Preserving fertility

From South Korea to The Jackson Laboratory

Kelsey’s story

Understanding Alzheimer’s

Single cell genomics
THE SEARCH
A PUBLICATION OF THE JACKSON LABORATORY

ON THE COVER
Using single-cell technology, JAX researchers are deciphering genomic function one cell at a time. Learn about single cell genomics on page 26. Illustration by Zoë Reifsnyder

LEFT
This is a sagittal section of an adult mouse cerebellum stained with cresyl violet, which stains cell bodies, and luxol fast blue, which stains myelin a darker blue.

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Single cell genomics

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THE MULTIPLIER EFFECT. IT’S WHAT SETS JAX APART.

We are not just advancing science more quickly in our own research labs. We are fueling discovery on a global scale — developing the tools and technologies that are used in biomedical research in laboratories around the world, and building innovative partnerships to accelerate research progress and train new generations of scientists.

The work of Assistant Professor Gareth Howell, featured in this issue of The Search, highlights this multiplier effect at work. Dr. Howell’s study of Alzheimer’s is revolutionary in its potential to unlock new approaches to prevention, diagnosis and treatment. But just as important as the advances that come directly out of Dr. Howell’s lab is the global impact of his work to develop better mouse models for Alzheimer’s research: models that can then be used by scientists everywhere.

We can also see the power of this multiplier effect — and our global impact — in our collaborations with other institutions. Our partnership with South Korea’s Ewha Womans University, for example, demonstrates the power of JAX to inspire young scientists around the globe and serves as a catalyst for collaboration. Over the summer, JAX hosted a group of graduate students from this prestigious women’s university, galvanizing their confidence in pursuing careers in science. This October, JAX and Ewha cohosted an international symposium on genomic medicine as a step toward forging more extensive research collaborations.

Philanthropic support for JAX further amplifies this multiplier effect. Each gift we receive advances our mission, with ripple effects that have an impact far beyond our campuses. Whenever someone gives to JAX, they are accelerating discovery at The Jackson Laboratory and around the world.

That’s the power of the multiplier effect. That’s the power of JAX. And it’s all made possible by you, our partners in discovery.
$1.5 MILLION GIFT TO THE JACKSON LABORATORY
ESTABLISHES SIMS FAMILY FUND FOR SMARD RESEARCH

A $1.5 million gift to The Jackson Laboratory from Mr. Grant Sims and Ms. Patricia (Patty) Sims of Houston, Texas, will fund research in a rare, fatal motor disorder: spinal muscular atrophy with respiratory distress, or SMARD. SMARD is an exceptionally rare condition, with fewer than 70 reported cases. Symptoms of SMARD appear within the first six months of life in infants who inherited a defective gene from both parents. SMARD undermines muscle function, compromising mobility and breathing. Few SMARD babies live past their first birthdays.

As rare as SMARD is, research in the disorder is even rarer. Jackson Laboratory Associate Professor Greg Cox, Ph.D., is among a handful of scientists worldwide that study SMARD. Mr. and Mrs. Sims first learned about The Jackson Laboratory through the fundraising efforts of a student at the University of Notre Dame, where the Sims’ son, Eric, is an associate professor. Eric Sims and his wife, Jill, are the parents of two children born with SMARD. After donating to the fundraiser, the Sims connected with Cox to learn more about the SMARD research program, and subsequently established the Sims Family Fund for SMARD Research.

JAX RESEARCHER BURGESS LANDS TWO GRANTS
FOR STUDY OF NEUROLOGICAL DISORDER

Professor Robert Burgess, Ph.D., has received a three-year, $300,000 grant from the Muscular Dystrophy Association and a $412,500 continuation grant from the National Institute of Neurological Disorders and Stroke for his work in understanding the genetic basis of Charcot-Marie-Tooth disease. Charcot-Marie-Tooth is a genetic neurological disorder that causes damage to the peripheral nerves, the bundles of nerve cell fibers that connect the brain and spinal cord to muscles and sensory organs. The disease is associated with a mutation in a gene known as GARS. Burgess and co-investigator Scott Harper, associate professor at Nationwide Children’s Hospital Center for Gene Therapy in Columbus, Ohio, will test a new gene therapy approach to specifically block the altered form of the GARS gene in a newly developed mouse model.

NIH AWARDS $2 MILLION FOR JACKSON LABORATORY
COMPUTATIONAL STUDIES OF ALCOHOLISM, ADDICTION

The National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health has awarded a five-year, $2 million grant to Associate Professor Elissa Chesler, Ph.D., to develop online resources to aid researchers in the study of genes associated with alcoholism and addiction.

Chesler and colleagues at JAX, Baylor University and the University of Tennessee have created GeneWeaver.org, an online “knowledge discovery environment” for researchers to share and compare functional genomics results: genes associated with behaviors and biological processes for many different species, including humans and mice.

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

“At JAX, I’ve been able to learn from journalists, educators, filmmakers, scientists and my fellow students. I could not imagine anywhere else I would have rather spent my summer.”

– Michelle Ng, 2015 JAX Summer Student
**Preserving fertility**

STORY BY MICHELLE NG
PHOTOGRAPHY BY MARIE CHAO
ILLUSTRATION BY KAREN DAVIS

Ewelina Bolcun-Filas, Ph.D., researches how to protect female fertility despite radiation-induced DNA damage, so female cancer patients retain the option of having children later in life.

Battling cancer is difficult enough. Unfortunately, current treatments can make it even harder for female patients, who could be impacted for the rest of their lives by irreversible side effects. In particular, women who receive radiation therapy (especially combined with chemotherapy) near their reproductive organs are often left with shortened reproductive life spans or complete infertility. They are thus unable to have children even after their cancer has been eliminated or has gone into remission.

Ewelina Bolcun-Filas, Ph.D., is exploring how to protect female fertility despite radiation-induced DNA damage, so female cancer patients retain the option of having children later in life.

“[Reproduction] is a fabulous system because it’s very complicated,” Bolcun-Filas says, “and very important for the success of any species.”

Infertility as a side effect of radiation therapy is due to the mechanism by which radiation attacks cancerous cells. If a cell is exposed to radiation, it incurs DNA damage in the form of double-strand breaks, which means that both strands of the DNA double helix are severed. The goal of radiation treatment is essentially to damage the DNA of rapidly proliferating cancer cells to the extent that they die.

While this may be an effective way to rid the body of cancerous cells, radiation indiscriminately attacks all cells. Though the majority of normal cells are able to repair such breaks and recover, others succumb to the damage. These include not only the targeted cancerous cells, but also hair follicles (which causes patient hair loss) and, most importantly for Bolcun-Filas’ research, oocytes.

Oocytes are female germ cells that become eggs during ovulation. They are located in the ovary and formed by the third trimester of gestation. As a result, by the time a female is born, she already possesses all of the oocytes she will ever have. And so if a female baby develops cancer during or after maturation and needs radiation therapy, she might lose the irreplaceable oocytes from irradiation’s consequential DNA damage.

“If the cancer is anywhere near the reproductive organs and they get radiation, there’s a very high chance the woman will become infertile,” Bolcun-Filas explains. After radiation causes double-strand breaks in the oocytes, the body — upon recognizing that they possess DNA damage — naturally eliminates them.

In addition to the woman’s inability to have children, secondary repercussions of oocyte death include the symptoms of menopause manifesting significantly earlier than usual. Premature hormonal imbalances — a consequence of no longer producing estrogen and other hormones during ovulation — can lead to a higher risk of osteoporosis and heart disease, as well as negatively impact a woman’s emotional health.
Currently, the best option for women about to undergo cancer treatments with a high likelihood of resultant infertility is to collect and freeze their eggs. And while they can still have children in this manner and take hormones after treatment, Bolcun-Filas believes there is a better way. In the years ahead, she hopes that a medical application of her research may help to protect female cancer patients from infertility and premature menopause.

“For women with problems conceiving, or who are losing pregnancies, if we understand the genes that are behind making a perfect egg, we can then look at their genomes and genetic predispositions,” she says. “A mutation in the ‘checkpoint’ gene allows bad oocytes to survive and repair their DNA.”

Unfortunately, doctors will not be able to fix any genetic problems with oocytes, since oocytogenesis occurs before the female is born. However, with the knowledge that there is a good egg among the rest, they could recommend assisted technologies, such as in vitro fertilization, so “a ‘good egg’ can be fertilized.”

“Sometimes it’s quite difficult to work on fertility because it’s not thought of as a life-threatening disease,” Dr. Bolcun-Filas reflects, citing its lack of coverage in the media. “But the payback is really great. In the end, it has tremendous importance for the human species.”

How the Chk2 inhibitor allows for DNA repair

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How the Chk2 inhibitor allows for DNA repair
Ten students from Ewha Womans University in South Korea were brought to Bar Harbor for the Short Course on Mammalian Genetics. The results were transformative.

For Jiyoung Kim, who has spent the past 10 years studying at Ewha Womans University in Seoul, South Korea, Ewha is more than just a school. Widely regarded as one of the top women’s universities in the world, it is no wonder that the 28-year-old decided to complete both her Bachelor’s and Master’s degrees there, and is now continuing to work for her Ph.D. at the School of Medicine.

Kim and eight other graduate or doctoral students from Ewha Womans University had the opportunity to attend The Jackson Laboratory’s Short Course on Mammalian Genetics this July. Although each of the women’s research interests varied widely, they were brought to Bar Harbor, Maine by Dr. Charles Lee, a faculty member at Ewha Womans University as well as scientific director at The Jackson Laboratory for Genomic Medicine.

Lee is interested in forging a partnership between JAX and Ewha, and sponsored the students’ travels this summer to spearhead the initiative.

“The Jackson Laboratory has so much to share with Ewha Womans University,” Dr. Lee says. “And it made a lot of sense that the Ewha students would be the ideal conduit for this sharing.”
During an intensive selection process, Lee sought out a “sense of fearlessness” first in 44 application essays, and then in the 20 students who were later invited to interview. He ultimately selected nine students whom he believed would take advantage of both the Short Course and travel opportunity while inaugurating the developing relationship between JAX and Ewha.

Thanks to his efforts, as well as those of a visiting scientist at The Jackson Laboratory for Genomic Medicine, Dr. Jeeyoung Kwon, the students flew halfway around the world to further their studies, and ended up learning about more than just genetics throughout their journey.

Before their departure, the students — Minjin Bahn, Ah Young Choi, Su Kyung Hae, Eutteum Jeong, Jiyoung Kim, Joo Hwa, Jiyoung Park, and Jihee Song — felt the nervous excitement that precedes any transformative experience.

“There are going to be a lot of researchers gathered with more experience than me,” Bahn anticipates. She planned to seek advice from the expert faculty of The Jackson Laboratory and Johns Hopkins School of Medicine for “gaining skills in getting past scientific problems.”

Along these same lines, Jeong added that through these senior researchers, she hoped to “learn about everything regarding genetics.”

In addition to opportunities to progress academically, several of the students also mentioned looking forward to making foreign friends, participating in outdoor activities and, of course, enjoying Bar Harbor’s fresh lobster.

After 17 hours in the air, the women arrived in Maine and checked into the Short Course, eager to explore the area in spite of the long journey.

“When you think about America, you think about a really overwhelming, grand place,” says Choi as she stood on top of Cadillac Mountain (the first spot to see the sun rise in the United States each morning). She smiles with her arms outstretched as a friend snaps a photograph.

“Because I’m going to America for the first time, I want to see and experience many things that I can’t do in Korea,” adds Park, citing the ocean as an example and admiring the nature that dominates Mount Desert Island. “I want to witness it all for myself.”

In between sharing slices of blueberry pie, shopping for Bar Harbor apparel and participating in genetics workshops at the Short Course, the women began to reveal more about themselves, their motivations for devoting their lives to science and insecurities about their futures.

“I actually decided to study pharmaceutics because I want my family to be healthy,” Park, whose mother had cancer, explains. “When a proposal does not work out, it’s tough. But I feel I need to do it right. I believe that out of 100 times it will work at least once, so I still work hard and research hard.”

Kwon agrees with Park about the pressure that naturally accompanies a career in science: “If the results don’t come out as well as we want or how we want, there’s a lot of difficulty. At those times, it’s important to have a positive ‘I can do this!’ attitude and try again.”

In addition to fears of scientific failure, Bahn admits that she was “a little stressed about [her] lack of skill in English” going forward in both the Short Course and her career.

Regarding the questions the women have about their abilities and futures, Lee comments, “I think many Korean students currently perceive glass ceilings and glass walls to their careers. I’m hoping that we can work together to bring down these barriers (real or perceived) and leave them...
with a vision of unlimited opportunities to pursue—limited only by their own imagination.”

Meanwhile, the students continue to study genetics by day and enjoy cruises around Mount Desert Island by night.

“At time goes by, I can understand more things than I could [not] understand before. I think my listening is better than yesterday,” Jiyoung Kim laughs.

She went on to describe, however, that in Korea, some women devote their lives to science while others focus on raising children, and the difficulties involved in balancing both. The other students also anticipated this challenge stemming from the demands of research, particularly as women.

“I am a female researcher, and as a female [in Korea] there are certain obstacles,” Heo says. She expressed her concern about obstacles that arise through marriage, pregnancy and parenting.

During the Short Course, JAX Principal Investigators Ewelina Bolcun-Filas, Carol Bult, Patsy Nishina and Kyuson Yun gather to discuss being a woman in science with the Ewha students.

From personal anecdotes—such as Nishina describing how people occasionally address questions about her own scientific poster to her husband next to her—to advice about finding support from mentors and spouses, the JAX researchers share their experiences and insight into the professional world of science.

“Don’t let people define you,” Bult urges. “You have to have an internal drive that allows you to weather any storm. You have to love what you do, and it’s hard not to love being able to get up every day and have the potential to discover something new.”

Yun believes it is becoming a better time for women to work in science, and Nishina agrees.

“I think it is possible to do everything,” she says. “I think it’s possible to have a family; I think it’s possible to do your science. You make compromises, like working before the kids wake up or after they go to sleep, but I think it’s okay to make them.”

Following the panel, the Ewha students express relief that they do not have to sacrifice hopes of a family for a career in science, or vice versa.

Heo in particular was “moved” by the discussion’s validations. “Through the Short Course, I have been learning about experiments and trends in science, and now I have also gained self-esteem.”

Jeong agrees. “I was a little bit confused before I came to The Jackson Laboratory about which career was best for me, so I was very impressed by the roundtable discussion. I think that [the JAX scientists] are all passionate about their work, and I’ll continue to do my best.”

The students return to the Short Course schedule for the remainder of the program. A few final talks and workshops later, and the women begin reflecting upon the impact that their time at The Jackson Laboratory will have on their futures.

Kwon, like Heo, comments that she is now more certain not just of her abilities in science, but also of herself. “In Korea, most people think about what others will think about them, but the panel discussion helped me a lot in that way because they gave us a lot of advice—not as scientists, but as human beings. So now, I think maybe it’s okay to be myself. I’m going to keep a positive mind and hold [to] my path.”

As each of these women headed home to dig deeper into their research, they return to Ewha Womans University with enhanced knowledge of genetics, newfound friends and the reassurances that they can be great scientists, and that being a scientist does not necessarily prevent or limit other life goals.

“I think after I graduate I can contribute my abilities to society,” Kwon reflects on her own potential. “Maybe I can make people have better lives.”

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Toward the end of her young life, Kelsey Gallagher told no one she had advanced cancer. As much as possible, she wanted a normal teenager’s life, not the sympathetic persona of a victim.

While taking palliative chemotherapy, she went to her high school prom, performed a leading role in a play, took classes at a community college, spent hours in the photography darkroom, practiced piano, painted, sculpted, made jewelry and even played three sets of tennis with a collapsed lung just weeks before she died in 2005, a month shy of her 18th birthday.

“She went off that cliff at 100 miles per hour,” recalls her father, Sean Gallagher, a software executive from Newtown, Pa., and a supporter of The Jackson Laboratory. “She was very active until the very end. We are still in awe. She was a student and artist — not a victim. There was never a complaint — only her mantra, ‘I feel good today; what do you want to do?’”

From the time she was diagnosed with Ewing’s sarcoma, a rare bone cancer, at age 11 as a sixth grader, Kelsey and her parents and three siblings endured an extreme physical and emotional ordeal in and out of the cancer ward at Children’s Hospital of Philadelphia.

First there were several cycles of chemotherapy to shrink a tumor in Kelsey’s leg, accompanied by hair loss, nausea, mouth sores and other brutal side effects. Then came a six-hour surgery to remove the remaining tumor from her fibula and more rounds of chemo.

After this grueling series of treatments was finally complete, all seemed well. Kelsey went to the 8th grade dance and went on to join the high school tennis team. “At that point we thought we were in pretty good shape,” Gallagher remembers. “We were pretty sure she was cancer free.”

Even so, a few years later, routine blood tests revealed the onset of leukemia, a secondary cancer likely caused by the chemotherapy treatments for the Ewing’s sarcoma. The leukemia required more harrowing medical treatments — total body irradiation, followed by a bone marrow transplant using marrow donated by her older sister, Thea.

Kelsey had a friend in the cancer ward whose Ewing’s sarcoma prognosis was much worse than her own, because the cancer had spread to the ribs and sinuses, where it was inoperable. “You just say, ‘This kid isn’t going to make it,’” Gallagher says. But that friend today is in complete remission.

The story of Kelsey Gallagher highlights the hope and the limitations of current therapies for cancer. The future of cancer treatment lies in more personalized, precise medicine, fueled by the latest scientific advances.
remission as an adult, while Kelsey’s cancer later recurred in her lungs and proved fatal. “I guess what it shows you is that these treatments are guesswork in a certain way,” Gallagher says. “At the end of the day, whatever we tried didn’t work, and we didn’t have the time to figure out what would work.” Gallagher was baffled by how two patients with the same cancer diagnosis and treatment could have such drastically different outcomes. He has since learned it’s because every person is genetically different, and so is his or her cancer. A treatment that works for one won’t necessarily work for another.

**Precision medicine with cancer avatars**

“The historical approach to treating cancer is kind of a one-size-fits-all treatment, a treatment approach that’s no different from one cancer patient to the next,” says Jackson Laboratory Associate Professor Kevin Mills, Ph.D., who researches cancer. “Now that we’re in the genome era, we can begin to think about a different way of treating cancer.”

One novel approach to finding the right therapies for each patient’s specific cancer is under way at The Jackson Laboratory. It relies on a special JAX mouse with an altered immune system that can tolerate implanted human tumors. “That mouse becomes your surrogate, your avatar, in the experimental space,” says cancer researcher Edison Liu, M.D., JAX’s president and CEO. A small piece of solid tumor is taken from a patient and transplanted into one mouse. As it grows, the tumor is subdivided and implanted into five more mice, and so on. “It’s almost like a photocopying process where you have many mice now all carrying a tumor from an individual patient,” explains Professor Carol Bult, Ph.D., scientific director of the cancer avatar program. “And you start treating those mice as if they were the patient.”

Various drugs and drug combinations are tested in the mice to see which ones work and which ones don’t. “And you say, aha, treatment A works, treatment B doesn’t work. And you do that testing in the tumor-bearing mice instead of on the patient,” Bult says. Unlike with patients, who receive treatments sequentially over long periods, multiple experiments can be done simultaneously in mouse avatars, accelerating the identification of effective treatment options. “So now we have the ability to actually test new ideas and new drugs in a matter of months, not in a matter of years,” says Susie Airhart, senior director of strategic opportunities and product development. Avatar experiments are also enabling researchers to correlate cancers to precise genetic sequences and mutations in the human genome. “We’re going to take all of the information we get, not just for one patient but for tens of thousands of patients, and we’re going to put all of that information into a database,” Bult explains. “And eventually we’ll have such a rich knowledge base that we won’t have to use those mice anymore. You put in the DNA sequence, and a doctor will get back a report that says patients with this DNA sequence pattern responded best to these treatments. That would be cheap enough and easy enough to apply virtually anywhere.”

“That’s where personalized medicine is going,” Gallagher says. “It’s to understand what works, why, and how we can be more precise, more exact, and minimize the difficulty that we sometimes put these children through. So next time, maybe if a Kelsey comes in the hospital, they’ll say, ‘Oh, you’re different than the last Kelsey and we’ll give you this particular protocol because of your immune system, because of the way that your genes are, the way that the cancer’s expressing itself.’” Gallagher learned about the cancer avatar program during a chance meeting with Ed Liu a few years ago in Bar Harbor, Maine, where his family has a summer home. “That’s exactly what Kelsey could have used,” he remembers telling Liu. “That kind of research is exactly the type of work that will lead to cures for children like Kelsey.”

To see a video of Kelsey’s story, visit www.jax.org/kelsey.
Alzheimer’s disease is the most common form of dementia, a progressive, age-related neurodegenerative disorder that can rob its victims of even the most basic functions of memory and meaning. As our population grows older, the incidence of Alzheimer’s is rising dramatically.

At The Jackson Laboratory (JAX), neurobiologist Gareth Howell, Ph.D., is working toward solutions.

“Alzheimer’s disease is the HIV-AIDS of our age,” he says. “It’s front and center in so many people’s lives, directly or indirectly. So far, our mouse models have enabled understanding aspects of the biology of the disease. But we need better models now to identify and test the drugs that will work best against Alzheimer’s disease.”

Recent studies have revived interest in therapeutics that have proven disappointingly ineffective in slowing or reversing the course of Alzheimer’s. Now, some of these same drugs have been shown to work better if the disease is caught and treated early on. So the Howell lab is using genetic and genomic approaches to identify changes that flag the earliest stages of the disease, before the characteristic amyloid plaques begin forming on the brain’s neural cells and before sticky tangles of broken protein strands begin congesting the neurons.

In addition, and working in partnership with colleagues at Cardiff University, Howell’s lab is using new analytic tools to untangle the genetic configurations that set the stage for Alzheimer’s. But Howell says it is clear that for many individuals, lifestyle plays an essential role in determining the risk of developing the disease.

“For some, it’s the intersection of genetics, lifestyle and aging that ultimately determines whether or not you get Alzheimer’s disease,” says Howell. So his team works with mouse models to measure the impact of diet and exercise, in combination with aging processes, on the risk of developing Alzheimer’s. “I felt we could make a real difference,” he says.

Howell, a native of Wales, completed his undergraduate studies in molecular biology at The University of Manchester, U.K. in 1993. Throughout his graduate studies, he worked at the Sanger Institute’s Wellcome Trust Genome Campus, in Cambridge, U.K. where he was part of the research team that helped sequence the first complete human genome. “Once we did that, we had the parts list, but we still didn’t really understand how the genome worked,” he recalls. “I saw then that what I really wanted to do with my career was to understand how genes in humans work by understanding how they function in a model organism, the mouse. And there’s only one place on the planet where you would want to go to learn mouse genetics, and that’s The Jackson Laboratory.”

He did a postdoctoral fellowship at JAX in 2003, then returned in 2005 as a research scientist. He was promoted to assistant professor in 2012.

At JAX, Howell became interested in the mechanisms that underlie the processes of aging and its attendant disorders. “When I first came back to JAX (in 2005), I worked in the lab of Howard Hughes Medical Institute Investigator Simon John, who was applying genetic and genomic approaches to understanding glaucoma. We did a lot of work in identifying the early stages of glaucoma in mice,” he says.

“STORY BY MEG HASKELL
PHOTOGRAPHY BY MARIE CHAO

Understanding Alzheimer’s

For some, it’s the intersection of genetics, lifestyle and aging that ultimately determines whether or not you get Alzheimer’s disease.”

— Gareth Howell, Ph.D.

“And as I began to think about transitioning to my own lab, I realized that similar approaches could be applied to studying Alzheimer’s disease. I felt that we could make a real difference in using the unique resources we have at JAX to learn more about Alzheimer’s disease.”

It’s a timely focus. Not only is the Baby Boom population of the 1940s and 1950s aging, but many in that group are also affected by obesity related to poor diet and inadequate exercise. And aging and obesity are both associated with loss of cognitive function, Alzheimer’s disease and other forms of dementia.

“So those people may have an increased risk of Alzheimer’s disease,” Howell says of the Boomer generation. “My major motivation is to prevent or slow its progress. It’s a disease of the elderly, so if you can prevent it or delay the onset by a decade or two, that’s a huge improvement in quality of life.”

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The typical mouse, both in the wild and in the lab, eats a “pretty healthy vegan” diet, Howell says — plant-based, high in vitamin and mineral content, low in fats and proteins. Howell’s lab worked with Simon John, who had developed a diet for mice that models the diet consumed in the western world. They have determined that mice fed their regular diet demonstrate healthy brain function for longer as they age compared to mice fed the western diet. Mice maintained on the western diet — which contains animal proteins, increased fats and decreased micronutrients — often develop a chronic state of inflammation in their brains and the rest of their bodies. This inflammation is an element of the immune response, an otherwise healthy reaction to allergens, infections and trauma. But on a sustained basis, inflammation causes problems of its own.

Lifestyle factors alter immune responses in the brain

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“Our hypothesis is that these immune responses we’ve been seeing in the brain, and systemically, play a major role in ultimately leading to brain dysfunction, including cognitive decline and an increased risk for Alzheimer’s disease,” Howell says.

In related studies, mice that are allowed to exercise normally by running on a spinning wheel maintain a healthy cognitive function longer than those that are allowed only limited activity, Howell notes, and their brains are slow to develop the amyloid plaques associated with Alzheimer’s disease, compared with their more sedentary peers.

All of these changes in the mouse brain tissue can be tracked using high throughput genomic approaches, Howell says, particularly in the regions associated with learning and memory. Sequencing technology allows Howell and his team to determine which mouse genes get altered in response to genetic variation, aging, diet and exercise, and to make precise comparisons to human aging and disease.

Emerging genomic engineering technologies, such as the CRISPR/Cas9 gene editing tool, are allowing researchers more precision in building mouse models that should be more predictive of Alzheimer’s disease, allowing for more accurate testing of potential therapies.

“We’re in the middle of a revolution in genomic research,” Howell says. “Two major things are happening. One is that we can very easily sequence many, many human genomes and identify variants that are causing disease or increasing susceptibility to disease. The second is our ability to precisely manipulate the mouse genome. At a rate not previously thought possible, we are identifying variants in humans, modeling the consequences in mice to understand exactly how changes in our genome increase our susceptibility for complex diseases like Alzheimer’s.”
According to Paul Robson, Ph.D., director of single cell genomics at The Jackson Laboratory for Genomic Medicine, “if you want better insight into how biology works, you need to look at its fundamental unit.”

That unit is, of course, the cell. Until recently, however, researchers have studied biological tissues in bulk preparations containing huge numbers of cells. It is very difficult to isolate and work with individual cells, and each cell contains only a tiny amount of material, far too little for most research methodologies.

Genomic medicine requires deep understanding of how the genome functions in various healthy and diseased tissues, and with single cell genomics we now have the ability to decipher that function one cell at a time.

Taking advantage of recent advances in automation and microfluidics — systems that can manipulate very small volumes of liquid — Robson and other researchers can now effectively analyze individual cells.

The new capability provides many opportunities for discovery. Analyzing individual cells during development, for example, will reveal the precise time at which cells achieve their unique identity and function within the body, and how disruption of the development process might contribute to disease. At this time, cancer is a prominent focus. For example, it is well established that different cells are genetically different within the same tumor, and it is now possible to track genetic mutations on a cell-by-cell basis throughout the tumor. Also, the study of which genes are expressed and how much they are expressed within each cell provides the opportunity to identify potential drug targets.

Many fields of biology will be impacted by single cell genomics. JAX will reap tremendous benefits by having in-house technology and expertise, and is applying single cell genome sequencing in many areas.
Leaders from all areas of the healthcare industry — insurers, hospital systems, physicians and providers, researchers, precision medicine advocates and more — gathered at The Jackson Laboratory for Genomic Medicine for the second annual Forum on Healthcare Innovation. The two-day event featured presentations, panel discussions and networking as participants discussed the healthcare innovations most needed to achieve better medical outcomes at lower cost.

*Photograph by Marie Chao*