SEARCH

YOUNG BLOOD COULD SOLVE AN AGE-OLD PROBLEM

YOUNG BLOOD • BREAKING THE BOTTLENECK

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SEARCH

ON THE COVER

JAX Assistant Professor Jennifer Trowbridge wants to know why older people are more likely to get acute myeloid leukemia. She is investigating aging stem cells (shown above) that should be building blood cells but are developing cancer cells instead.

PHOTOGRAPHY BY TIFFANY LAUFER | ILLUSTRATION BY MATT WIMSATT

The Jackson Laboratory
Leading the search for tomorrow's cures

FEATURES

DEPARTMENTS

from the President

NEW FRONTIERS NEAR AND FAR.

At JAX, we are pioneers. We are opening up new frontiers of research, discovery and collaboration — from our own campuses all the way to Australia and from measuring the characteristics of mouse populations to understanding the inner workings of the human brain and our DNA in diseases like Alzheimer's.

Already this year, we've marked important milestones including the completion of the steel structure for the new Center for Biometric Analysis (CBA) on our Bar Harbor campus. This state-of-the-art facility will enable our scientists to track and measure virtually every aspect of mouse anatomy, physiology and behavior — enabling us to make more effective use of mouse models than ever before.

Our expertise in mouse models is advancing research to deepen our understanding of diseases including leukemia and other cancers, Alzheimer's and Parkinson's — just to name a few highlighted in this issue — and accelerating discovery in the search for cures for these and myriad other diseases. Both the CBA and resources like the Collaborative Cross are making this possible.

Collaboration has always been fundamental to our science, and here, too, we are entering new territory. Like a growing number of JAX faculty with joint appointments, pediatric cancer specialist Ching Lau, M.D., Ph.D., conducts research at JAX while teaching future physicians and treating patients at UConn School of Medicine and Connecticut Children's Medical Center. He joins cardiologist Travis Hinson, M.D., as another clinician-scientist joint faculty member who expands our translational reach. Joint appointments enable JAX and our partner institutions to attract world-renowned experts who enhance the level of clinical care and education in medical subspecialties.

Our collaborations extend far beyond our campuses. For many decades The Jackson Laboratory has been the key resource for scientists around the globe who use our mice and scientific services in their research. Now, we are exploring opportunities for global collaborations that will further accelerate the progress of precision medicine.

I look forward to keeping you updated as we make progress on all these frontiers and discover new ones yet to be explored.

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

did you know?

Each day, about 4,600 Americans receive a cancer diagnosis — and 48 of them are children. When Clarence Cook Little founded The Jackson Laboratory (JAX) in 1929 as one of the world's first cancer genetics research institutions, few scientists suspected cancer's genetic nature. Little's early research, and his work establishing the first inbred strains of mice, would be fundamental to countless insights in cancer biology, at JAX and at research institutions around the world. JAX was one of the first U.S. research institutions to receive the National Cancer Institute's Cancer Center designation in 1983. Today the JAX Cancer Center includes more than 50 scientists who bring multidisciplinary expertise to research aimed at understanding and targeting the genetic complexity of cancer.

connect with us

PHOTOGRAPHY BY GRETA RYBUS

BREAKING GROUND

New JAX facility in Ellsworth, Maine

The Jackson Laboratory recently celebrated the groundbreaking for its new, state-of-the-art vivarium, a 134,900-square-foot facility to maintain research mouse models, in Ellsworth, Maine.

U.S. Senators Susan Collins and Angus King were joined by Congressman Bruce Poliquin, Maine Governor's Senior Policy Advisor John Butera and Ellsworth Mayor Robert Crosthwaite to launch the new facility, which is the first step in the Laboratory's long-range plan to gradually migrate mouse production from Bar Harbor to Ellsworth, freeing up space in Bar Harbor to expand research and education programs.

Charles Hewett, Ph.D., JAX executive vice president and COO, noted that the institution's Maine-based mouse production operation is on an international scale.

"Last year, The Jackson Laboratory provided mice and services to 23,527 research labs in 52 countries," Hewett said. "Most important, JAX® Mice have enabled breakthroughs in cancer, Alzheimer's disease, Parkinson's, amyotrophic lateral sclerosis, cardiology, diabetes, glaucoma and many more diseases and conditions."

To date, the Ellsworth project has been supported by a $1.74 million Pilot Grant from the Maine Technology Institute and a $1.82 million Structural Improvement Grant from the U.S. Economic Development Administration. The Laboratory will contribute $71.44 million to Phase 1 of the project, which is scheduled for completion at the end of 2017 and will employ 230 people.

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BIG TURNOUT

Community discussion about opioid addiction

More than 150 people gathered at The Jackson Laboratory for a community discussion about opioid addiction. "The Behavior and Biology of Addiction" program focused on treating addiction as a chronic illness with genetic, environmental and social aspects, and shared the latest efforts toward prevention and treatment.

Panelists included Daniel Johnson, Ph.D., LCPS, CCS, executive director, the Acadia Family Center; Elissa Chesler, Ph.D., associate professor, JAX; Sheriff Scott Kane, Hancock County Sheriff's Office; and Jonathan Fellers, M.D., Maine Medical Center. Charles Hewett, Ph.D., JAX executive vice president and COO moderated the discussion.

The need to develop robust treatment and counseling programs, especially in conjunction with law enforcement, was a theme throughout the night. "This is a disease. It can be treated, but not easily or casually or without commitment," Hewett said. "We need to combine treatment with love, compassion and acceptance, and create connections with each other."

RUNNING FOR DYLAN

SMARD research at The Jackson Laboratory

For the fourth straight year, runners ran the Philadelphia Marathon to raise funds in honor of Dylan Kunkel. Kunkel is battling spinal muscular atrophy with respiratory distress (SMARD), a life-threatening disorder caused by the degeneration of the motor neurons responsible for gross muscle movement. It severely affects respiratory function.

Dylan was born in March 2012 and was hospitalized at just two months old. Unable to breathe on his own, Dylan spent two months in a pediatric intensive care unit (PICU) attached to breathing machines while doctors searched for answers. One year later, a genetic test confirmed a diagnosis of SMARD. Over the years, Dylan's Runners have raised over $63,000 for SMARD research at JAX — one of the few laboratories worldwide that study the genetic disease. Learn more at ***www.jax.org/dylan***.

Ching Lau, M.D., Ph.D.

BY SARAH LASKOWSKI | PHOTOGRAPHY BY TIFFANY LAUFER

Connecticut Children's Medical Center, The Jackson Laboratory and the UConn School of Medicine have made their first joint appointment: the distinguished pediatric oncologist and cancer researcher Ching Lau, M.D., Ph.D.

Lau serves as the medical director of hematology-oncology at Connecticut Children's Medical Center, as professor at JAX where he specializes in pediatric brain and bone tumor research, and as head of the division of pediatric hematology-oncology in the department of pediatrics at the UConn School of Medicine. He is focused on accelerating the pace and success rate of clinical trials in pediatric cancer patients.

"Although the incidence of cancer among children is much lower than that in adults," he says, "it can be just as deadly. And because of the smaller number of patients available, clinical trials of new treatments for pediatric cancers are conducted at a much slower pace. Typically patients are enrolled in clinical trials after their cancers progress or are found not to be responsive to standard therapy."

As a result, he says, pediatric cancer patients are exposed to side effects of standard therapy without therapeutic benefit. "This is a particularly serious problem for children because they are still undergoing normal growth and are particularly vulnerable to the side effects of anti-cancer drugs."

By using the combined approach of genomic medicine and accurate mouse models to choose the best therapy for each patient, Lau hopes to improve the speed and outcome of clinical trials as well as to reduce unnecessary side effects for children with cancer.

Photo courtesy of Connecticut Children's Medical Center

BREAKING THE BOTTLENECK

OF ALZHEIMER'S DRUG DEVELOPMENT

JAX researchers Mike Sasner (left) and Greg Carter now have the tools to build new mouse models that truly represent patients with Alzheimer's disease.

BY JOYCE DALL'ACQUA PETERSON
PHOTOGRAPHY BY TIFFANY LAUFER & AARON BOOTHROYD
ILLUSTRATION BY ZOË REIFSNYDER

The stats are grim.

About 5.4 million Americans are living with Alzheimer's disease, and the Alzheimer's Association projects that number to grow to 13.8 million by 2050.

The costs are huge: This year about $236 billion in this country will be spent on care for Alzheimer's patients, with another estimated $221 billion representing the economic value of family members' unpaid care.

And, because it robs people of their memories, their ability to recognize loved ones and in some cases even their personalities, Alzheimer's disease wreaks human devastation beyond calculation.

While several drugs on the market temporarily abate some symptoms of Alzheimer's disease, not one drug can prevent or treat the disease itself. In late November yet another drug, solanezumab, failed clinical trials. And a report by the Tufts Center for the Study of Drug Development pegs the cost of bringing a new drug to market at $2.6 billion.

By comparison, one of the largest grants the National Institute on Aging (NIA) has awarded this year — $25 million over five years to The Jackson Laboratory (JAX) and Indiana University (IU) — seems modest, yet it could transform the troubled drug development system and deliver new treatments for Alzheimer's disease.

Here's how: "For the first time, we have the tools to build new mouse models that truly represent patients with Alzheimer's disease," says JAX Associate Professor Gregory Carter, Ph.D., one of the principal investigators of the new center for Model Organism Development and Evaluation for Late-Onset AD (MODEL-AD). "Our goal is to break the bottleneck of Alzheimer's drug development."

Modeling Alzheimer's disease in the mouse

Alzheimer's disease is a progressive degenerative disorder, and is the most common cause of dementia in people over age 65. The disease attacks neurons, causing them to break connections with other neurons and die, leading to memory loss, language problems and other deficits. The brains of people with Alzheimer's disease typically have beta amyloid plaques and tau tangles, but it's unclear whether these unwanted protein deposits are a cause or effect of the disease.

One of the difficulties in diagnosing and treating Alzheimer's, Carter notes, "is that most of the symptoms of the disease are behavioral, and they don't appear until there's already damage to the brain. If we could identify new early biomarkers that could be used to diagnose Alzheimer's at an earlier age, we might be able to arrest or reverse the damage at an earlier time point."

For more than 100 years, scientists have studied mice to understand the genetic basis for human diseases. Because mice and humans share up to 98 percent of their genes, a mouse with a genetic variation that's analogous to one found in a human with a given disease can serve as an experimental model for that disease. In the 1980s, gene transfer technology allowed scientists to engineer changes in the mouse genome to create transgenic models of human disease, and today gene editing technologies such as CRISPR enable even more precise model-building.

The first Alzheimer's disease mouse models carried a genetic mutation associated with a relatively rare, early-onset version of the disease. But most Alzheimer's patients have the late-onset version of the disease, which to date has not been successfully modeled in mice.

JAX Associate Professor and Alzheimer's disease researcher Gareth Howell, Ph.D., a co-principal investigator of the Alzheimer's disease center grant, comments, "There have been more than 400 unsuccessful clinical trials for Alzheimer's disease since 2004. Some of those were based on research using mouse models. Unfortunately, although those

Alzheimer's is the most common cause of dementia in people over age 65.

JAX Associate Professor Gareth Howell with Neurobehavioral Expert Stacey Rizzo will analyze new Alzheimer's mouse models. WANT MORE? SEE VIDEO AT *www.jax.org/endalz*

models have been fantastic to teach us about the biology of Alzheimer's disease, they haven't been appropriate as preclinical models, and so a major aim of the MODEL-AD center is to develop models that much more appropriately recapitulate human Alzheimer's disease, particularly nerve cell loss."

The MODEL-AD center is a partnership of JAX and Indiana University (IU), including co-principal investigators Bruce Lamb, Ph.D., whose work includes understanding the role of the immune system in Alzheimer's disease, and biomedical imaging expert Paul Territo, Ph.D.

"Our center also includes individuals who are seeing Alzheimer's disease patients," Howell says, "all the way through to individuals who are assessing mouse models. We've never had access to this level of data before. For the first time, we have the entire pipeline within one program that will enable us to really determine which aspects of Alzheimer's disease our new AD mouse strains model. And probably more importantly, which models are most appropriate for performing preclinical testing of new targets."

Moreover, notes Michael Sasner, Ph.D., a JAX expert in mouse model development and the MODEL-AD center co-manager, a major goal of the center is to put new and better mouse models of the disease in the hands of researchers worldwide.

"Right now the Alzheimer's field is very limited by the available Alzheimer's disease mouse models," he says. "We know that mouse models will be important for developing and testing new drugs. Once we generate and validate new models of late-onset Alzheimer's disease, JAX will make them widely available so that anyone in the pharma and biotech industries, as well as academic research, can use them as well as the data and associated protocols that we will provide about them."

Howell, whose lab has published research linking the Western diet and Alzheimer's disease, notes that genetic factors account for only 40 to 70 percent of an individual's

risk of the disease. "We're not only thinking about the genetics of Alzheimer's," he says, "we're also thinking about aging and environmental risk factors such as diet and levels of physical activity. Aging is the greatest risk factor for Alzheimer's disease, and in previous iterations of mouse models that hasn't been fully appreciated. JAX has a long history in aging research, and we're putting these Alzheimer's disease genetic variants in the context of aging and really beginning to understand the interplay between genetic susceptibility and the aging process."

Recent advances in genetic and imaging technologies have enabled a better understanding of the basis of Alzheimer's disease in humans, including genetic and environmental risk factors. Moreover, clinical researchers now have new ways to measure Alzheimer's disease and its progression through advanced, noninvasive imaging techniques, and genomic techniques that characterize the entire brain at the gene-by-gene level.

The center takes advantage of the vast patient datasets that have accumulated across the nation over the last five years or so, notes Carter, a computational biologist. "Our partner, Sage Bionetworks, is providing us with data from very large patient cohorts, those without Alzheimer's as well as those with Alzheimer's, so we can to try to identify genetic variants that tend to show up on the Alzheimer's side."

Using computational approaches, Carter explains, the MODEL-AD team can determine which of those variants, separately or in combination, might be the most relevant and predictive of Alzheimer's, and develop an array of mice with those variants. Neurobehavioral expert Stacey Rizzo, Ph.D., at the new JAX Center for Biometric Analysis, will conduct advanced analyses of the new mouse models, providing data to compare with the human clinical data and to inform drug testing.

"We're still learning about the pathologies that lead to full Alzheimer's disease," Carter says, "and our center and the models we create and share with the community will greatly expand that knowledge, and accelerate the translation of this basic research knowledge into realistic cures for Alzheimer's disease."

The effort to solve and treat Alzheimer's in a dramatically different way starts now with the $25 million grant for this transformative research project. Yet the future will not be fully realized without your philanthropic support, as only together can we bring hope to those we love who will be affected by Alzheimer's disease.

Join us today to change tomorrow for Alzheimer's patients.
Visit *www.jax.org/give*.

> *Our study has revealed two potential novel molecular mechanisms for the treatment of subsets of gastric cancers. Moreover, our approach of integrating genomic molecular profiling and PDX mouse models provides a valuable platform for novel drug-target discovery and validation.*
>
> *– Charles Lee*

JAX and Ewha collaborators in South Korea

Yijun Ruan and Edison Liu

ADDRESSING GASTRIC CANCERS, A LEADING CAUSE OF CANCER DEATHS IN ASIA

Gastric cancer is the third-leading cause of cancer-related deaths in the world, with more than 50 percent of cases occurring in East Asia. About 17 million Americans are of Asian descent, putting them at increased genetic risk for the disease. Researchers at The Jackson Laboratory are making significant breakthroughs in understanding and targeting gastric cancers.

Charles Lee, Ph.D., FACMG

The Scientific Director of JAX Genomic Medicine, Charles Lee is recognized worldwide for his discovery of widespread structural variation in the human genome, in the form of copy number variation (CNV). This is a state in which cells have an abnormal number of copies of DNA sections, sometimes associated with susceptibility or resistance to disease, including cancer. Lee is also a distinguished professor at Ewha Womans University in Seoul, South Korea. In collaboration with Han-Kwang Yang, M.D., Ph.D., one of the world's foremost clinical researchers in gastric cancer research at Seoul National University Hospital in South Korea, the Lee lab published a study in *The Proceedings of the National Academy of Sciences* (PNAS 112: 12492-7, 2015) of gastric cancer specimens from 103 patients and identified two new potential targets for some of the gastric cancers. The study approach itself offers a blueprint for expediting the discovery and validation of new drugs for this disease.

Yijun Ruan, Ph.D.

JAX Professor, Director of Genome Sciences and Florine Deschenes Roux Chair Yijun Ruan, Ph.D., has a grant from the National Cancer Institute to explore the role of noncoding RNAs (ncRNAs) in cancers, including gastric cancer, and other diseases. Most RNAs manufacture proteins from the "blueprint" provided by DNA, but there are many kinds of ncRNAs that carry out other vital roles in cells. Ruan and his lab are using new technologies to identify novel ncRNAs and the interactions between ncRNAs and their target DNAs. Because ncRNAs are associated with diseases such as cancers, such novel ncRNAs and their target DNAs have the potential to be diagnostic biomarkers and novel genomic therapeutic targets for disease.

As published in *Cell Reports* (Cell Reports 12: 272, 2015), Ruan's lab identified five recurrent fusion genes in the gastric cancers of 15 Southeast Asian patients. They discovered that one of these fusion genes, CLDN18-ARHGAP26, appears to lead to cellular changes involved in acute gastritis and cancer.

Jennifer Trowbridge researches the regulation of stem cells in the blood in normal development, aging and leukemia transformation.

YOUNG BLOOD

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

As we age,

we grow more likely to develop cancer. Jennifer Trowbridge, Ph.D., wants to know why, specifically, older people are more likely to get acute myeloid leukemia (AML).

"The link between cancer susceptibility and aging is very well established," Trowbridge says. "And in the blood system we grow more susceptible to particular types of blood tumors. We're looking at changes in the stem cells that are responsible for building blood cells but develop cancer cells instead."

The average age of onset of AML is 67, with slightly more men than women getting the disease. Chemotherapy is effective in about two-thirds of patients, but older patients don't respond as well. As with all cancers, the earlier AML is detected, the better the prospective outcome, but today there is no screening test to find AML before symptoms occur, and the symptoms themselves — which include weight loss, fatigue, fever and night sweats — could point to any number of other conditions or diseases.

The Canadian-born Jackson Laboratory assistant professor has figured out a way to profile blood tumor cells that offers a powerful new prognostic tool, and is now exploring strategies for targeting AML before it even starts.

Joining JAX for her first faculty position in 2012, following her postdoc at Dana-Farber Cancer Institute and Children's Hospital in Boston, Trowbridge has already published research in top journals and has captured the attention of several prominent funding organizations. She has earned a New Scholar Award in Aging from The Lawrence Ellison Foundation, a National Cancer Institute Provocative Questions Initiative award, a Maine Cancer Foundation grant and a newly announced V Scholar award from the V Foundation for Cancer Research.

"THIS APPROACH IS KIND OF ANOTHER DIMENSION. IT'S AN INCREDIBLY PRECISE TOOL FOR LOOKING AT THE BIG PICTURE OF A CANCER."

– Jennifer Trowbridge

Trowbridge's postdoc mentor was Stuart Orkin, M.D., David G. Nathan Distinguished Professor of Pediatrics and Howard Hughes Medical Institute investigator at Harvard Medical School, who is also on the external advisory board of the JAX Cancer Center. "Jen has the uncanny ability to focus on the critical issues and then design her experiments to address them clearly," Orkin says. "Always upbeat and enthusiastic, Jen has always been a terrifically positive person. These traits make for a strong foundation, and have allowed her to transition to her independence smoothly and rapidly, becoming an important faculty member at JAX."

A DIFFERENT PATH

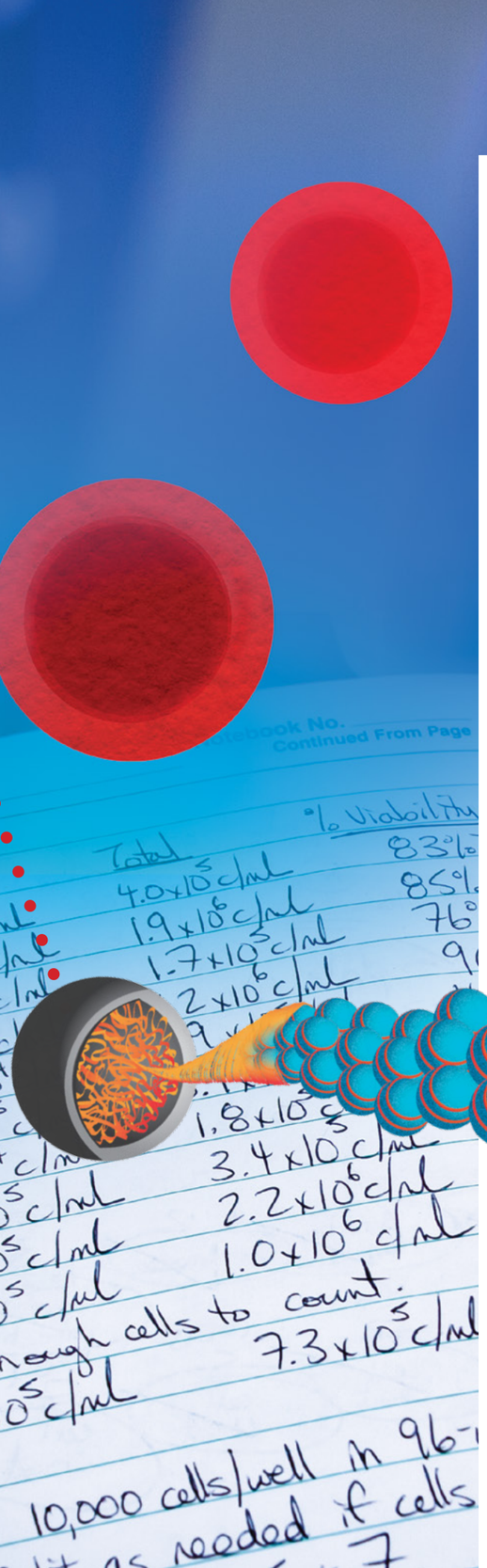
Despite all of her precocious success, Trowbridge didn't start out planning to be a research scientist. Though she enjoyed math and science as a kid, by her senior year at the University of Western Ontario she was on a path to become a genetic counselor. But one lecture on signaling pathways in stem cell biology by a new faculty member sparked a passion for exploring genetic mechanisms.

"The thing I liked about genetic counseling," Trowbridge says, "was the idea of interacting directly with people, and being able to feel like I was making a difference in their lives. But this professor was addressing genetic diseases directly, and showed me a different path to helping people."

Fired up to go to graduate school in immunology and stem cell biology, but with only basic genetics and biochemistry courses under her belt, Trowbridge emailed the lecturing professor, Mick Bhatia, to ask whether he would take her on as a grad student. Bhatia declined but Trowbridge persisted, asking one of her professors to "please talk to him and tell him that I'm smart and I have good hands in the lab and I'll work really hard, and that he should let me be in his lab."

Bhatia, who is now Canada Research Chair in human stem cell biology at McMaster University, agreed to be Trowbridge's mentor. "Having had many graduate students before," Bhatia says, "I suggested directions where techniques and preliminary data were available, so she could continue on a pre-developed track. This, however, was not a regular graduate student.

"A few months after her arrival, Jen would walk into my office and sit on the carpeted floor, where she insisted she was more comfortable. There we would start discussions about the conceptual framework of experimentation, how controls for the variables could be designed and what interpretations from the experiments (that I later learned she was already doing) could be drawn out. These starting discussions were clearly the end of my contributions as a supervisor, and I quickly realized I had a stem cell biologist peer."



Bhatia adds, "It's a delight to watch her achieve her goals, although I too often look at my empty carpet floor and miss Dr. Trowbridge."

Trowbridge would, in fact, have made a first-rate genetic counselor. She has a serene, calm demeanor and listens thoughtfully, ignoring the frequent "ping" sounds of incoming emails on her computer. The people in her lab describe her as caring and supportive. She's also a family woman who — with her husband Mike Kiers, a nurse at the local hospital and, like Trowbridge, tall and athletic — has two young sons and is expecting a daughter in the spring.

Like most principal investigators, Trowbridge has to spend most of her time at her computer, writing grant proposals and drafting research papers. This morning she has carved out time in her lab to meet with her small staff for a progress check on the quest to understand what goes wrong in AML.

A PRECISE TOOL

All blood cells start from a common origin, hematopoietic stem cells (HSCs). HSCs in turn produce more specific progenitor cell types, each of which are responsible for producing various kinds of blood cells: red, white (including myeloid cells) and platelets.

Over the years, the stem cell compartment in the bone marrow expands, but that's not good news: Some of the stem cells it cranks out don't function properly and instead produce more of the myeloid cell types, which increases the chance of these cells becoming cancerous.

Data from AML patients show that the stage of a progenitor cell when it becomes transformed to leukemia has an impact on its clinical progression. The earlier the transformation occurs, the more aggressive the cancer. But how can you triage the different kinds of cells to determine the cells of origin?

In what could be described as a conceptual discovery, Trowbridge found a framework to sort out and evaluate tumor cells: their open chromatin profiles.

Chromatin is the material in the cell's nucleus that condenses to form chromosomes during cell division. Just as every species of tree produces leaves of a certain shape, every type of cell has a characteristic chromatin profile: a distinctive combination of closed (tightly wound and relatively inactive) and open (looser and more active) chromatin.

"We realized we could analyze open chromatin in bulk tumor cells," Trowbridge says, "to determine what kind of cell the tumor had developed from. That cell-type specificity of chromatin structure provides a major clue for diagnosis and treatment."

Working with a mouse model of AML, the Trowbridge lab began with five distinct, normal cell types found in bone marrow: long-term HSCs, short-term HSCs, multipotent progenitors, common myeloid progenitors and granulocyte macrophage progenitors. The AML that developed from these different cells of origin had varying levels of aggressiveness when engrafted in mice, with the stem-cell-derived lines being the most aggressive.

To profile the open chromatin in these distinct AML samples, and compare them to open chromatin patterns in normal cells, Trowbridge collaborated with Duygu Ucar, Ph.D., a JAX assistant professor who develops computational models to study gene regulation including chromatin structure. Together they identified open chromatin signatures and gene expression patterns in AML samples that enabled them to distinguish the more aggressive, stem-cell-derived AML.

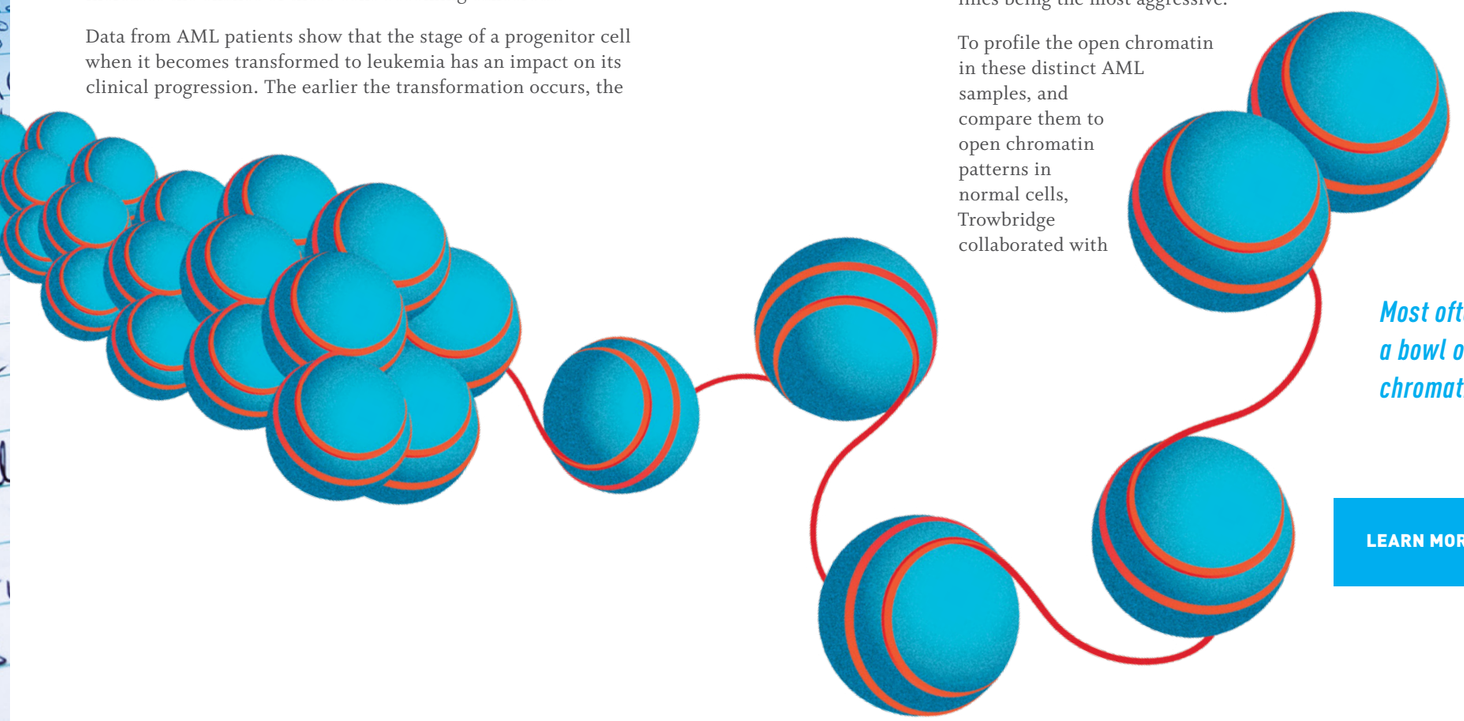
"This approach is kind of another dimension," Trowbridge says. "It's an incredibly precise tool for looking at the big picture of a cancer. It reveals what's happening in terms of how the cancer cells are behaving, where they've come from, what they've been exposed to and, potentially, what's going to be effective to treat them."

Ucar describes Trowbridge as "a dream collaborator" for a computational scientist. "It's a great pleasure to work with her. She generates top-quality data and asks very smart research questions."

Back in her office, Trowbridge reflects on the struggles inherent in being a principal investigator in today's complex research environment, which she describes as finding a balance between positivity and realism.

"I've learned that it's okay to have to lean on somebody else, to ask somebody for help, to collaborate with somebody because you can't get this particular technique to work and they're an expert in it. Working with Duygu is a perfect example of this."

By the same token, she says, "The hardest lesson that I have had to learn is to know when to cut a project, because it's not going as well as you had hoped and you're just sinking a lot of resources and time into it. Ultimately it does better justice to the process and to science to be able to make those difficult decisions."



Most often chromatin (illustrated here) resembles a bowl of spaghetti. During cell division chromatin condenses to form chromosomes.

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Bridging the gaps in DNA sequencing

BY MARK WANNER | PHOTOGRAPHY BY JENNIFER TORRANCE

The rapid improvement of DNA sequencing technology over the past 15 years has been a true innovation success story. Astonishing progress in sequencing speed, cost and accuracy has drastically changed biomedical research. But it has also come with problems that are well known but rarely mentioned in genetics or precision medicine stories. As a result, new technologies are being pursued that have the potential to push sequencing capabilities well beyond their current state.

Progress, with caveats

Even the best short-read whole genome sequences aren't whole. At least five percent of the DNA bases — more than 150,000,000 of them — aren't included in whole genome data. Short-read sequences also leave out other information that can be vital for disease diagnosis. Why is that?

The technology that has driven most of the sequencing progress is short-read, massively parallel sequencing, with a high percentage of it done on equipment from a company known as Illumina. DNA is first fragmented into short segments, usually around 150-300 base pairs long, and huge numbers of these small fragments are sequenced simultaneously. After sequencing, however, each of the short sequences has to be fit onto a reference template in what's known as sequence assembly. Think of a puzzle that's mostly featureless blue sky — reassembling highly repetitive regions is a similar challenge, only many orders of magnitude larger and more difficult.

Software engineer Zeeshan Ahmed, Ph.D., shows a MinION handheld DNA sequencer at The Jackson Laboratory for Genomic Medicine.

Long reads, big hurdles

To help researchers more easily solve this puzzle, two commercially available long-read sequencers have emerged, using technologies known as single-molecule, real-time sequencing and nanopore sequencing. They provide the ability to sequence DNA segments of 5,000-10,000 base pairs and even more in one read, and the companies that make them continue to increase those lengths.

So why is most sequencing still short-read? Simply put, long-read technologies have been hampered by relatively high cost and accuracy problems. They are currently being used effectively for certain applications, however, and recent advances have them poised to make a significant impact.

SMRT is the more mature long-read sequencing technology, implemented by a company — Pacific Biosciences (PacBio) — that commercialized it in 2011. It uses the same basic components as short-read sequencing but reconfigures them to allow for the sequencing of much longer single molecules. Researchers at JAX have used the system to sequence entire microbial genomes at once, a hugely valuable attribute when sorting through samples with dozens or hundreds of different microbial species present. Researchers are also using it to sequence an entire messenger RNA (after reverse transcribing it to DNA) to see what different forms — called isoforms — are present in the cell.

Nanopore sequencing, in which a DNA molecule is fed through a tiny pore and the bases sequenced by the slight differences in current disruption each combination of bases produces, has long been an intriguing possibility.

The first commercial nanopore product, the MinION, is a small sequencer not much bigger than a flash drive. It doesn't have huge capacity or high accuracy, but it can go just about anywhere and has been particularly valuable for sequencing pathogens. It has been used to quickly identify the sources of hospital infection outbreaks, helped track the Ebola and Zika epidemics in Africa and South America, and even went into space, where it was used to sequence microbes in the International Space Station. Improvements have now made it capable of sequencing larger genomes — such as humans — which offers some intriguing possibilities.

Impact on biomedical research

The contributions of long-read sequencing to isoform research, microbial sequencing and pathogen tracking are already profound. The potential is there for human genome sequencing with better coverage and little assembly needed as well. If the methods continue to improve, they would provide better data more quickly for individual diagnoses of rare diseases, cancer and more. The technologies are still new and changeable, so predictions are difficult, but the payoffs could be enormous in the years ahead.

THE COLLABORATIVE CROSS

BY JOYCE DALL'ACQUA PETERSON | ILLUSTRATION BY DANIELLE MEIER

Ask JAX Professor Gary Churchill, Ph.D., whether a mouse is a good model for a human, and he'll likely answer, "No, but a human is a terrible model for a human." People's genomes are so varied, in other words, that no one individual's genome can truly stand in for all people. Properly designed populations of laboratory mice, on the other hand, can provide a powerful tool for teasing out the multiple gene variants involved in complex human diseases.

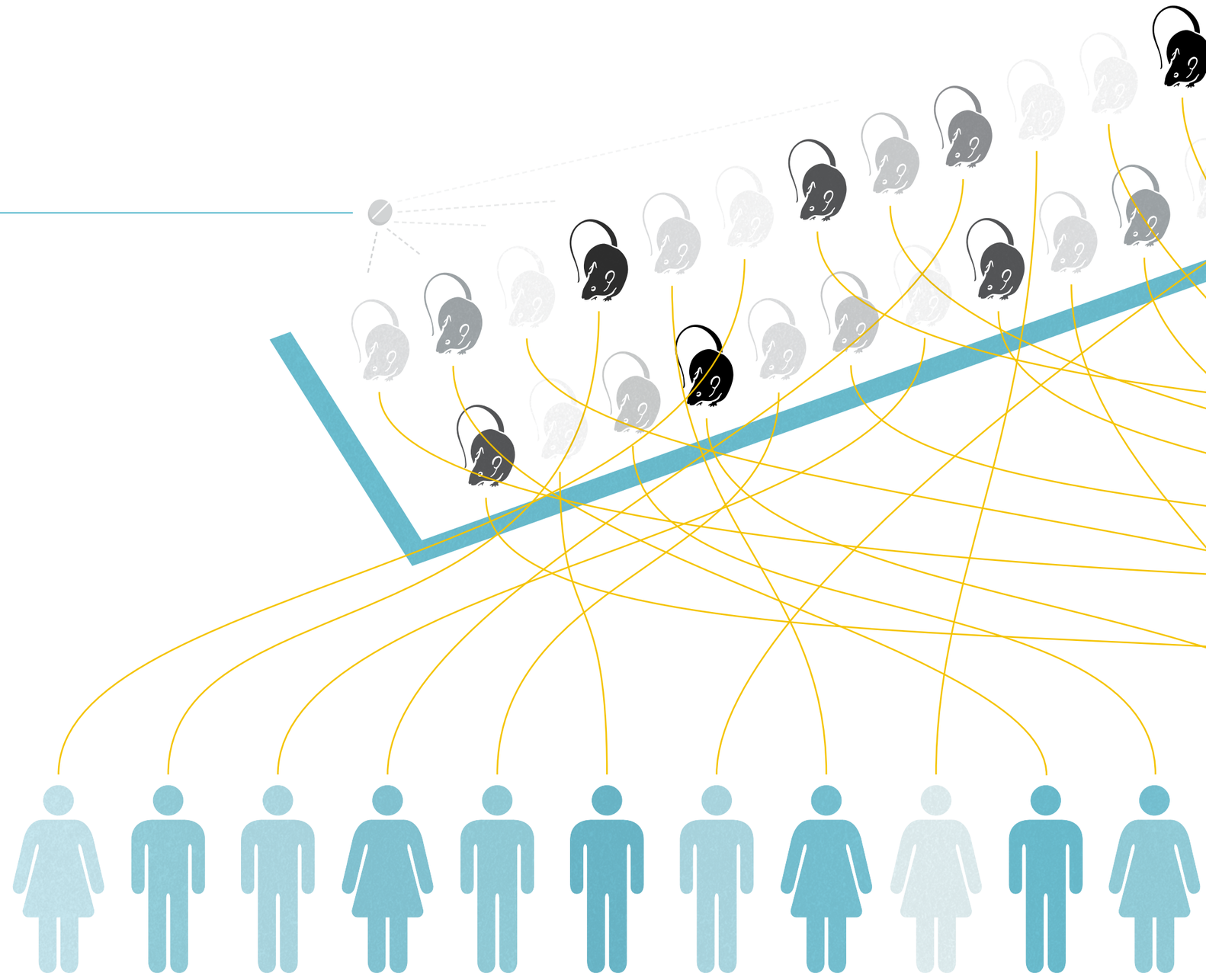
In 2004 Churchill and other leading laboratory mouse experts around the world devised the Collaborative Cross: a mouse population established with eight different founder strains, including standard inbred strains but also some wild-type mice.

Crossing these animals shuffles the genetic deck to yield populations of mice with greater genetic diversity than is present in the entire human race. And that variety is visible to the naked eye.

"Some are as big as capybaras," Churchill jokes. "Some are small, some are yellow, some are fat, some live a very long time." Sequencing the DNA of each animal allows the researchers to peg physiological and behavioral characteristics (phenotypes, in the vernacular) to specific genetic variants.

Today the Collaborative Cross concept is a Big Idea in the research community, with more than 1,400 citations in scientific literature.

New advances in phenotyping and genome sequencing mean that researchers can quickly gain a sophisticated picture of how the action of a drug, a specific gene of interest, or even complex diseases and traits such as addiction or Parkinson's disease, vary in a diverse population.



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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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