

SEARCH

A close-up photograph of a man's hands holding a green apple in his left hand and a purple frosted cupcake with colorful sprinkles in his right hand. He is wearing a dark long-sleeved shirt and a silver watch on his left wrist. The background is blurred, showing a window with a view of trees.

EXPLORING THE
DIET-LIFE SPAN
CONNECTION

OUR MICE, OUR HOPE • SEARCHING THE GENOME'S DARK CORNERS FOR CLUES

FALL 2017 • VOL.10 • NO. 3 • THE JACKSON LABORATORY



SEARCH

ON THE COVER

What's wrong with too many cupcakes? Mauro Costa's research with mice is revealing the metabolic effects of our dietary choices.



The Jackson
Laboratory

*Leading the search
for tomorrow's cures*

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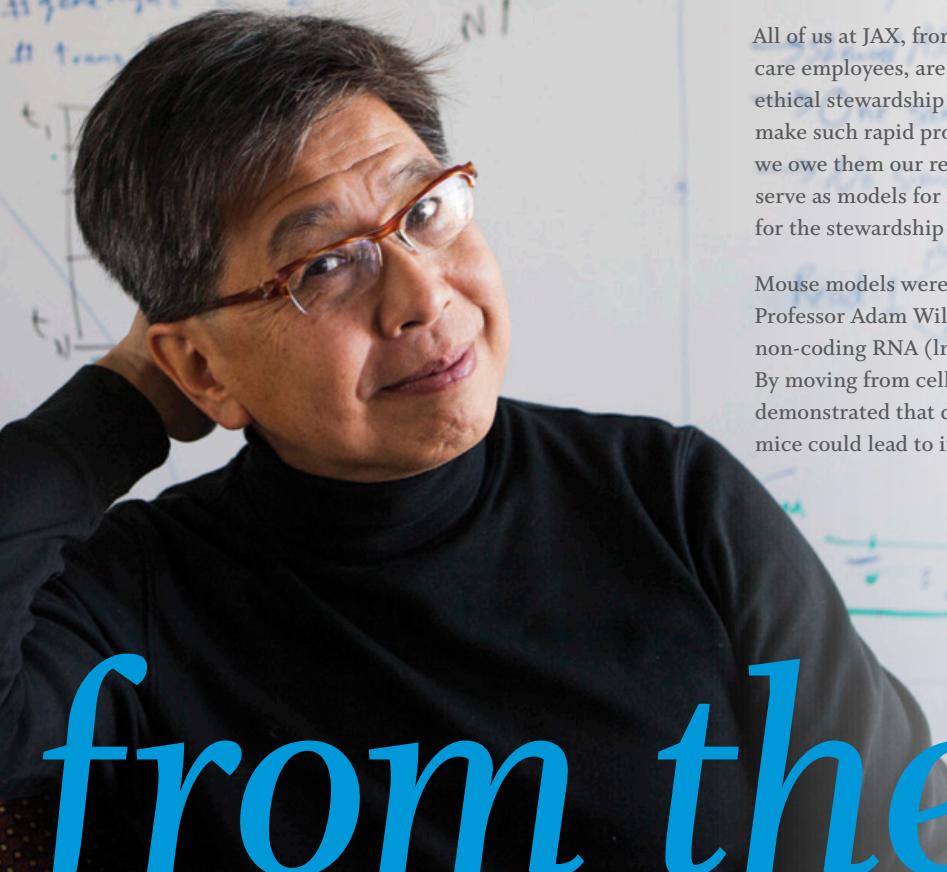
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COVER PHOTOGRAPHY BY AARON BOOTHROYD
INSIDE COVER PHOTO BY JENNIFER TORRANCE

from the President

did you know?



HOPE FOR LONGER AND HEALTHIER LIVES

Advances in biomedicine are not simply about curing disease, but about building a firm foundation for longer, healthier lives. At The Jackson Laboratory (JAX), our fundamental aim is to extend both life span and health span in humans — and one of the best tools for accomplishing this is the mouse.

All of us at JAX, from our leadership and faculty to our animal care employees, are deeply committed to the humane and ethical stewardship of our mice. Without them, we could not make such rapid progress in scientific research, and for that, we owe them our respect and gratitude. Just as JAX® mice serve as models for human disease, JAX strives to be a model for the stewardship of model organisms.

Mouse models were the key to discoveries made by Assistant Professor Adam Williams, Ph.D., about the role of long, non-coding RNA (lncRNA) in cells in the immune system. By moving from cell-based models to engineered mice, he demonstrated that defective lncRNA in the immune cells of mice could lead to inflammation and inflammatory diseases

like asthma. Williams, who joined our faculty in 2014, is now studying human lncRNA to understand — and potentially develop new ways to treat — asthma and other complex immune diseases.

JAX is known first and foremost as a genetics research institute, but our scientists are also exploring questions that go beyond the genome. Indeed, while new gene engineering tools like CRISPR are making rapid, precision gene editing a real possibility for the first time, health is also affected by factors other than genes that are potentially easier to control. Diet and physical activity are prime examples. As this issue of *Search* highlights, a number of our scientists are using mouse models to elucidate the roles diet and activity play — in concert with the genome — in health, disease, aging and longevity. The goal: helping people to live longer, healthier lives.

None of this work would be possible at such a rapid pace and large scale without mouse models. And new resources like our Center for Biometric Analysis — the state-of-the-art “mouse hospital” nearing completion on our Bar Harbor campus — enable us to study all aspects of our model mice with greater precision, comprehensiveness and insight than ever before.

Our mice are our hope for a healthier future — for everyone. And, as always, it is the support of friends like you that accelerates progress toward that future, transforming hope into health.

Edison Liu, M.D.

President and CEO, The Jackson Laboratory

The Jackson Laboratory is the world's most collaborative biomedical research institution, and consequently the world's most significant catalyst for innovation in health and disease.

JAX scientists are sought-after collaborators on national and international research projects. We are taking the lead in fostering partnerships between bench and clinical researchers around the world that build on each discipline's work and accelerate insights into the genetic causes of disease and the development of new treatments.

We found the link between viruses and cancer, the existence and nature of stem cells, the basis of transplantation biology — among many other pioneering discoveries that helped make the medicine of today possible. In fact, 26 Nobel Prizes have been associated with JAX research, resources and educational programs.

connect with us





PARTNERS IN DISCOVERY

This summer, about 150 donors visited The Jackson Laboratory in Bar Harbor, Maine, to hear from JAX scientists whose research is revolutionizing how we understand and treat disease.

Attendees heard firsthand how the discoveries of JAX scientists are fueled by our shared passion for transforming human health and by the generous support of our donors. Philanthropic support plays an especially vital role in launching the research programs of early-career scientists. Young researchers at JAX are at the forefront of discovery in their fields, tackling big diseases like cancer as well

as rare and orphan diseases. Francesca Menghi, from the laboratory of JAX President Edison Liu, M.D., showed how identifying the molecular fingerprints of some of the deadliest cancers affecting women is leading to new, more targeted therapies.

Also during the event, Gareth Howell, Ph.D., spoke about how JAX is building new mouse models that, for the first time, truly represent patients with Alzheimer's disease.

Learn how you can help fund the researchers of tomorrow by visiting www.jax.org/helix.

EDUCATING THE SCIENTISTS OF THE FUTURE

The JAX Summer Student Program is designed for students who want to immerse themselves in genetics and genomics research. It emphasizes laboratory discovery, communication of knowledge and professional growth.

In 2017, JAX hosted another incredibly diverse community of 48 students who share a love of science and a common goal to achieve success.

The students participated in ongoing research programs with the support of experienced scientific mentors, tackling diseases like addiction, Alzheimer's, cancer and diabetes.

They developed independent projects, implemented their plans, analyzed the data and reported the results. At the end of the summer, they presented their findings to researchers, their peers and their parents at a special symposium before graduating.

The program is available at The Jackson Laboratory in Bar Harbor, Maine, and The Jackson Laboratory for Genomic Medicine in Farmington, Conn. Learn more at www.jax.org/ssp.

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PHOTOGRAPHY BY AARON BOOTHROYD, CHARLES CAMARDA & TIFFANY LAUFER

our mice our hope

BY CHARLES E. HEWETT, PH.D. | PHOTOGRAPHY BY STANTON SHORT,
JENNIFER TORRANCE & JON SHAPLEY

The use of mice in biomedical research has contributed dramatically to medical progress.

In fact, medicine today is built on a foundation of mice as models of human disease. 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.

For more than a century, scientists have used the mouse as a genetic model of the human being to understand our fundamental biology, and to identify and test better treatments and cures for the most devastating diseases. Mice were used to demonstrate the effectiveness of penicillin in fighting bacterial infection — progress that has saved the lives and limbs of hundreds of thousands of people. Research with mice led to treatments for leukemia that have extended the lives of countless children. Forty years of research with mice led to the introduction of the Salk vaccine that has protected millions of us from polio. And, meningitis vaccines developed through mouse research have prevented numerous others from life-threatening disease. In the past 20 years alone, the Centers for Disease Control and Prevention estimates that vaccines have saved the lives of three quarters of a million children and avoided 21 million hospitalizations.

Similarly, work in mice to understand the body's immune system enabled organ transplants. In 2015, there were more than 30,000 transplants in the United States alone and tens of thousands more globally; nearly all extended and improved quality of human life. Therapies for breast cancer that will afflict one in eight women were also developed using mouse models: tamoxifen, Herceptin and aromatase inhibitors all arose from mouse studies of the most common cancer to affect the female half of our population.

Mouse-based research has contributed to better therapies and care for animals as well.

But this important and lifesaving work is not done. Stem cell research in mice is ongoing to tackle heart disease, stroke, Alzheimer's, spinal cord injury and numerous other life-threatening or debilitating conditions. Gene therapy discovery to treat



“The quality of the care for our mice and our facilities set the global bar for animal health. – Charles Hewett

inherited childhood diseases such as cystic fibrosis, muscular dystrophy and sickle cell depends on mouse models. Vaccine research in mice may ultimately prevent Alzheimer's, malaria and HIV/AIDS. And the Cancer Moonshot depends on in-depth work with mice. All of this research would be slowed, if not stopped altogether, without the mouse models that underpin it. Mice are essential in medical research because most diseases cannot be modeled in a test tube and require experimentation in a whole organism.

The Jackson Laboratory pioneered the use of mice in disease research, and our mice and research programs have contributed to important medical breakthroughs ever since. Organ transplants, glaucoma prevention and treatment, obesity management, stem cell research, a spinal muscular atrophy cure and leukemia treatments were all advanced at The Jackson Laboratory.

We are extremely proud of our research that is dedicated to curing and preventing human disease and of the mouse models and services we provide to over 20,000 laboratories around the world. We are equally proud of the compassionate care we give to the mice in our own research studies as well as to the millions more that we raise to support the important research work of the global biomedical community.

At The Jackson Laboratory, we give our mice the utmost respect and provide them ethical and humane care and treatment. The quality of the care for our mice and our facilities set the global bar for animal health. Our mice are raised under clean-room conditions that are required for manufacturing the most sensitive pharmaceutical products — a standard higher than most hospital operating rooms. Each mouse's welfare is checked at

least once per day to ensure it is healthy, has ample food and water, and that its bedding is clean and dry. Trained animal welfare technicians give the utmost attention to the mice they care for every day. Our technicians must take and pass a minimum of two demanding courses in animal care and participate in a six-month internship before handling mice without direct supervision.

Our institutional Animal Care and Use Committee, which includes outside community members, overlooks our entire program, reviews and approves every protocol of research and care and conducts semi-annual inspections to ensure they are being followed. The Association for Assessment and Accreditation of Laboratory Animal Care International, an independent, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs, sends a team of people to review our entire program on a regular basis and consistently comments on how rigorous and progressive it is. We transparently self-report welfare concerns to the Office of Laboratory Animal Welfare, the federal regulatory body that oversees the care of laboratory mice by those who receive federal funding. And, we institute programs and practices to continuously improve the quality of our facilities and care.

There are those who believe that the use of mice in biomedical research is unnecessary. We strongly disagree. The solution to many diseases continues to hinge on precise mouse models of the human condition. Our mice benefit humankind. As their stewards, we provide them with the best care possible so that they can empower the global biomedical community in our shared quest to conquer human disease.



JAX Professor Robert Burgess and collaborators are using mouse models to develop a personalized gene therapy for Caroline, a child suffering from a debilitating neuromuscular disease called Charcot-Marie-Tooth. Read her story at www.jax.org/caroline.

Give to JAX

Your gift to JAX could speed the pace of discovery of lifesaving therapies by giving our scientists flexible funds for advanced technologies, tools, education and laboratories to develop new, precise disease therapies — or to prevent people from developing illnesses in the first place.

Please make a gift today to The Jackson Laboratory, and know that your gifts are always dedicated to our shared goal: leading the search for tomorrow's cures. Every dollar you contribute to JAX goes to scientific research.

Donate today at www.jax.org/support.

Health, fortune telling and genome sequences

BY MARK WANNER

PHOTOGRAPHY BY TIFFANY LAUFER, ILLUSTRATION BY KAREN DAVIS



I waited years for my genome sequence — all 3.2 billion letters.

When it was finally in hand, I opened the web page containing the data with excitement. Then I took a look at the top of the report. I'll admit I was a little surprised.

You see, I have a genetic variant that's clinically significant. But more on that later.

I had my genome sequenced through the Personal Genome Project (now called Open Humans), a research effort seeking to address many of the data challenges facing genomics. Participants agree to freely share all their genomic and phenotypic (trait) data in hopes of advancing scientific understanding and, ultimately, perhaps medical progress. And they get their genomes sequenced and learn a few things about themselves along the way.

The sequence of a healthy person today is not likely to be medically actionable or even useful. But I'm curious and believe that we will know far more in the near future, so pursuing my own sequence was a very easy decision to make.

Little is known about how most people react to getting their genomes sequenced, however, and whether ambiguous or potentially alarming results might worry them needlessly. Research is just beginning to emerge regarding how healthy people view the process and how the knowledge gained affects them. The numbers are still small, but so far it appears that most respond as I did — with more interest than distress — and a small but important percentage do learn something of medical value.

Which brings me back to my genome data. My reports shows that I have six variants that are clinically significant — they're the ones most

likely to affect my health — 35 with a lower clinical significance rating, and 2,776 that are "insufficiently evaluated." Those numbers alone say a lot about how much there is left to learn.

I learned that I am likely to have blue eyes and burn to a crisp in the sun. Yup. I also have variants that are known to raise prostate cancer susceptibility if, and only if, I have a family history. I do. My prostate-specific antigen (PSA) level is now baselined and as yet no cause for concern.

And then there's the top one. Like about 14 percent of the population, I have one copy of ApoE4, the variant that increases the risk of Alzheimer's disease. Some people choose not to learn their ApoE status, and the wisdom/ethics/value of reporting it to healthy people or patients sequenced for other reasons has been hotly debated for years.

Homozygous people, those having two copies of ApoE4, have been found to have a 13-times-greater risk of Alzheimer's disease, while heterozygous people with one copy, like me, have about a four-times-greater risk. And there's nothing that can be done about it. At least not yet.

I can't deny that the ApoE4 result caught my attention and led to some Googling for a day or two. On the other hand, I lost no sleep nor do I think about it much at all now after some time has passed. I exercise and eat healthy foods (most of the time) and work at a job that makes me think a lot, all things that are supposed to help maintain brain function.

And so I'll just hope the dice land in my favor. Probably with more jogs and fewer cookies along the way.

CGTA

SEARCHING THE GENOME'S DARK CORNERS FOR CLUES

BY NICOLE DAVIS, PH.D. | PHOTOGRAPHY BY TIFFANY LAUFER

By studying a new and emerging class of genomic elements, Adam Williams is turning up new ideas about how the immune system functions.





**"The ultimate goal is
to be able to personalize therapy...
that's really where the field wants to go."**

- Adam Williams

The field is so new that we don't actually know how many lncRNAs exist, with estimates ranging from 10,000 to 100,000 — more than three times the number of human protein-coding genes. To date, only about 100 have been studied in depth, and they are implicated in a variety of human diseases, from cancer to Alzheimer's to heart disease. Moreover, lncRNAs are beginning to show promise as diagnostic tools. One lncRNA, known as PCA3, forms the basis of a molecular test now used to help diagnose some forms of prostate cancer.

Notably, Williams is one of only a handful of scientists worldwide who are studying lncRNAs to illuminate their roles in immune cell development and function.

"We are discovering a whole new world within the genome," says Williams, who thinks lncRNAs have enormous potential in explaining individual variability in both health and disease. "An interesting feature of lncRNAs is that they generally are very tissue- and species-specific — much more so than proteins. So while many cell types in the body express similar proteins, maybe only one cell type will express a particular lncRNA," says Williams.

Although the field is small and unexplored, he has some big ideas about how these molecules might be operating in the immune system — and how they might one day be manipulated therapeutically in diseases such as asthma.

"It's possible that by targeting just one lncRNA, we might be able to fundamentally alter immune cells and how they behave," says Williams. That suggests lncRNAs could form the basis of novel diagnostic and prognostic tools. This idea is already being borne out in cancer, and it may also hold true for immune disorders like asthma.

Like explorers in a new world, scientists must often plot their course judiciously — deciding not only where to look, but also where not to look.

For decades, researchers have focused on genetic clues tucked away in a highly scrutinized portion of the genome: protein-coding genes.

"It is clear that these genes do not provide the full story," says Adam Williams, Ph.D., assistant professor at The Jackson Laboratory (JAX).

Williams and his colleagues have turned their attention to a poorly understood — and understudied — segment of the genome. This noncoding portion houses a new and intriguing class of molecular regulators known as lncRNAs (long, non-coding RNAs). These molecules were initially deemed genomic oddities.

Some two decades ago, only a handful of lncRNAs had been identified. It has since become clear that they constitute a vast and important group.

What is precision medicine? Precision medicine is a new and better approach to health care based on each person's unique genetic makeup. Williams' passion for science flows from a deep curiosity about biological systems and what makes them tick.

"I've always been intrigued by how things work. Since I was a small child, I knew I wanted to do science — it was my favorite subject in school, and it always made sense to me."

He was drawn to the immune system by its remarkable power, and its utility as a model system to figure out how genes work. As a graduate student at the National Institute for Medical Research in London, England (now part of the Francis Crick Institute), he exploited the advantages of the immune system to explore questions about gene regulation. Later, as a postdoctoral fellow, he began to delve into immune-related diseases.

"Those experiences gave me an appreciation of not just how important the immune system is, but also how beautiful and complex it is — and how devastating it can be when just one step in the process goes awry," he recalls.

A recent study by Williams and his colleagues, including Richard Flavell of Yale University and Jorge Henao-Mejia of the University of Pennsylvania's Perelman School of Medicine, helps illustrate the promise of his lab's approach to understanding lncRNAs. The work began several years ago, when Williams was a postdoc in Flavell's lab and first hatched the idea to explore the role of lncRNAs in the immune system. He and his colleagues collaborated with lncRNA expert John Rinn at Harvard University. Rinn and his laboratory have pioneered techniques for systematically profiling the lncRNAs present in different cell types.

"Adam was way ahead of the game," says Rinn. "He had the foresight that lncRNAs would be important in the immune system, and he really went after them."

Rinn explains that at the time, most researchers were confining their studies of lncRNAs to cell-based models, because it wasn't clear that engineering mice with defective lncRNAs would yield interesting — or interpretable — results. But Williams took the big leap to mouse models. His reward: a remarkable result that shines a bright new light on the immune system.

In their paper, published last August in *Nature*, the researchers describe a novel lncRNA in mice that regulates the life span of a key subset of immune cells. These cells circulate in the blood and typically are short-lived. But if they persist too long or proliferate abnormally, they can cause excessive inflammation, such as that found in hypereosinophilia syndrome and other inflammatory disorders such as asthma.

Throwing light on asthma

In his own laboratory at JAX, Williams is focused on understanding the function of human lncRNAs in mechanisms of immune system function and dysfunction. "We hope to shed more light on complex immune diseases such as asthma," he says.

Nearly every project in the lab revolves around a different human cell type. These include key immune cells, such as Th2 cells, which play a prominent role in allergic responses, and eosinophils, which drive much of the tissue damage and remodeling that unfolds in asthma. Williams' team collects some of these cells directly from asthma patients, providing a critical window on the biological processes that underlie this disease.

He also probes the cells that line the lungs and upper airways. The biology of these cells is interesting because the cells persist at a unique interface: one side contacts air, the other blood. Williams and his colleagues have developed a three-dimensional culture system that recapitulates this unique environment. Remarkably, these "lungs-in-a-dish" produce mucus; extend tiny, finger-like projections (called cilia) that beat and help remove foreign particles that enter the airways; and respond to viruses — just like their counterparts in the body. The system provides a critical test bed to study mechanisms of immune regulation in the lung and analyze the functions of specific lncRNAs.

Ultimately, these multi-faceted efforts could point to better ways to intervene. "If we can understand how immune cells are acting, and why they are overreacting in diseases such as asthma, then hopefully we can find ways of suppressing and silencing them."

"The ultimate goal is to be able to personalize therapy. That's really where the field wants to go," says Williams. "If we can help realize that goal, that would be amazing." Amazing because scientists will help lay the foundation for a new generation of more precise asthma treatments. In turn, these new tools will give doctors the power to prescribe therapies that are more directly targeted at the root causes of illness.

EXPLORING THE DIET life span connection



What are you having for dinner tonight?

BY JOYCE DALL'ACQUA PETERSON
PHOTOGRAPHY BY AARON BOOTHROYD

Now, think about what you would have for dinner if your health and longevity depended on what and how much you choose to eat. Research in diseases of aging, and in aging itself, is revealing a powerful role in our diet.

In short, the so-called Western diet, high in fat and sugar, is contributing to the rise in obesity, type 2 diabetes, hypertension and high cholesterol among Americans. And all these conditions, in turn, exacerbate risk for the most deadly genetic diseases such as heart disease, cancer, Alzheimer's disease and kidney disease.

"Unfortunately the curve of type 2 diabetes is going in the wrong direction, and we're living longer as well," says Gary Gibbons, M.D., director of the National Heart, Lung and Blood Institute. Speaking at the 58th Annual McKusick Short Course at JAX, co-presented with Johns Hopkins University, Gibbons comments, "So we have an aging population that's more and more obese, and has more and more hypertension." He calls this "a conspiracy" against the hearts, brains and kidneys of aging Americans.

At the heart of the matter

The leading cause of death worldwide is coronary artery disease, a complex disorder that may involve hundreds of specific genes. Thanks to the widespread prescription of statins, drugs called PCSK9 inhibitors and aspirin therapy, as well as smoking cessation, the incidence of heart disease has declined. Yet that decline has leveled off due to — you

guessed it — the increase in the diet-driven conditions of obesity and type 2 diabetes.

"Heart disease is less prevalent than it was 50 years ago," says JAX Research Scientist Mauro Costa, Ph.D., "because we've been able to treat the preliminary symptoms of the disease by reducing hypertension and cholesterol. But we are not yet able to address the genetic causes of heart disease, and thus provide truly preventive treatments."

Evidence is accumulating that a healthy lifestyle can counter some of the genetic risk for heart disease. Sekar Kathiresan, M.D., a physician-scientist and human geneticist with Massachusetts General Hospital, the Broad Institute and Harvard Medical School, is the lead author of a paper in the *New England Journal of Medicine* analyzing the results of multiple studies of lifestyle and heart health, representing 55,685 participants. He shared the findings in a talk at the McKusick Short Course, confirming that adherence to a healthy lifestyle was associated with a reduced risk of coronary artery disease within each category of genetic risk.

What is this so-called healthy lifestyle? In the NEJM study, the researchers culled factors from the strategic goals of the American Heart Association: no current smoking; body-mass index of less than 30; physical activity at least once weekly, and a healthy diet involving higher consumption of fruits, nuts, vegetables, whole grains, fish and dairy products; and a reduced amount of refined grains, processed meats, unprocessed red meats and sugar-sweetened beverages.



JAX Research Scientist Mauro Costa works with mouse models to study congenital heart disease.

Costa is looking at the role of diet in a specific kind of heart disease, which involves a mutation in a single gene. As the name suggests, congenital heart disease (CHD) is a genetic disorder that causes heart defects during gestation. Today, postnatal and even prenatal diagnosis and treatment are enabling many infants born with CHD to survive and live a normal life span. But this success also means that parents born with CHD are more likely to pass the condition on to their own offspring. And adults with CHD may be more susceptible to obesity, type 2 diabetes and other factors that can trigger heart damage.

Costa studies a mouse model of CHD, one with the same genetic defect as human patients carry. Some of the CHD mice receive a normal, mostly grain mouse food, others receive a high-fat diet and a third group a formulation meant to represent the nutrient profile of the so-called Western diet.

"The two organs of the body that do the most work and consume the most nutrients are the brain and the heart," he says. "And they have different nutrient needs: The brain consumes primarily sugar, in the form of glucose, and the heart's main fuel source is fat." Preliminary findings in Costa's lab indicate that CHD causes metabolic changes that make a high-fat diet an even more potent trigger for heart failure than for normal individuals.

An ideal "healthy lifestyle" may not be the same for all kinds of disease, or even for all kinds of heart disease, Costa says. "Talking about cardiovascular disease is like talking about cancer — it's not just one disease," he says, "and in the future, doctors may be able to prescribe specific diet and exercise regimes" based on an individual's specific genetic risk for cardiovascular disease.

Brain food?

Researchers are also exploring the connections between diet and Alzheimer's disease. Leah Graham, Ph.D., a postdoctoral associate in the laboratory of Associate Professor Gareth Howell, Ph.D., published in *Nature Scientific Reports* 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.

Graham is now 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," she says, "we could potentially develop new therapies for people who are unable to exercise."

Cutting calories to extend life span

Diet, and specifically restricting calories, also appears to have a strong link to aging itself. Research dating back to the 1930s has demonstrated a link between a limited-calorie diet and extended life span, in a wide variety of research models: yeast, drosophila and *c. elegans* (laboratory fruit flies and nematodes), rats and inbred mice.

JAX Professor Gary Churchill, Ph.D., is taking these studies to the next level, looking at how different individuals respond to variations in caloric intake to pinpoint the genetic and physiological variations involved.

Humans are notoriously poor at sticking to any kind of calorie-restricted diet, and it's impossible to conduct lifelong studies of this kind in humans. Mice provide an experimental stand-in, given their relatively short life span (average two years) and the ability to control every aspect of their laboratory environment, including diet.

Churchill is one of the architects of a special kind of mouse colony known as Diversity Outbred (DO). The result of carefully orchestrated cross-breeding of genetically defined inbred strains, these mice nevertheless represent the kind of random-looking genetic variation you'd find in the human population.

"Some calorie-restricted mice in the DO population have incredibly long life spans," Churchill comments, "some reaching almost five years of age," the equivalent of a human living about 160 years.

Churchill is now segregating DO mice into groups receiving different feeding regimes throughout their life span. Control animals are on an *ad libitum* ("all-you-can-eat") diet. Some mice are fed daily but receive a reduced amount. Fasting animals are provided food *ad libitum* on most days but spend a period of time each week with no food access.

Along the way all the mice will receive frequent and extensive physical evaluations to collect data that can later be correlated to how long they live. And because the genomic sequence of every mouse is known, overlaying this physiological data should provide unprecedented insights into the genetic impact of calorie restriction on health and longevity.

"While it is clear that some animal models, like the inbred C57BL6/J mouse strain, benefit from caloric restriction, there is also evidence that the effects can differ depending on the genetic makeup of the animal," Churchill notes. "The same will likely be true for people: caloric restriction may be a good thing for one person and not for another. Until we understand these individual differences, we have to be very cautious about recommending dietary changes for people."

Understanding how diet influences the genetic components of aging and age-related diseases could someday lead to treatments that trounce the ill effects of poor nutrition.

In the meantime, all the evidence shows that the best way to stave off the diseases of aging is to maintain that American Heart Association-recommended healthy lifestyle. So skip the fries and reach for an orange, then go for a walk.



*Sweet
stuff*



*Western
diet*



*Strictly
vegan*



How do you make a Western diet for a mouse?

Jeffrey Harder, Ph.D., preps meals, but he's not in a kitchen and he's not exactly cooking.

The JAX postdoctoral associate in the laboratory of Professor Simon John, Ph.D., is exploring the role of diet in neurodegeneration in age-related diseases, specifically in glaucoma.

"A number of studies show that some age-related diseases are less common in Asia," Harder says. "So we are looking at the role of diet in preventing or exacerbating diseases involving neurodegeneration."

Harder has concocted a range of feeding regimes for the mice in his study, which are now in use in other JAX labs for research in Alzheimer's disease and aging. The grain-based chow that JAX® mice regularly receive is "as healthy as you can get," he says. To provide mice with a diet that provides adequate nutrition yet represents a typical Western diet, Harder formulated a chow with a less-healthy protein source and increased animal fat, cholesterol and salt.

"It smells exactly like the inside of a fast-food restaurant," Harder reports. He says he tastes all of his "recipes" and while he doesn't find this high-fat diet appealing, mice given a choice will eat the Western-diet offering and leave the normal, healthy food untouched.

SWEET STUFF With more than 50 percent fat and plenty of sugar, this is the mouse equivalent of living on premium ice cream. Because it packs on the pounds (or more precisely in the case of mice, the grams), this is the diet of choice for understanding obesity-related diseases such as diabetes.

WESTERN DIET The fat-protein-carbohydrate profile of this chow mirrors what you'd find on a fast-food menu, including the extra cholesterol and salt. Mice on this diet exhibit vascular inflammation, glial reactivity and other symptoms common to dementia, Alzheimer's and other diseases of aging. Do you want fries with that?

STRICTLY VEGAN This is the standard laboratory diet of JAX mice, composed of whole grains fortified with vitamins and other supplements for maximum mouse health and longevity. In diet studies, this chow is fed to the mice that are the controls in the experiment.

The JAX headquarters in Bar Harbor, Maine, is halfway around the globe from Monash University in Melbourne, Australia,

but the two institutions share strong research connections thanks to Nadia Rosenthal, Ph.D. who joined JAX as professor and Bar Harbor's scientific director in 2015.

Rosenthal's mission to expand mouse genetics in the international biomedical research community includes establishing the mouse biology program for the European Molecular Biology Laboratory (EMBL), a Rome-based network of biomedical research institutes. In 2009, Rosenthal brought Australian laboratories into EMBL as the first non-European members. That year she also established the Australian Institute of Regenerative Medicine at Monash University, which now leads Australia in biomedical research grants.

The team of scientists that Rosenthal brought with her from Australia to JAX has wide-ranging research interests, including the genetics of muscle and heart development, immune control of cardiac disease and the regeneration of adult tissues.



Nadia Rosenthal



Sarah Stephenson

JAX DOWN UNDER

BY JOYCE DALL'ACQUA PETERSON | PHOTOGRAPHY BY TIFFANY LAUFER & MARIE CHAO

Research scientist and Australian native James Godwin, Ph.D., who also has a joint appointment at the Mount Desert Island Biological Laboratory a few miles from JAX, studies the regenerative powers of axolotl salamanders to develop strategies to improve repair of human tissues after surgery, disease or traumatic injury.

"I wanted to move my discoveries in the salamander regeneration model into mouse models to try and stimulate regeneration in mammals," Godwin says. "The Jackson Laboratory gives me affordable access to all the mouse strains not possible in Australia on a small junior faculty budget." He says his accountant wife, Michelle, is also "flourishing" in her new role in

the JAX finance office. "Bar Harbor is very different from Australia, but we are both loving the adventure."

Just a few months after the Rosenthal lab moved to America, JAX and Monash University entered into an agreement to establish cooperative research exchange opportunities for short- and long-term faculty and students, and to partner together in new education training and research initiatives. "Breakthroughs in science ultimately depend on the quality of the scientists," Rosenthal says. "Australia has a strong tradition and

"For what I'm trying to do, everyone has told me, 'You have to do that at JAX.'"

— Sarah Stephenson



Monash University, Melbourne

MELBOURNE, AUSTRALIA—IMAGE BY BOYLOSO, VIA THINKSTOCK BY GETTY IMAGES

firm foundations in scientific endeavor, contributing two percent of the world's knowledge from a population of only 24 million. I'm capitalizing on my global network of research colleagues to forge new international connections and opportunities with the Australian research community."

Rosenthal's international network of scientific contacts has brought other Australian investigators to spend time at JAX for collaborative research. Sarah Stephenson, Ph.D., based at Murdoch Children's Research Institute in Melbourne, spent eight weeks at JAX last year to fast-track her studies of Parkinson's disease by using a new kind of experimental platform: genetically diverse mouse colonies known as the Collaborative Cross.

"These mice offer an opportunity to ask and answer questions that we haven't had before," says Stephenson. "We're in a new era where we can really start teasing out how genes are interacting with each other." An important goal, she says, is to develop new and better mouse models for Parkinson's disease that can be shared with researchers worldwide and used for drug discovery. "For what I'm trying to do, everyone has told me, 'You have to do that at JAX.'"

TUMORS ON OUR MINDS

Precision medicine has been hailed as the future of cancer therapeutics.

JAX Professor and Associate Director of Computational Biology Roel Verhaak, Ph.D., is taking us a few steps closer to that future.

BY GRACE NIEWIJK | ILLUSTRATION BY ZOË REIFSNYDER

The most widespread form of malignant brain cancer in adults is also the most aggressive and deadly. Glioblastoma multiforme (GBM) tumors are fast-growing and often contain many different types of cells, making them very difficult to treat.

Although researchers have been investigating it for many years, GBM remains common and high-profile. The tumors have affected many well-known figures, including politicians like Delaware Attorney General Beau Biden and Senators Ted Kennedy and John McCain.

But it isn't all doom and gloom — the future may be looking up, thanks in part to Verhaak. In 2010, he was first author on a landmark paper in *Cancer Cell* that classified GBM tumors into four subtypes. The paper became a standard in the field, with over 3,200 citations to date.

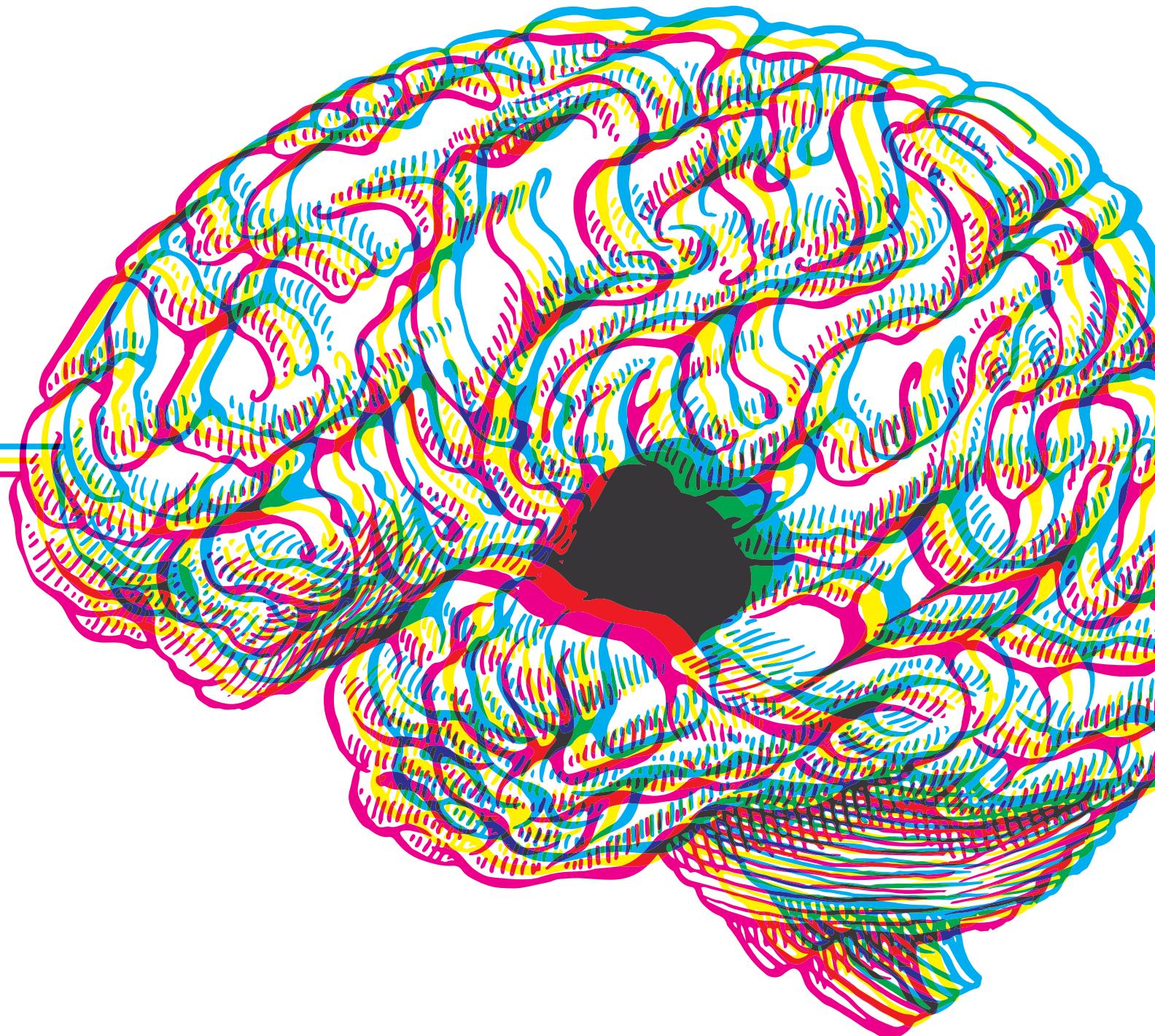
"These subtypes are biological," says Verhaak, "so they really reflect different types of glioblastoma, but they haven't yet translated into different types of treatment. A lot of research is ongoing toward that goal."

Verhaak and his lab at JAX have remained a crucial part of that ongoing research. After moving his lab to JAX from University of Texas M.D. Anderson Cancer Center, Verhaak led a study — also published in *Cancer Cell* — that refined the 2010 paper's results by looking at gene expression in a set of 364 GBM tumors. By carefully filtering out the data from the non-cancerous cells in the "microenvironment" surrounding the tumor, they found that there are, in fact, only three true subtypes of GBM.

The paper laid out new strategies for determining tumor subtype, which could make it easier to apply the classifications in a clinical setting. The study was also one of the first to examine tumors before and after various treatments in order to characterize the effects.

Some findings could lead directly to treatment options. For example, the data suggest that some GBM tumors might respond to a type of immunotherapy known as checkpoint inhibition.

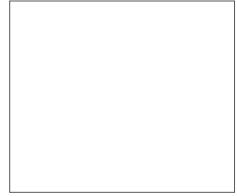
Where do we go from here? Hopefully this leads to immunotherapy trials for the different GBM subtypes. Verhaak's gene expression data sets are publicly available, which will help researchers find precise targets for more effective treatments.





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