



Masonic Cancer Center News

A publication for those who support cancer research, education, and care at the University of Minnesota

The tale of Sleeping Beauty

How a fish project begun in 1988 rocked the genetics world and spawned a generation of breakthrough cancer research

Perry Hackett, Ph.D., would have hated to see all his team’s work go to waste.

The University of Minnesota professor was charged by the Minnesota Department of Natural Resources in the 1980s with re-engineering fish that would grow faster and larger. He succeeded, producing fish that grew up to three times their normal size. But the public balked at the idea of introducing transgenic “super fish” into the wild, and the whole project was shut down.

Still, the idea of engineering a safe, fast-growing food fish had captured Hackett’s imagination, and the team persisted. In their work they identified a long dormant—ahem, 14 million years dormant—gene in salmon that they could resurrect and use to introduce growth genes into a fish chromosome. This particular gene, basically a “jumping gene,” could bounce from one place to another in the genome.

Photo by Scott Strebbe



In 1997, the work that led to this “jumping gene” became known as the Sleeping Beauty Transposon System, and today it is considered one of the most important and prolific research yields in the history of the University of Minnesota—and not just for

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Born from a project to produce larger and faster-growing fish, the Sleeping Beauty Transposon System developed in the lab of Perry Hackett, Ph.D., has led to the discovery of many cancer genes and even cancer therapies.

Growing accessibility of DNA sheds light on childhood cancers **page 4**

A homegrown imaging technique helps to fight breast cancer **page 5**

Masonic Cancer Center joins VP’s Cancer Moonshot **page 7**

The tale of Sleeping Beauty *(continued from cover)*

fish. One of its most promising applications is in the field of oncology, where it's used in the lab to identify genes that cause cancer, but also as a delivery vehicle that carries therapeutic genes into cells, thus allowing a person's immune system to attack and kill invasive cancer cells. This is 21st century gene and cell therapy.



Photo by Jim Bovin

David Largaespada, Ph.D., has used the Sleeping Beauty technology to identify hundreds of potential cancer-causing genes.

“We were very excited about the discovery of SB and really believed it would be hugely important,” recalls Hackett, a Masonic Cancer Center member and genetics professor in the U’s College of Biological Sciences. “But even in that excitement, we didn’t realize how big it would become.”

So big that, last year, two biotech companies licensed a cancer treatment strategy that was developed with the Sleeping Beauty system for more than \$100 million. A few months later, pharmaceutical giant Merck upped the ante, paying those two companies nearly \$1 billion for the rights to the new treatment. (The companies were not licensing the treatment from the U, but the U does hold the Sleeping Beauty patents.)

Ripple effect

By awakening this gene from its evolutionary sleep (hence the “Sleeping Beauty” moniker), Hackett had discovered a way to move a precise DNA sequence to another host’s DNA sequence in a predictable way. When his paper was published in 1997, it rocked the genetics world and in 1999 led to a

grant from the Arnold and Mabel Beckman Foundation that funded the Beckman Center for Transposon Research and the work of University professors Scott McIvor, Ph.D., David Largaespada, Ph.D., and founding director Steve Ekker, Ph.D.

The Beckman Center is now known as the Center for Genome Engineering; in 2008, Daniel Voytas, Ph.D.—“a heroic figure, an international rock star,” says Hackett—came to Minnesota to lead it.

“I was really drawn to the University by Perry Hackett and others here who had so much enthusiasm for Sleeping Beauty, but also for the field of genetics,” says Voytas, who, as a plant scientist, does not work directly with Sleeping Beauty, which is used only in vertebrates.

According to Voytas, the effects of Hackett’s Sleeping Beauty discovery have rippled far beyond University borders and across the world.

“Sleeping Beauty has now been distributed to thousands of researchers,” he says, noting that the Center for Genome Engineering shares Sleeping Beauty free of charge with other scientists interested in using it for basic research.

Finding suspect genes quickly

Largaespada, the Masonic Cancer Center’s associate director for basic sciences and holder of the Hedberg Family/Children’s Cancer Research Fund Chair for Brain Tumor Research, was an undergrad at the U when he first met Hackett in the mid-1980s. Largaespada’s subsequent work in the field of cancer research convinced him, he says, that if they had the right transposon (“jumping gene”), it could be a powerful tool for studying cancer.

When he returned to the U to take his faculty position in 1996, he read Hackett’s Sleeping Beauty paper before it was published and had his “a-ha!” moment.

“It was just the tool I needed to use in my mouse genetics work,” Largaespada recalls.

In his lab today, Largaespada's team works to identify cancer-causing genes. It's daunting research, one he likens to the search for a murderous criminal in a town of 30,000 people.

"You could call up each of the 30,000 on the phone and interview them," he says, "but that's going to take a very long time. What you need is a tool to help you find the best suspects quickly. That's what Sleeping Beauty is for us."

Using Sleeping Beauty, Largaespada and his team study cancer genetics with an end goal of developing genetic screening tests and new treatments for solid tumor cancers such as colorectal, sarcoma, prostate, and lung cancer.

"Broadening our basic scientific knowledge of how cancer develops will really be the basis of the important breakthroughs in treatment," Largaespada says. "In that way, our approach to cancer has really undergone a fundamental shift, as new therapies are developed in response to very specific genetic mutations."

Even more significantly, Largaespada adds, Sleeping Beauty has implications for treating other diseases as well. It has been used, for instance, as a tool to deliver a gene that can cure hemophilia in mouse models.

Powerful legacy

Scientists involved at this level of genetic research tend to know one another and follow closely the work of their colleagues. It's amazing, says Largaespada, to see how

many careers and companies have been spawned by the Sleeping Beauty technology and other work from the U's Center for Genome Engineering.

"Companies doing gene editing on pigs and cows, companies working on gene editing to make better plants for agriculture, companies developing successful new cancer drugs ... all of this really started with Perry and the discovery of Sleeping Beauty," Largaespada says.

Voytas agrees.

"As scientists, we launch projects out of curiosity, not necessarily seeing in the moment that what we've discovered might meet needs far flung from our own projects, but that's what happened here," he says.

So, a quest for bigger fish led Hackett to Sleeping Beauty, which led the U to philanthropy from the Beckman Foundation, which funded the Center for Genome Engineering, which is now enabling scientists to develop breakthroughs not just in cancer but in agriculture and livestock, which will help feed the world's booming population.

"No one could have predicted just how big Sleeping Beauty would become," Hackett says. "Just as it takes a village to raise kids to their full potential, that's what University of Minnesota researchers have done with Sleeping Beauty."





Exploding data, exploding possibilities

The constantly growing availability of genetic information for research gives a Masonic Cancer Center epidemiologist that 'kid in a candy store' feeling

Photo by Scott Strebbe

The exploding accessibility of DNA and other data that can help shed light on childhood cancers makes epidemiologist Logan Spector, Ph.D., think of a certain '70s pop tune.

"You know that Carpenters song, 'We've Only Just Begun?' Pretend I'm singing that," Spector says.

With support from Children's Cancer Research Fund, Spector and his colleagues are beginning to parse a universe of data that can help predict, prevent, and fight pediatric cancers. What they've found so far is the tip of the iceberg, Spector says.

Much of Spector's research takes the form of case-control studies: comparing people who have a certain disease with people who don't. Sometimes those studies include examining both groups' DNA; other times they involve scrutinizing different slices of "big data."

One of the Masonic Cancer Center member's recent papers—analyzing 13 studies involving a total of 33,571 people and coauthored by Erin Marcotte, Ph.D.—identified an apparent link between prelabor Cesarean delivery and acute lymphoblastic leukemia. The reason isn't known but might have to do with exposure to both the mother's stress hormones and to her unique microbes during vaginal delivery, Spector says.

"That's why we originally looked at that, because there's going to be a microbiome difference [between vaginal and C-section deliveries], and leukemia is a cancer of the immune system," he says. "How that immune system gets stimulated is thought to play a part in leukemia."

Currently, he's conducting the first genome-wide association study for hepatoblastoma, looking for genetic variants that

increase the risk of that cancer. His team is also doing exome sequencing—"where we look at the 1 percent of the genome that codes for proteins"—for people who have osteosarcoma.

"We're doing more agnostic searches, meaning we don't give any preconception to what we may find. And it regularly turns up genes that were on nobody's radar," he says. "[It's] like being a kid in a candy store—only instead of candy, we have DNA."

The sheer volume of data available on cancer patients is skyrocketing. Storing and analyzing all of the information is expensive, however, so support from Children's Cancer Research Fund and other philanthropic organizations is invaluable.

Spector, who holds the Suzanne Holmes Hodder Chair in Pediatric Cancer Research, dreams of launching a long-term cohort study of 10,000 families at the U, and his team has started to make it happen. "There's a certain power to collecting data within families: You'd have the ability to look at familial genetics, at intergenerational transmission of risk," he says.

"We're designing this mainly around cancer, because cancer epidemiologists are the ones starting it. But we would collect cardiovascular outcomes, diabetes, you name it," he adds.

One potential recruitment site: The Minnesota State Fair, where Spector and his colleagues have gathered epidemiological data since 2014. "On max attendance days, it's more crowded than Tokyo, and it's a wide cross-section."

It's a privilege to play a part in fighting childhood cancer, Spector says: "That moment when you're just about to see what the world is telling you—it's exciting."

An innovative approach to magnetic resonance imaging (MRI) developed at the University of Minnesota is showing tremendous promise in fighting advanced breast cancer.

Masonic Cancer Center member Deepali Sachdev, Ph.D., is using a technique called SWIFT (SWEEP Imaging with Fourier Transformation) to effectively scan lung tissue that couldn't be read using traditional MRI—yielding information that may prove invaluable in treating metastatic breast cancer.

The SWIFT technique that Sachdev and her colleagues are adapting—with critical support from the Regis Foundation for Breast Cancer Research—could

soon be used for imaging metastasis in bone, too. (Lungs and bones are the two most common sites for breast cancer metastasis.)

The goal: to evaluate the effectiveness of different drugs on women who have stage IV breast cancer.

Sachdev is using the SWIFT technology—the brainchild of Masonic Cancer Center member Michael Garwood, Ph.D., of the U's world-renowned Center for Magnetic Resonance Research—to identify biomarkers in patients and track their response to specific treatments. It's in line with an emerging

A better look at cancer

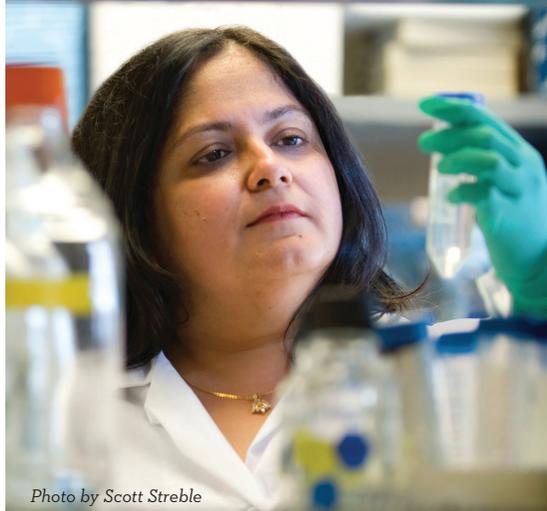


Photo by Scott Strebler

Deepali Sachdev, Ph.D., is conducting critical research focused on improving treatment outcomes for women who have advanced breast cancer.

emphasis on precision medicine: tailoring treatments to individuals for the best possible outcomes.

“Not every patient is going to respond to every drug,” Sachdev explains. “So we need to develop methods where you can select patients who might respond to a [particular] therapy.”

So far the research has been conducted in mice; she's optimistic that, with help from oncologists, it will be readily adaptable for humans.

Sachdev is grateful to the Regis Foundation for supporting a research concept that many funding agencies would have deemed “too risky,” she says. “This is cutting-edge technology that has not been used in this way before.”

Regis CEO Dan Hanrahan says it was an easy decision. “We have great confidence in and admiration for the good work happening at the U—and it's local,” he says. “It wasn't difficult at all for us to say yes.”

Sachdev believes the technique could have wider applications, perhaps in treating other solid tumors such as ovarian cancer.

“My hope is that one day this could be used routinely in medical practice to help select patients for [specific] therapies,” she says.

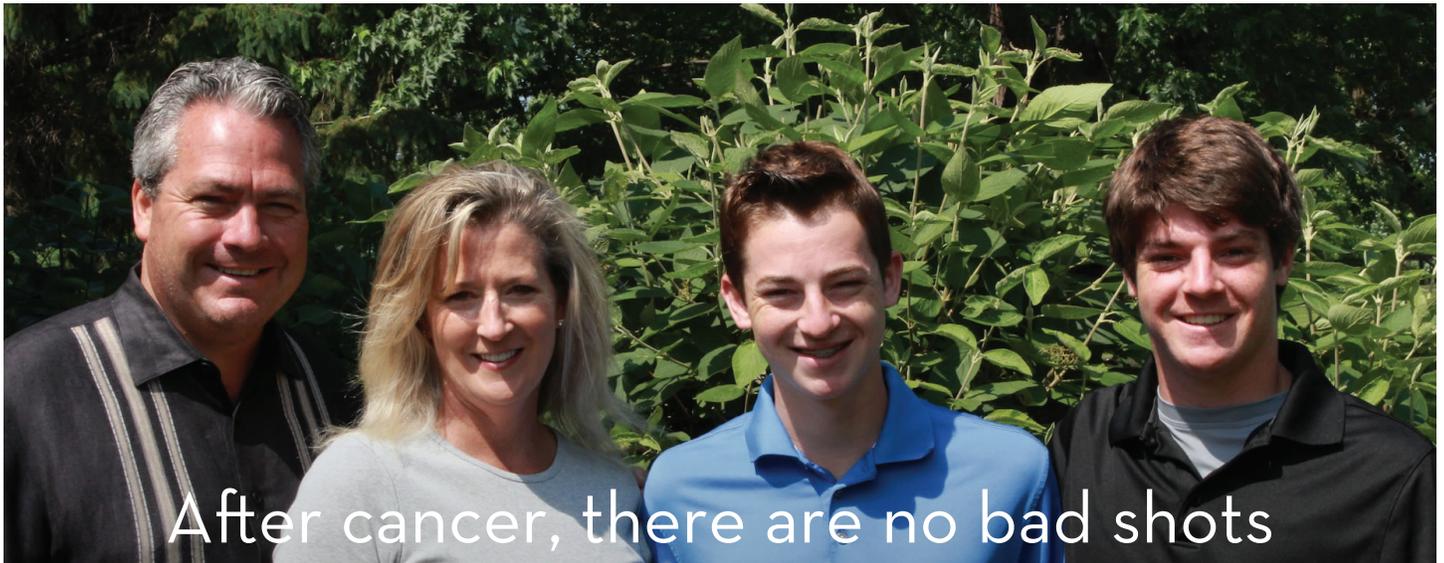


Clip for the Cure

Saturday, October 15, at all Regis corporate salons

Ten percent of the proceeds from every haircut will benefit the Regis Foundation for Breast Cancer Research, which supports efforts in prevention, early diagnosis, and treatment. For a list of participating salons, or to donate to the cause, visit

clipfortheure.org.



Mike Neeson makes it a priority to enjoy every day with his wife, Patty, and sons, Ben and Nick. "Because of the donations, because of the work, there are still four people in this photo where there easily could have been three," he says.

For Mike Neeson, any day on the golf course is a great day.

Neeson says he has always been a positive person. "But getting a little dose of your mortality is not necessarily a bad thing," he adds.

Neeson had barely been to a doctor in his life before the spring of 2008, when the 45-year-old husband and father of two was found to have a large mass in his lower colon. His doctor referred him to Masonic Cancer Center member and University of Minnesota Department of Surgery chairman David Rothenberger, M.D., who confirmed that the mass was colon cancer, and that it had spread to Neeson's seminal vesicle, prostate, and lungs.

In the following seven years, Neeson went through radiation, more than a year's worth of chemotherapy, and numerous surgeries—and still, he insists on being optimistic. He's so grateful to his care team that he volunteers to speak to others who are facing the same procedures he has had. He and his wife, Patty, also help to raise money for colon cancer research at the Masonic Cancer Center.

In fact, Masonic Cancer Center research is behind many stories of treatment successes like Neeson's. And behind that research is a legion of steadfast supporters, including the annual Killebrew-Thompson Memorial Golf Tournament in Sun Valley, Idaho. This event has resulted in nearly \$8 million in research funding for the Masonic Cancer Center over the past 40 years, which has been leveraged at least fivefold by federal and industry support.

The Killebrew-Thompson Memorial event has supported many novel investigations over the years, including one exploring the potential of a natural killer cell-based therapy. Natural killer cells are important mediators of the body's natural anticancer immune response. Masonic Cancer Center researchers Daniel Vallera, Ph.D., and Jeffrey Miller, M.D., have discovered a way to enhance natural killer cells' effectiveness so they destroy cancer via a drug called TriKE.

Scaling up production of TriKE for preclinical and Phase I studies is very expensive, and federal funding doesn't cover the cost, says Tucker LeBien, Ph.D., associate vice president for research of the University's Academic Health Center.

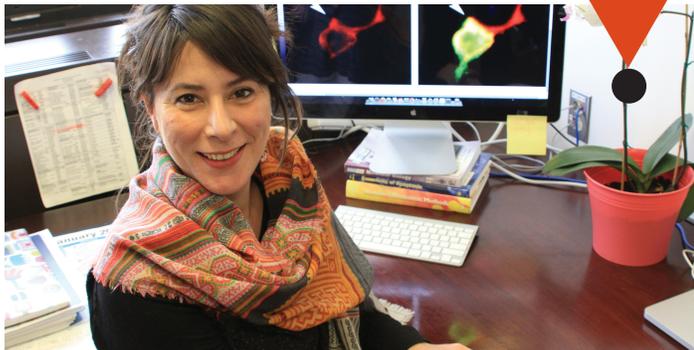
"The flexibility afforded by the Killebrew-Thompson Memorial funding is essential for this type of work," LeBien says.

The researchers first have targeted blood cancers such as leukemia and lymphoma with this new therapy and eventually plan to expand the work to include solid tumors like colon cancer. And that's great news for those people following in Neeson's footsteps.

Neeson himself is back to golfing with his buddies—who first ask how he's doing, then ask about his golf game.

"I'd say, 'It's perfect! I haven't hit a bad shot all year,'" Neeson quips. "Then they'd kind of roll their eyes. I try to tell people, it could go in the sand trap, it could go out of bounds, it could go in the water—there are no bad shots."

Biomarker may predict recurrence in women who have endometrial cancer



Martina Bazzaro, Ph.D.

Most cases of endometrial cancer, the most common gynecologic cancer in the United States, are diagnosed early and have good a prognosis.

But some women with early-stage, low-grade endometrial cancer experience a recurrence—and the reasons are not entirely clear. When the cancer recurs, it's often resistant to chemotherapy and can be deadly.

Now new research from the Masonic Cancer Center suggests that there's a biomarker—specifically deubiquitinating enzyme (DUB) USP14—that may indicate a risk of recurrence in women who have endometrial cancer. The research was supported by the Minnesota Ovarian Cancer Alliance, Randy Shaver Cancer and Community Fund, and U.S. Department of Defense Ovarian Cancer Research Program.

Martina Bazzaro, Ph.D., a U medicinal chemist and cancer biologist, and her team have discovered that women with high levels of USP14 are seven times more likely to experience a recurrence than women with low levels of it.

DUBs historically have been linked to cancer initiation, progression, and chemotherapy resistance. Thus, inhibiting certain DUBs has been proposed as a targeted therapy for cancer. This is the first time, however, that DUBs are being used as a cancer biomarker.

An assistant professor in the Medical School's Department of Obstetrics, Gynecology, and Women's Health, Bazzaro is currently leading an international effort to validate the findings in a larger cohort study involving low-risk endometrial cancer patients.



Mark your calendar to support the Masonic Cancer Center on Minnesota's day of giving! GIVE.UMN.EDU

Shooting for the moon

When the White House called, the Masonic Cancer Center answered.

Vice President Joe Biden convened a national Cancer Moonshot Summit, inviting individuals and organizations across the country to come together to double the rate of progress toward curing cancer. The Masonic Cancer Center and University of Minnesota Health hosted the conversation locally on June 29.

More than 500 researchers, oncologists, care providers, philanthropists, data and technology experts, advocates,

patients, survivors, and family members gathered at the University of Minnesota to generate ideas and make commitments that will accelerate advances in cancer research.

And the conversation continues. Join the Minnesota Cancer Moonshot Summit Google Group—dedicated to finding novel and collaborative ways to catalyze our efforts against cancer—to share opportunities, ask questions, get involved, and make a difference at cancer.umn.edu/cancer-moonshot.



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Thanks a billion!

Our Vision 2017 fundraising campaign to advance medicine and promote health at the University of Minnesota, including the Masonic Cancer Center, was a huge success. It was so successful, in fact, that we surpassed our \$1 billion goal a year early. Here are a few reasons we're celebrating.

\$165,475,758

in private gifts made to cancer-related research, education, care, and outreach at the University of Minnesota



\$65 million

largest gift made during the campaign, from Minnesota Masonic Charities in 2008 (it was also the largest gift made to the University of Minnesota ever)



31,756

people gave to cancer

\$36 million

given by Children's Cancer Research Fund during the campaign



84,858

gifts made to cancer



3,000+ *guests*

who attended University of Minnesota Foundation-sponsored cancer-related events since 2010

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To find out how your gift can make a difference, please contact:

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