Curtain up

A new drug for pancreatic cancer takes the stage for clinical trials, thanks to the Masonic Cancer Center experts who developed it

What does it take to get to that moment in a clinic when a doctor gives a patient a compound never before used in modern medicine? The story of Minnelide, an investigational drug for pancreatic cancer patients now in a Phase IA clinical trial at the University of Minnesota, illustrates just how complex and exhilarating that journey can be.

“What we did here with Minnelide, we did at the speed of light,” says Gunda Georg, Ph.D., director of the College of Pharmacy’s Institute for Therapeutics Discovery and Development (ITDD) and a member of the Masonic Cancer Center. “Going from drug design to clinical trial in just five years is almost unheard of. Ten years is more typical.”

While Georg played a key role, the Minnelide team stretched across campus and beyond, encompassing laboratory investigators, veterinarians, clinical physicians, attorneys, administrators, philanthropists … the group would need a pretty big stage if they all gathered together.

“Each person has their own core area of expertise,” says Georg, “but bring them all together, and you can do powerful things.”

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Ancient mystery

To begin at the true beginning of Minnelide, we’d have to go back hundreds of years to China, where healers used the thunder god vine, or lei gong teng—a perennial vine native to Korea, Japan, and China—to treat rheumatoid arthritis and other autoimmune diseases associated with inflammation.

Now flash forward to 1972, when scientists discover that an active compound within the thunder god vine, dubbed triptolide, not only relieves swelling but also stops cell growth in its tracks. They don’t know yet how it works, but it does. So, scientists wonder, could they harness the power of triptolide to stop the growth of cancer cells?

Georg, who holds the Robert Vince Endowed Chair and the McKnight Presidential Chair in Medicinal Chemistry, was brought to the U nine years ago to create the ITDD, a place dedicated to discovering and developing new drug therapies. (She is also a professor and head of the Department of Medicinal Chemistry.)

At that time, the Masonic Cancer Center’s Ashok Saluja, Ph.D., was studying the protein HSP 70 in his lab and had discovered that it helped pancreatic cancer cells grow; with additional investigation, he found that triptolide, an inhibitor of HSP 70, stopped pancreatic cancer cell growth. But his “aha” moment was quickly replaced with another challenge: to turn triptolide into an injectable drug that might help stop the growth of pancreatic cancer cells in humans, it would have to be water-soluble. It wasn’t.

Enter chemist Georg.

“The molecule Dr. Saluja had isolated was basically a grease ball,” Georg explains. “We had to figure out a way to make it both water-soluble and patentable. You can’t invest millions to bring a drug to market without patent rights.”

Georg and her team actually solved the water-soluble challenge in short order and named the new compound “Minnelide” (Minnesota + triptolide). Then it was back to the lab.

Crossing the Ts

Saluja’s findings in the lab—supported by the Eugene C. and Gail V. Sit Chair in Pancreatic and Gastrointestinal Cancer Research, Dr. Robert and Katherine Goodale Pancreatic Cancer Research Fund, and Wellner Family Fund in Pancreatic Cancer Research—were nothing short of amazing. In one mouse study, 21 days of Minnelide treatment made large pancreatic tumors undetectable. Professional journals published the exciting results, and patients who had pancreatic cancer, which Saluja calls “the worst cancer known,” started lining up to try Minnelide.

But there was still much work to be done. Triptolide, which has to be meticulously
isolated from the thunder god vine, is expensive to produce, so the team needed more money to produce a large batch. The U’s Center for Translational Medicine, under the leadership of Masonic Cancer Center member Bruce Blazar, M.D., helped perform these tasks. They also had to modify the drug design to ensure shelf-life stability. Then there were toxicology studies to be done and manufacturing protocols to develop. Across campus, lawyers worked on gaining a patent and then licensing Minnelide.

“The [ITDD] was the lynch pin,” explains Georg, “a place where all the many pieces of the puzzle came together. So in that way, Minnelide is our poster child, proof that this collaborative approach works, and can work quickly.”

Clinical trial

Last year it was finally time for hematologist/oncologist Edward Greeno, M.D., to take center stage as he enrolled about 30 people with pancreatic cancer for the Phase IA Minnelide clinical trial conducted at the U and a partner institute in Arizona.

“It’s been really exciting to get Minnelide into clinical trial,” says Greeno, who is medical director of the Masonic Cancer Clinic and executive medical director of University of Minnesota Health Cancer Care. “We’ve seen tumors shrink at this early stage, so, yes, I think people should be excited about the potential.”

Greeno thanks the altruistic patients who participate in clinical trials.

“All of these patients have failed every other existing therapy and know they might not get any benefit from the trial, but their participation yields immense benefits to patients who come after them.”

From ancient China to the Masonic Cancer Clinic—you could say that Minnelide has been centuries in the making. But acting in concert, this Masonic Cancer Center team moved quickly to turn hypothesis into reality, basic science into a new drug to be wielded in the war on cancer. Researchers eventually hope to evaluate Minnelide’s efficacy against not only pancreatic cancer but also breast, brain, liver, prostate, and blood cancers.

“This was a natural product that had been used for a long time,” says Georg of triptolide, “and there are many more compounds out there. But which ones should we pursue? Which ones will be viable?

“It all comes down to that collaboration between the different specialties and, for that, the U is one of the best, most comprehensive centers in the country.”
The new, state-of-the-art University of Minnesota Health Clinics and Surgery Center opened its doors in February. The 342,000-square-foot facility houses 37 medical specialties, as well as lab and imaging services, a retail pharmacy, a café, an outpatient surgery center, and other clinical services. The Masonic Cancer Clinic (including blood and marrow transplant, gynecologic oncology, medical oncology, and surgical oncology), Breast Center, and Advanced Treatment Center (including infusion and apheresis) make up the building’s second floor.

Housing so many specialties under a single roof promotes greater communication between the various medical specialists who may be part of each patient’s care team. In fact, the building incorporates several “collaboration spaces” for care providers to discuss patients’ care plans.

The Clinics and Surgery Center also makes prominent the latest research and medical innovations through its “Discovery Experience.” Visitors will find video monitors promoting clinical trials and other research opportunities in the center, as well as kiosks throughout the building that offer quick access to StudyFinder, a U of M website that highlights health research opportunities for patients and volunteers.

Other enhancements to the patient experience include an easier-to-access location (just off of I-94), extended clinic hours, convenient scheduling, easy check-in and check-out, and improved valet parking services. Learn more [here](mhealth.org/clinics-and-surgery-center).
There were no gowns, mortarboards, or long speeches, but Douglas Yee, M.D., still felt a sense of great accomplishment when three drugs recently “graduated” from the I-SPY2 clinical trial—proving effective enough to warrant further study.

Launched in 2010, the multicenter study was designed to compare the effectiveness of several breast cancer medications simultaneously. Yee, who directs the Masonic Cancer Center, University of Minnesota, also coleads the national committee in charge of selecting drugs for the trial.

The I-SPY2 trial is unique among clinical trials. Typically, a clinical trial examines one drug at a time and often involves five years or more of collecting data—followed by another five years or so to analyze the treatment’s effectiveness. In the I-SPY2 trial, multiple drugs are approved for testing simultaneously. Additionally, each participant’s tumor is profiled according to its molecular signature and then matched with the drug that researchers believe will be most effective in treating it.

Typically, women with breast cancer receive chemotherapy after surgery. In the I-SPY2 trial, women first receive the standard-of-care chemotherapy and may also receive another drug—and then surgery. The goal is to increase “pathologic complete responses,” Yee says, or total elimination of the tumor when examined by a pathologist.

The trial has tested roughly 15 chemotherapy drugs since it started. Medications are evaluated after they’ve been in use for six months, and the least effective medications are dropped from the study. Six drugs are currently being tested in the 17-site trial.

So far, Yee says, the “graduated” drugs have doubled the chances of participants achieving that “pathological complete response”—suggesting that the new drugs are improving responses to the standard-of-care treatment.

U of M chemistry professor Lee Penn, Ph.D., was diagnosed with triple negative breast cancer, a particularly aggressive form of breast cancer, in July 2011. When her surgeon recommended she become involved with the I-SPY2 study, Penn signed up.

“It seemed like a way to make some kind of positive contribution in the face of a horrible situation,” she says.

After her treatment, doctors found no live cancer cells in Penn’s tissue. “It was the best result you could possibly hope for,” she says. “I’m really lucky, right? I not only have excellent health care, but I’m right here on campus, one of the home sites for the I-SPY2 trial.”

Yee finds the many positive outcomes he’s seeing encouraging. And he’s particularly pleased with the speed of the trial: “To me, it demonstrates that we can identify active agents that are effective in the treatment of breast cancer in a much shorter timeline.”

The study—assisted by the Masonic Cancer Center’s Clinical Trials Office, which is supported by Minnesota Masonic Charities—also confirms what many researchers have been finding: breast cancer is heterogeneous, and diverse approaches are required to address its different manifestations, Yee says.

Yee and his colleagues are now developing an arm of the study called I-SPY2 Plus, which will allow doctors to switch drugs if a patient isn’t responding favorably to her assigned treatment.

Lee Penn, competing in a bike race last fall, worked hard to get back to a strong level of fitness after breast cancer treatment.
Register for the 11th Annual Cancer Survivorship Conference

Saturday, April 23
8 a.m. to 1:30 p.m.
McNamara Alumni Center
University of Minnesota

A cancer diagnosis can alter the landscape of your life. Join us for this educational conference that focuses on questions and issues survivors and their families often face after cancer treatment or stem cell transplantation.

The event is free, but registration is required. Visit z.umn.edu/mccevents to learn more or sign up.

What do you say to someone who saved your life? Cancer survivor Travis Moore (right, in photo below) admits he was speechless when he reconnected with University of Minnesota Masonic Children’s Hospital’s John Wagner, M.D., in February, 20 years after he received an experimental bone marrow transplant under Wagner’s care.

Moore, who is now 30 years old and a globe-traveling fisheries scientist, made a visit to Minnesota from his Florida home to thank Wagner and other members of his care team—and to give hope to kids who are battling leukemia today.

Wagner, a renowned pioneer in blood and marrow transplantation, says the therapy that Moore received 20 years ago provided a framework for the leukemia therapies patients receive today.

The National Institutes of Health is tapping University of Minnesota experts to better assess the impact of environmental exposures on children’s health and development.

The Children’s Health Exposure Analysis Resource (CHEAR) has three primary goals: to develop new tools to enhance research on how the environment affects disease in children; to take a closer look at exposures during in utero development and their impact on future conditions; and to foster collaboration and enhance this area of study.

Masonic Cancer Center members Stephen Hecht, Ph.D., and Lisa Peterson, Ph.D., are leading the U’s $5.1 million portion of the study, which is focused on providing wider access to laboratory data and analyses and expanding collaborations.

Environmental exposures are a leading cause of morbidity and mortality for mothers and children worldwide. Numerous factors—from chemical and biological factors such as air pollution, pesticides, and infectious diseases to psychosocial factors such as education, stress, and neglect—can play a role.

Exposures during crucial developmental windows, including conception and pregnancy, early childhood, and puberty, can have long-lasting effects.

Projects through CHEAR are designed to provide researchers with an expanded range of tools to accurately measure, record, and analyze environmental exposures. This will help improve understanding of how these exposures change human biology to affect child health and development and inform strategies to reduce the risk of childhood illnesses and disabilities.
In the mid-1990s, University of Minnesota graduate Jack Henningfield ('74 B.A., '77 Ph.D.) and a colleague published an article in the New England Journal of Medicine theorizing that if nicotine levels in cigarettes were reduced below a certain threshold, they would no longer be addicting. It was an intriguing premise—but largely unproven and unlikely to be tested by the companies that made cigarettes.

In 2009, however, Congress passed the Tobacco Control Act, giving the U.S. Food and Drug Administration (FDA) the authority to regulate tobacco products, including the amount of nicotine in cigarettes.

Around the same time, Masonic Cancer Center member and tobacco researcher Dorothy Hatsukami, Ph.D., a professor of psychiatry at the U, convened a meeting of tobacco control researchers, policymakers, and government agencies to assess the feasibility of reducing nicotine in cigarettes as a national policy measure.

While the science supported such an approach based on results from prior studies conducted by Hatsukami and others, more research was needed. Would lowering the amount of nicotine reduce addiction? And what reduction was required to do so?

In 2013, Hatsukami co-led a year-long study of 840 smokers at 10 sites across the United States. Researchers provided participants with cigarettes that either matched the nicotine levels of their preferred brand, or switched them with one of five investigational cigarettes with lower nicotine levels—a reduction that ranged from 66 percent less to 98 percent less. Participants in the double-blind study were asked to track the number of cigarettes they smoked each day for six weeks.

On average, the study showed, participants given lower-nicotine cigarettes smoked less per day at the end of the six weeks. “Cigarettes with lower nicotine content, as compared with control cigarettes, reduced exposure to and dependence on nicotine, as well as craving during abstinence from smoking,” the study’s authors wrote. This study was published in the New England Journal of Medicine last fall.

Quit attempts were most likely to occur when the nicotine content dropped to 0.4 mg per gram of tobacco, Hatsukami says. That level (roughly 2 percent of the nicotine dose found in a regular cigarette) no longer delivered enough nicotine to the brain to make smokers want to smoke more cigarettes.

“If you reduce dependence on cigarettes, then you are likely to reduce the number of people who smoke,” Hatsukami says.

Hatsukami’s group is now looking at whether it would be best to reduce nicotine content in cigarettes to minimally addictive levels immediately or more gradually. Then, she adds, with the mounting research data, it will be up to the FDA to decide if, when, and how to enact standards for lower nicotine levels in cigarettes.
When it comes to cancer research, hundreds of heads are better than one. That was the belief held by founders of the University of Minnesota Cancer Center, as it was originally named. Their vision: bring scientists together to collaborate and advance research faster—and get cancer breakthroughs to patients as quickly as possible.

Twenty-five years later, today’s Masonic Cancer Center, University of Minnesota, has become one of the elite centers in the country. It’s one of 45 National Cancer Institute (NCI)-designated Comprehensive Cancer Centers. Among its 565 members representing dozens of academic disciplines are some of the world’s leaders in research on blood and marrow transplantation, childhood cancers, cancers of the breast and bone, cancer genetics, tobacco control, immunology, therapeutics development, and epidemiology.

As the Masonic Cancer Center marks its silver anniversary, researchers are building on their legacy of leadership—having performed the world’s first successful bone marrow transplant in 1968—to continue finding cancer causes, identifying better therapies, and improving outcomes to create and provide the gold standard in cancer care.

See highlights from the Masonic Cancer Center’s first quarter-century at z.umn.edu/mccmilestones.