinical genomic market development, JAX® Mice and Clinical & Research Services, is leading the establishment of the new platform, which functions like a Google or Bing search engine. Using the JAX-CKB, doctors are able to find the most relevant and recent information from researchers about a specific gene or therapy.

With search options including genes and treatments, the JAX-CKB condenses the vast body of scientific knowledge about specific genes, treatment options and clinical trials into succinct summaries. These summaries are currently available for 900 genes that have downstream cancer effects and include links to original research.

In essence, the JAX-CKB provides decision support for oncologists answering two questions:

- What genomic mutation is causing this cancer?
- What targeted therapies can treat this tumor, based on its mutational profile?

"The goal is to build an informatics platform at JAX that integrates these genetic pieces, works with other groups and can be offered to the scientific and clinical translational world," says Mockus.

Machine learning and artificial intelligence

The JAX-CKB has received more than 100,000 visits since its launch in 2016. While its current functionalities are making a difference for doctors and patients, the original curation process was astonishingly complex. The database is updated manually, which means that curators have to identify a seemingly endless number of new papers in order to keep the database up to date.

To address this, Mockus and her team have developed a triaging process to help ensure curators are not missing important and relevant scientific papers. This process includes a public-private partnership with Microsoft's Project Hanover.

Project Hanover creates artificial intelligence to advance precision medicine and is led by Hoifung Poon, Ph.D., director of the Precision Healthcare machine reading component. Mockus and Poon are working together to create

PHOTOGRAPHY BY RYAN MCVAY/DIGITALVISION/THINKSTOCK

technologies that support doctors and researchers, with immense potential benefits for patients.

Poon believes there is a more effective way to identify the most relevant scientific papers, FDA trials and clinical trials, and curate that information for clinicians. Poon's team is introducing "machine reading," which uses intelligent algorithms that can quickly scan through all publications, identify the relevant papers and highlight their most applicable sections.

This technology would empower curators by reducing their cognitive load and offer a quicker, more efficient method of updating the JAX-CKB. More importantly, it helps ensure that no important information — which ultimately could be the difference between life and death for patients — falls between the cracks.

"The goal is to leave no relevant fact behind," says Poon.

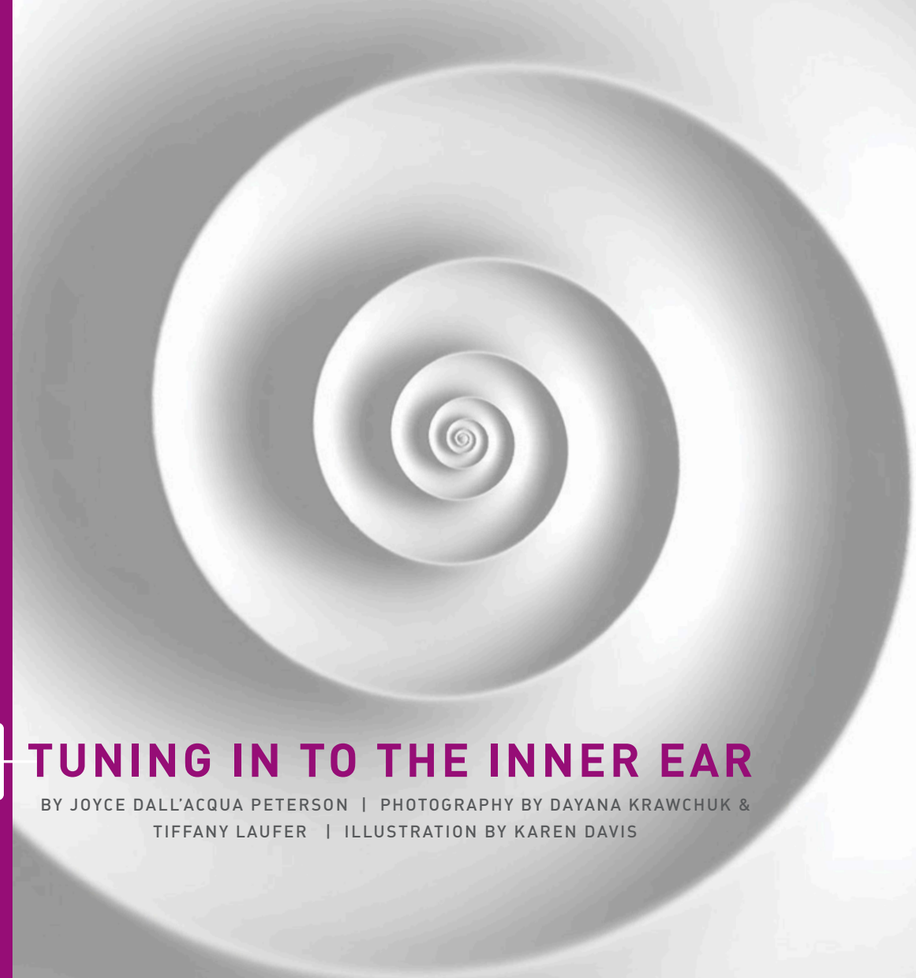
While Poon's machine reading system is currently in its pilot stage, he and Mockus look forward to integrating it into the JAX-CKB curation process.

Mockus' next steps for the JAX-CKB include rolling out more connections between germline mutations (hereditary genetic alterations in a germ cell such as egg or sperm) and somatic mutations (non-hereditary genetic alterations in a non-germ cell). This additional information could shed more light on what is causing a patient's cancer and result in a more targeted therapy for the patient.

She also looks forward to scaling the JAX-CKB by leveraging Microsoft's machine-learning so that the JAX team can expand its scope in other areas of cancer research, such as the oncobiome (the community of microorganisms that may contribute to cancer).

"By working together and sharing our findings, we may soon have an effective treatment for even the rarest and hardest-to-treat cancers," Mockus says.

Technological innovations like the JAX-CKB platform are made possible with help from our generous supporters. To join us in our search for genomic solutions for patients, visit *www.jax.org/give*.



TUNING IN TO THE INNER EAR

BY JOYCE DALL'ACQUA PETERSON | PHOTOGRAPHY BY DAYANA KRAWCHUK & TIFFANY LAUFER | ILLUSTRATION BY KAREN DAVIS

Did you hear that sound?

If so, you can thank your stereocilia.

These tiny fibers form bundles sitting atop sensory hair cells deep inside your inner ear, and give them their name. Stereocilia are as fragile and scarce as they are vital to your ability to hear.

Basile Tarchini, Ph.D., studies stereocilia, which convert sound into hearing through complex signaling operations with the brain. The Jackson Laboratory assistant professor's work has revealed unexpected aspects of how stereocilia develop.

Normal inner-ear stereocilia grow in a "staircase" formation, with a short-to-tall graduation of hairs in the bundle, arranged like kids in a class photo. "This staircase-like architecture of the hair bundle is essential for hearing and considered instrumental for direction-sensitivity to sound stimuli," Tarchini says.

Working with mice, Tarchini discovered a signaling pathway that regulates the distinctive short-to-tall organization of stereocilia during development. If this signaling pathway is disrupted, he showed, stereocilia are shorter and of more even height, and the animal is deaf. Understanding the basic mechanisms underlying hair cell development holds the promise to unlock regeneration potential in adults and restore hearing following injury.

IMAGE BY 3D_KOT/ISTOCK/THINKSTOCK

How do we hear?

The inner ear is something we take for granted. It allows us to perceive where our body is in space, to walk upright and to sense gravity.

Here, in broad strokes, is how you hear. Sound waves enter the external ear and swirl down the ear canal until they reach the eardrum and set it vibrating. Tiny middle-ear bones connected to the eardrum amplify the sound waves and deliver them to the auditory portion of the inner ear, or cochlea.

Shaped like a snail shell and filled with fluid, the cochlea is divided into an upper and lower part by an elastic partition called the basilar membrane. In this liquid environment, the sound waves become fluid waves that travel along this membrane. Inner-ear hair cells on the basilar membrane literally ride these waves.

The stereocilia at the top of the hair cells sway and bend in the flow.

"There are tiny links between stereocilia," Tarchini says, "linking the tallest to the next tallest and so on. Tension on those links cause pore-like channels at the tips of the stereocilia to open up, and ions rush into the cells, creating an electrical signal.

"This whole structure acts as a motion sensor."

The auditory nerve carries the electrical signal to the brain, which recognizes and interprets the sound. Amazingly, the hair cells are arranged along the basilar membrane like the keys of a piano, high to low: Those near the entrance of the cochlea are responsible for detecting high-pitched sounds like birdsong and those close to the center of the "snail" sense lower-pitched sounds like far-off thunder.

A blueprint for hearing

In a healthy human cochlea, just about 16,000 hair cells handle this elaborate choreography of sound signaling, and only 4,000 of them are true sound receptors. By comparison, the retina of the human eye has about 127 million photoreceptors — rods and cones — to process visual signals.

Not only are hair cells rare, but they're also vulnerable to environmental damage. Sustained loud noise from working in construction or the military, or attending a 1980s tribute band concert, can kill hair cells, and some antibiotics and cancer drugs also cause hair cell destruction.

Humans develop their hair cells very early in life — starting about 10 weeks post-conception. And humans, like mice and other mammals, are born with all the hair cells they will ever get, so once they're lost they're gone for good. On the other hand, birds, fish and other non-mammals have the capacity to recover lost hearing through various regenerative processes.

The staircase organization of the stereocilia bundle also means that each hair cell shows directionality, like the magnetized needle of a compass. In addition, neighboring hair cells orient their bundles in concert, in the same way a collection of compasses would all point to the north magnetic pole. Working with colleagues at The Rockefeller University, Tarchini showed that a single protein, Daple, is required to shape the architecture of the stereocilia bundle in individual hair cells and establish their concerted orientation in the surrounding organ. In mice lacking Daple, hair bundles are misshapen and misoriented in a pattern indicating both single-cell and organ-wide defects.

Tarchini joined the JAX faculty in 2015. A year later he secured his first federal research funding, a five-year, $1.9 million grant from the National Institute on Deafness and Other Communication Disorders.

Tarchini was born in Switzerland, and French is his first language. He is an accomplished jazz musician who once considered taking the path of the professional performer instead of the scientist. He recently performed on bass at a concert at the Bar Harbor town library with JAX President and CEO Edison Liu on piano.

A musician-scientist who studies hearing? Actually, Tarchini says with a laugh, "the older I get, the more I like quiet. I can't stand background music, for example!"

And in fact, his research interests, while staying in the inner ear, are moving to include the vestibular system, which is located right next to the cochlea.

"The inner ear is basically two systems in one, auditory and vestibular," he says. "It's something we take for granted, the ability to perceive where our body is in space, to walk upright, to sense gravity. But it's incredibly important that it functions correctly: otherwise, you couldn't get out of bed in the morning."

To contribute to exciting research like Tarchini's and help us improve human health, visit *www.jax.org/give.*

FAST-TRACKING

Alzheimer's disease research

BY JOYCE DALL'ACQUA PETERSON | PHOTOGRAPHY BY TIFFANY LAUFER | ILLUSTRATION BY DANIELLE MEIER

New mouse models and research approaches could change the future of AD diagnosis, treatment and prevention

"Alzheimer's research is a frontier where we can dramatically improve human life — both the lives of people who have the disease and their loved ones."

Technologist, business leader and philanthropist Bill Gates, whose father has been diagnosed with Alzheimer's disease (AD), recently wrote these words in his blog. Gates describes the frustrating, uncertain process of diagnosing AD once symptoms appear. And, he notes, "most people don't want to find out if they have the disease earlier when there's no way to treat it."

AD is the sixth leading cause of death in the United States. Currently no treatments are available that prevent or slow the disease. Genetics — including a specific genetic variant, APOEε4 — is thought to account for up to 70 percent of risk for developing AD, but a bewildering array of environmental risk factors is also suspected or implicated.

The race is on to develop accurate tools to diagnose AD before symptoms occur, and effective treatments to prevent the devastating destruction of the disease.

Given AD's complexity, the disease demands not one but a whole range of approaches. Thanks in part to the advocacy leadership of the Alzheimer's Association, the National Institute on Aging (NIA) now has substantially more resources available for innovative grantmaking. Several grants have been awarded to The Jackson Laboratory, which has launched a multi-track attack on AD with new mouse models, new experimental designs, new research programs and new kinds of collaboration with the worldwide AD research community.

"The recent quadrupling of U.S. federal funding for Alzheimer's and dementia research has created multiple new opportunities for innovative projects and partnerships to discover better methods of diagnosis, treatment and prevention," says Maria C. Carrillo, Ph.D., Alzheimer's Association chief science officer.

For example, she says, "the Association is working with JAX in the MODEL-AD consortium, which is an ambitious project to create better animal models of Alzheimer's to accelerate the development of drug therapies. With the aging of the global population and the increasing numbers of people living with and at risk for Alzheimer's and other dementias, the time is now — and the need is huge — for major advances."

Better AD mouse models

Targeted research in AD demands targeted mouse models. For decades, researchers have had access to mouse models carrying genetic mutations associated with a rare, inherited, early-onset version of the disease known as familial AD (fAD). Models of fAD on standard inbred mouse strains, such as

Research Scientist Michael Sasner (left) and colleague Associate Professor Greg Carter

the famous "Black 6" (C57BL/6J) strain, have been useful for identifying some mechanisms of AD risk, onset and progression.

But varying the genetic background of AD models greatly increases their utility in representing human AD, as demonstrated by recent research by JAX Associate Professor Catherine Kaczorowski, Ph.D., Evnin Family Endowed Chair in Alzheimer's Research; Sarah Neuner, a Ph.D. student in the Kaczorowski Lab; Associate Professor and Diana Davis Spencer Chair for Glaucoma Research Gareth Howell, Ph.D.; and Howell Lab Postdoctoral Associate Kristen Onos, Ph.D.

On the other hand, the vast majority of Alzheimer's patients have late-onset AD, or LOAD, which to date has not been successfully modeled in mice. JAX and its collaborators in the MODEL-AD consortium, an NIA-funded project to develop and distribute precise mouse models of LOAD, have already released more than a dozen new mouse models carrying mutations found in LOAD patients, with another dozen or so available by the end of 2018.

The early collaboration among JAX researchers in the MODEL-AD consortium was catalyzed by the President's Innovation Fund. This fund — fueled in part by gifts to the Laboratory — provides crucial seed money to fund novel and creative research ideas proposed by JAX scientists. With these resources, scientists are empowered to pursue their most exciting ideas, investigating innovative concepts that have the capacity to have a dramatic impact on our understanding of health and medicine at a small scale. These activities help launch large-scale projects, like the MODEL-AD.

"Creating these new models would not have been possible even five years ago," says JAX Research Scientist Michael Sasner, Ph.D. "Patient genetic testing, now commonplace, has generated massive databases to mine for gene variants associated with late-onset AD. CRISPR/Cas9 technology enables us to quickly create new mouse models with precise genetic mutations — even multiple mutations in a single mouse. And we now have a wide range of sequencing and imaging technologies to evaluate how well a given mouse can model LOAD."

Howell, who studies age-related neurodegeneration associated with AD, dementia and glaucoma, is a co-principal investigator of the MODEL-AD Center along with JAX Associate Professor and computational biologist Greg Carter, Ph.D., and Indiana University scientists Bruce Lamb, Ph.D., and Paul Territo, Ph.D. U.S. Senator Susan M. Collins invited Howell to address the Senate Special Committee on Aging on June 19 on "Changing the Trajectory of Alzheimer's Disease."

"We are joining a new era in research," Howell stated in his testimony, "where individuals are no longer working behind closed doors to seek the best solution. We are combining our strengths and working together through the concept of open science to accelerate the discovery of cures for Alzheimer's disease."

Howell and other researchers involved in MODEL-AD are participating in an animal models "think tank" session convened by the Alzheimer's Association in November in Washington, D.C.

Zeroing in on APOEε4

Some direct-to-consumer genetic tests assess your risk of developing certain diseases. In these tests the risk for LOAD is represented by whether or not you inherited one or two copies of a specific genetic variant known as APOEε4 (the ε4 mutation of apolipoprotein E), the greatest known genetic risk factor for LOAD. Inheriting APOEε4 is associated with a 15 to 20 percent increase in the likelihood of developing LOAD, yet the majority of people who inherit APOEε4 do not get the disease.

In the past, researchers studied the effects of APOEε4 on a few inbred mouse strains. That standardized approach is helpful in working out the molecular mechanisms of the mutation itself, but doesn't demonstrate how APOEε4 operates in different individuals with widely varying genetic backgrounds, as in the human population.

Instead, Sasner and JAX Investigators Howell and Carter are placing the APOEε4 mutation in mouse populations with a high level of genetic diversity, an NIA-funded effort to sort out the complex genetic interactions involved in developing AD. The results will provide the most detailed picture to date of how other genes interact with the APOEε4 mutation to affect how likely an individual is to develop the disease, and how mild or severe the symptoms may be.

In search of resilience against AD

In fact, certain genes may provide protection or resilience against AD, notes Kaczorowski, who earlier this year was designated the Evnin Family Chair in Alzheimer's Research, the result of a $1.5 million gift to the Laboratory.

"Several genetic mutations have been traced to the rare, early-onset type of Alzheimer's disease (fAD) that runs in families and appears in patients as young as 30 years old," she says. "Some people inherit these mutations and even

develop the brain changes associated with the disease, yet they nevertheless manage to maintain their cognitive capabilities."

Though fAD is much less common than LOAD, there are likely common mechanisms between the two versions of Alzheimer's. With NIA funding, Kaczorowski studies mice carrying fAD mutations to identify other genetic factors that may overcome the cognitive decline that usually comes with Alzheimer's disease. Understanding the genetic factors behind this so-called cognitive resilience could provide targets for treatment and prevention of both fAD and LOAD.

Genes + diet + sex

Another project in the Kaczoroswki Lab is focused on understanding the role of diet in AD progression. Postdoctoral Associate Amy Dunn, Ph.D., says, "Feeding a high-fat diet to a genetically varied mouse population carrying fAD mutations, we observed a decline in working memory in most of the mouse strains. But some of the strains maintained their cognitive function on the high-fat diet, and we're looking into the specific genetic factors contributing to this resiliency."

In 2016 the Howell Lab published a study in *Nature Scientific Reports* showing the results of feeding the lab-formulated Western diet to mice from a normal inbred strain as well as a mouse model of Alzheimer's. All the mice showed several danger signs of disease susceptibility. This included loss of neurons, increased plaques (protein clumps) and more inflammation in their brains, all symptoms of Alzheimer's disease in human patients.

Colby College student Yoona Chun and Leah Graham

The Howell Lab is exploring how exercise — the other side of the lifestyle equation — could counter these negative effects and protect the brains of aging mice. "If we knew what genes respond to running, and how those genes function," says Leah Graham, Ph.D., a former postdoc in the lab. "we could potentially develop new therapies for people who are unable to exercise."

Many Alzheimer's disease patients experience weight loss as early as 17 years before the onset of their memory loss and cognitive decline. Is this merely a coincidence, or could a poorly functioning hypothalamus (the brain region that controls appetite and weight control among many other processes) have a causative role in Alzheimer's disease? JAX Assistant Professor Kristen O'Connell, Ph.D., and Kaczorowski are exploring the role of hypothalamic dysfunction in AD.

"We propose that hypothalamic dysfunction during the preclinical stage of Alzheimer's disease is an early causative step in a cascade of events culminating in dementia," O'Connell says.

O'Connell and Kaczorowski have also observed that sex plays a critical role in determining the impact of high-fat diet and body weight on the onset and severity of memory deficits, with females exhibiting more rapid decline, paralleling what has been reported in humans.

In fact, brain changes associated with menopause may contribute to the cognitive decline. Sasner is now working with Roberta Brinton, Ph.D., of the University of Arizona, to examine the combined roles of APOEε4, sex and age.

Neuner observes that "JAX is really taking a two-pronged *reciprocal* approach to fighting AD. MODEL-AD is starting with new human genomic data in order to nominate gene candidates and using the mouse to understand them (human to mouse). And the resilience, gene-diet and APOEε4 projects are using the mouse to understand AD and nominate gene candidates (mouse to human)."

Taken together, the MODEL-AD Center and JAX studies could provide significant new insight into how genetic and modifiable environmental factors (such as diet) influence risk of Alzheimer's disease, and could identify new biomarkers and therapeutic strategies targeting the very earliest preclinical stages of the disease, to delay or even prevent Alzheimer's disease.

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

The Healthy Genome

BY MARK WANNER | ILLUSTRATION BY KAREN DAVIS

By now, anyone with an interest in health care has seen at least a few articles about personalized medicine. While its advent in the clinic has been somewhat slower than one might have hoped, as is the case with so many things in medicine, it's generally accepted now that personalized medicine will change medicine as we know it in the relatively near future.

There are already notable successes in specific areas — the diagnosis of early childhood rare diseases, for example, often accompanied by important treatment insight, and oncology and pharmacogenomics (the right drug at the right dose at the right time) are also seeing important progress.

In addition, large precision medicine initiatives such as the U.K.'s 100k Genome Project and the U.S.'s new All of Us program are making news on a regular basis.

While sequencing for rare-disease diagnosis and cancer therapy guidance is now widely accepted, many have advocated against large-scale sequencing of healthy individuals — at least not yet. This is understandable in the current context, given the costs involved and lack of predictive insight. Many who have their genomes sequenced do so out of curiosity and/or for a great writing topic, not for medical insight.

But there's one area of the United States where large numbers of people of all kinds are being sequenced: rural Pennsylvania. That's where the Geisinger Health System is based. Geisinger is somewhat unique, in that it serves as both insurer and provider for its customers. Therefore, the more it can help its patient population stay healthy and lower the cost of care, the better it will do on the insurance side. This provides Geisinger with opportunities to experiment with what it provides in its clinics. And experiment it has, particularly with genetic sequencing, through a program it calls MyCode.

MyCode offers exome sequencing (all coding regions of the genome, about 1.5 percent of the total sequence) to all its customers, and interestingly, a large number of people have signed on. The numbers keep going up, and there are now approaching 200,000 people enrolled. That's a lot of exomes. And with clinical data accumulated over years for the patients, and those of family for most as well, the program provides a real-world look at what might be possible with numbers this large and various forms of data this integrated, including risks and benefits.

The preliminary results are highly intriguing. Analysis of the first 50,000-plus exomes sequenced indicate that roughly 3.5 percent of the participants may harbor a disease-causing genetic variant about which they were unaware, even though the list of such variants is deliberately small, due to the uncertainty associated with most variants. There have been several specific examples of cancer caught early, familial hypercholesterolemia identified and managed, and so on. Even if nothing manifests, monitoring protocols are put in place. And the return of results is managed with medical care and genetic counseling support to help each patient understand the ramifications of the data.

The Geisinger model is limited, but it provides an interesting indication of what precision medicine may become if carefully coordinated and implemented on a large scale. The take-home lessons may change as more data are compiled, of course, but as of now, even with all the imprecision still surrounding precision medicine, the message is that there may be more benefits to widespread sequencing of healthy people than originally anticipated.

SUPPORTING LOCAL HIGH SCHOOL STUDENTS

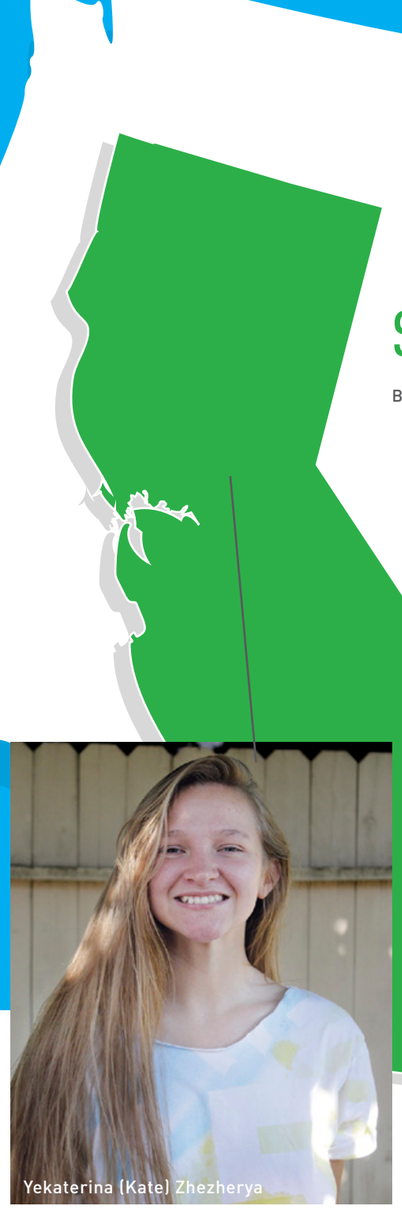
BY SARAH BAKER | ILLUSTRATION BY KAREN DAVIS

Many promising students are unable to pursue higher education on account of the financial burden a college education presents.

The Jackson Laboratory, through the JAX College Scholarship Program, annually awards a $10,000 scholarship to three students from under-served backgrounds who will pursue a college degree and aspire to a career in biomedicine.

This program is open to graduating high school seniors who live in Connecticut, Maine or Sacramento County, Calif. One student from each location will be awarded this scholarship.

The 2018 Connecticut JAX Scholarship award was presented to Guercie Guerrier of Norwich. Guerrier graduated from Norwich Free Academy and is now studying neuroscience at Temple University.



Yekaterina (Kate) Zhezherya

The 2018 Maine JAX College Scholarship awardee is Natalia Fuentes. Fuentes graduated from Waterville Senior High School. She is an accomplished musician and runner who is currently studying at Harvard University. She is focused on a career in biomedicine and plans to pursue a Ph.D. with a focus on infectious diseases that disproportionately impact people in impoverished communities.

The 2018 California JAX College Scholarship awardee is Yekaterina (Kate) Zhezherya. Zhezherya graduated from Rosemont High School in Sacramento. She is studying at the University of California Merced.

Guercie Guerrier

Natalia Fuentes

Will you support the next generation of scientific leaders? Visit *www.jax.org/give* to contribute to educational programming at JAX and ensure that more bright young scientists like Kate, Guercie and Natalia can pursue their dreams. Learn more about the JAX scholarship program at *www.jax.org/scholarship*.

UNDERSTANDING OUR INHERITANCE

A Q&A with Carl Zimmer

BY GRACE NIEWIJK | PHOTOGRAPHY COURTESY OF CARL ZIMMER | ILLUSTRATION BY ZOË REIFSNYDER

When we think about evolution, we often limit ourselves to oversimplifications of concepts like natural selection. We picture fish crawling determinedly out of the ocean and monkeys descending from trees to walk upright. In reality, evolution is a long, meandering process full of randomness. Furthermore, it turns out that evolutionary changes in genes aren't the only important things we can inherit from our ancestors.

To find out more about the complexities of this non-financial inheritance, The Jackson Laboratory spoke with author and *New York Times* columnist Carl Zimmer, who frequently writes about genetics and evolution. His new book, "She Has Her Mother's Laugh," tackles the vast concept of heredity — everything that living organisms pass on to future generations, and the means by which they do so.

How would you define evolution in just one sentence?

Evolution is the change in DNA that happens over many generations thanks to natural selection and other kinds of mechanisms.

What do you think is the biggest or most common misconception about evolution?

The one that I most often come across is the idea that a species will evolve something because it needs it or because there is some goal in mind. People will say "fish evolved legs in order to come on land," as if they woke up one morning and thought, "How am I going to get on land? I know! I'll make some legs." Evolution just happens as a generation-by-generation process. It's based on mutations which are basically random and don't have any connection to anything that they might be used for in the future.

What's the link between heredity and evolution?

Heredity is an essential ingredient to evolution. In order for a mutation to matter in the long term, it has to get passed down to future generations in a reliable way. There are some forms of heredity that may not have anything to do with evolution, but you can't have evolution without heredity.

What can we learn from different kinds of research on heredity and genetics — for example, from studies in mice or fruit flies versus human studies?

All of the really fundamental insights into human heredity got their start when scientists looked at other species — like mice or fruit flies — for the simple reason that we don't run experiments on people. Now we're at the point where scientists are studying people and their genes on an amazingly high level. You'll see a study of a million people or more, and there's incredible power in those studies. They uncover the genes with links to diseases or important traits, but we're still never going to stop needing those other species to help us learn new things. If you find a gene that seems to be important, you're going to need to engineer that gene into a fly or some other organism and then really look carefully to see how it's working as opposed to other variations of that gene. We're going to always need mice and flies.

What do you think are the roles of non-genetic factors in heredity or evolution?

In my book, I show that the microbiome is unquestionably an important part of heredity for a lot of species, although whether it's important for human heredity is up for debate. I think for humans, culture is incredibly important. We inherit genes which, among other things, make it possible for us to develop big powerful brains, but we also inherit all sorts of knowledge, beliefs, languages and customs. We can then build on the culture that came before us. We really depend on that for survival. In the book, I argue that everything throughout human history depends on this form of heredity, from the rise of agriculture to the industrial revolution.

However, I don't think that these other channels of heredity can produce their own really sophisticated sort of evolution; genes clearly do that. But different channels of heredity can work together or work against each other, so to understand the direction of evolution we might need to understand the other channels better.

What evolutionary discovery that happened during your lifetime do you think is especially significant?

The ability to get ancient DNA out of fossils has been a revolution that I didn't really see coming. Now we can get genomes of Neanderthals and other vanished peoples out of bones that are 70 or 80 thousand years old. I think that's pretty incredible. They're telling us things that we couldn't ever predict.

What's one thing you hope researchers come to understand in your lifetime?

I think it may be possible to get a pretty good handle on how life began. There have been so many exciting strides forward in different fields — from chemistry to physics to geology — and it all tends to be coming together in very interesting ways. There's a lot of work still left to do, but I'm feeling more optimistic. I used to think that it was something we could never know, but now I think we might.

The Jackson Laboratory

600 Main Street
Bar Harbor, ME 04609-1523

Forwarding service requested

A PUBLICATION OF **THE JACKSON LABORATORY**

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

Locations
Bar Harbor, Maine
Ellsworth, Maine
Farmington, Connecticut
Sacramento, California

Editor
Joseph Blanchette

Design & art direction
Karen Davis
Danielle Meier
Zoë Reifsnyder
Rebecca Hope Woods

Copy editors
Carol Lamb
Joyce Dall'Acqua Peterson
Rebecca Hope Woods

This publication was produced by JAX Creative.
Printed November 2018