University of Michigan researchers have launched the first clinical study to determine whether it’s safe to use gene therapy to treat chronic cancer pain. The study – a prime example of translational research – marks a pivotal moment. Researchers now have an opportunity to learn whether what they’ve discovered in the laboratory applies in humans.

The Concept: Targeting the Pain

Physicians have many ways to treat chronic pain, but some medications produce side effects strong enough to prevent patients from using these drugs at fully effective doses. U-M researchers are working on ways to use gene therapy to deliver pain relievers to precisely targeted sites within the body.

“Because the body uses the same receptors and neurotransmitters in many different places in the nervous system, medications we use often result in off-target effects that limit the dose we can administer,” says David Fink, M.D., Robert Brear Professor and chair of neurology at the U-M Medical School. “Our goal was to develop a gene-transfer vehicle – a vector – that releases substances precisely in the pathways affected, to block pain transmission from the spinal cord to the brain.”

Fink and his co-workers created a crippled form of the herpes simplex virus that they tested extensively in animal models. This form of HSV is ideal for delivering genes to sensory nerves because of the natural biology of the parental virus. For the study, the HSV vector was modified to carry the gene for enkephalin, an opioid peptide naturally produced in the body. Opioid peptides act on the same receptors through which morphine and other drugs achieve pain relief.

Steps Toward a Human Trial

Gene therapy for pain was effective in earlier animal studies using rodents and has reduced pain-related behaviors in rodents with cancer pain.

With the support of National Institutes of Health funding, Fink has studied herpes simplex virus vectors for 20 years and gene
At two weeks old, Mira Larrison went home to Mio, Mich., after undergoing a series of procedures - both as a fetus and immediately after birth.

Through the new Fetal Cardiac Intervention Program, U-M physicians can provide not only answers about what heart defects a baby may face, but they can also perform life-saving interventions prior to birth.

In Mira’s case, the problem was hypoplastic left heart syndrome – essentially, she had just half a heart.

“She’s been one of our highest risk fetal intervention babies and she’s actually done the best,” said Aimee K. Armstrong, M.D., an interventional cardiologist and Assistant Professor in the Department of Pediatrics and Communicable Diseases at the U-M Medical School.

“To be discharged at two weeks of life is absolutely amazing.”

A challenging heart defect

Mira’s parents Katie and Jeremy Larrison knew their second child would face challenges at birth. An ultrasound at 18 weeks gestation showed the poor heart function and underdevelopment characteristic of HLHS.

Babies with HLHS cannot pump enough oxygen-rich blood to meet the body’s needs. Without treatment, 95 percent of babies die within one month. HLHS is treated either by a heart transplant or a series of three heart surgeries, beginning at birth with what’s called the Norwood procedure. The surgeries are required to allow the right side of the heart to do the work of both sides of the heart.

Nearly one in 100 children born in the United States has a heart defect, and the U-M Congenital Heart Center is a Center of Excellence for treating HLHS, one of the most complex ones. The center is based at C.S. Mott Children’s Hospital and the U-M Cardiovascular Center.

The condition is often described as being born with half a heart because the left ventricle is underdeveloped. Traditional surgery was too risky for Mira, who had other health challenges. Instead, U-M used a combination of a fetal intervention, followed by hybrid procedures, which are less invasive than open heart surgery, to treat the heart defect.

U-M is one of the first hospitals in the country to use the combination to care for such a high-risk patient.

Aimee K. Armstrong, M.D.
Assistant Professor Pediatrics and Communicable Diseases

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was minimal. She also has a genetic abnormality called Turner Syndrome, which placed her at very high risk for traditional surgical approaches to HLHS. Given Mira’s three severe abnormalities, the Norwood procedure would be very risky. The newborn had three strikes against her, and doctors began treating her in the womb.

How U-M treated it

First, using a needle inserted through the mother’s abdomen and into Mira’s heart, doctors used a balloon to create the hole between the atria. The successful intervention allowed Mira to be stable at birth. The team took Mira directly from the delivery room to the cardiac catheterization laboratory, where the physicians placed bands on the pulmonary arteries to direct more blood flow to the body, and placed a stent between the atria of her heart to further improve blood flow. Once Mira stabilized, the same team placed a stent in her ductus arteriosus to ensure adequate blood flow to her body.

Next, physicians addressed HLHS using a hybrid approach, an emerging alternative to a Norwood. In hybrid procedures, interventional cardiologists and cardiac surgeons work side-by-side to treat patients without using a heart bypass machine.

A cardiac team, led by Armstrong and Jennifer Hirsch, M.D., a U-M pediatric cardiac surgeon, performed two hybrid procedures on Mira on Jan. 27, the day she was born, and another on Jan. 29.

Fetuses with two severe forms of congenital heart disease have been identified as potentially benefiting from cardiac intervention prior to birth.

• Hybrid procedures are emerging as an alternative to the Norwood approach for treating HLHS. Using the hybrid approach, interventional cardiologists and cardiac surgeons work side-by-side to treat patients without using a heart bypass machine.

The Center performs more than 850 cardiac operations a year.

Find More on the Web

U-M Congenital Heart Center
http://www.med.umich.edu/mott/chc/about.html

U-M Cardiovascular Center
http://www.med.umich.edu/cvc/
Tongue cancer can be among the most debilitating cancer types, as surgery to remove the tumor can leave patients unable to speak or eat normally.

Traditional, basic reconstruction focuses on merely closing the wound after removing the tumor. But the functionality that allows people to manipulate food, eat a normal diet and eat in public is often missing.

New techniques in tongue reconstruction developed at the University of Michigan Comprehensive Cancer Center maximize the mobility of the remaining tongue tip to ensure patients will still feel comfortable eating out or asking a stranger for directions.

“In the past, patients who have undergone tongue reconstruction would be very concerned about social interaction,” says Douglas Chepeha, M.D., M.S.P.H., director of microvascular reconstructive surgery and associate professor of otolaryngology at the U-M Medical School.

“With the type of reconstructions we’re performing now, our patients tell us that they’re willing to go into a restaurant and order a meal. They have no hesitation whatsoever in asking strangers for directions. They are also able to maintain their employment status and their interactions with friends and family,” Chepeha says.

More than 10,000 Americans will be diagnosed with tongue cancer this year and 1,880 will die from the disease, according to the American Cancer Society.

Chepeha and his team have developed many of the techniques used in tongue reconstruction, including innovative patterns, much like a dress pattern, that help the surgeons determine the size and shape of the skin tissue they will cut for transplanting. The tissue is taken from another part of the patient’s body, often the forearm, so there is not a risk of rejection.

The surgery, which includes removing a portion of the tongue and reconstructing the new tongue, is long and complex, lasting about 10 hours. It requires surgeons to dissect and reattach the blood vessels, just like with a typical organ transplant. The blood vessels are sewn together with tiny sutures, some smaller
Most tongue reconstructions focus on closing the wound and do not provide adequate functionality for speaking or eating. Patients are generally limited to a soft diet of mostly liquids after tongue reconstruction. Many feel self-conscious eating in public or speaking to strangers. Surgeons at U-M have developed new techniques that use patterns similar to dress patterns to help surgeons determine the size and shape of the skin they need to remove for transplanting. These techniques allow for greater functionality, so the reconstructed tongue functions more like a regular tongue. Using these new techniques, 12 of 13 patients resumed solid food intake and nine patients had no social restrictions or restricted diet when eating in public.

“Tongue reconstruction in the past would have limited a patient to a soft diet – mostly liquids, some soft solids. At present with the tongue reconstructions that we’re performing, patients are able to take a nearly full diet,” Chepeha says.

Lisa Bourdin-Krause was one of 13 initial patients to undergo the unique tongue reconstruction. The night before her surgery, the then-30-year-old realized she might never be able to speak to her toddler son again. So she sat up half the night recording messages to him: “Hi, how was your day?,” “You’re so handsome.” She read two of his favorite books.

“Now, eight years later, I feel like it’s just my normal tongue. I’m used to it. Within a couple weeks, really, I was back to what I considered as normal as I was going to be,” she says. “I try very hard not to take anything for granted, because having it almost taken away makes you realize just how special every minute is.”

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“Tongue reconstruction in the past would have limited a patient to a soft diet – mostly liquids, some soft solids. At present with the tongue reconstructions that we’re performing, patients are able to take a nearly full diet,” Chepeha says.
Pancreatic cancer is a challenging and difficult disease to diagnose and treat. It’s also one of the most deadly cancer types: 37,680 Americans will be diagnosed with pancreatic cancer this year and 34,290 will die from the disease. Only about three percent of people with pancreatic cancer live more than five years after diagnosis.

Researchers at the University of Michigan Comprehensive Cancer Center are making strides toward better understanding how pancreatic cancer develops and spreads, which they hope will lead to much-needed improvements in treatments.

“Over the last one to two decades we have not had a significant improvement in the long-term survival rates with pancreatic cancer. One of the challenges is that pancreatic cancer is biologically aggressive and it does not respond well to chemotherapy or radiation,” says Diane Simeone, M.D., Lazar J. Greenfield Professor of Surgery and director of the Multidisciplinary Pancreatic Cancer Program at the U-M CCC. Simeone’s lab recently identified a gene that is overexpressed in 90 percent of pancreatic cancers. Expression of the gene, called Ataxia Telangiectasia Group D Complementing gene, or ATDC, is on average 20 times higher in pancreatic cancer cells than in cells from a normal pancreas. What’s more, the gene appears to make pancreatic cancer cells resistant to current therapies.

“We found that ATDC not only causes the cancer cells to grow faster and be more aggressive, but it also makes the cancer cells particularly resistant to chemotherapy and radiation. By targeting this gene, we may be able to make cancer cells more sensitive to the therapies we already have in hand,” Simeone says.

Simeone’s lab was also the first to identify a small group of cells, called cancer stem cells, in tumors from patients with pancreatic cancer. Cancer stem cells are the small number of cancer cells that replicate to drive tumor growth. Researchers believe current cancer treatments sometimes fail because they are not attacking the cancer stem cells. By identifying the stem cells, researchers can then develop drugs to target and kill these cells.

“If we can target cancer stem cells within pancreatic cancer we may have an avenue to really make a breakthrough in therapy for this
awful disease. Since pancreatic cancer is resistant to chemotherapy and radiation, we need new treatments that can kill the small number of cancer stem cells within the tumor. Studying pancreatic cancer stem cells will help us identify targets for new drugs or therapies,” Simeone says.

All of this provides hope to patients who face a dim prognosis.

Pancreatic cancer patients frequently suffer with multiple symptoms, and don’t know where to turn for the expert help they need. The University of Michigan Comprehensive Cancer Center’s Multidisciplinary Pancreatic Cancer Clinic addresses this by offering timely and comprehensive consultations and patient services. The clinic brings together specialists in all disciplines involved in treating pancreatic cancer. This includes surgeons, medical and radiation oncologists, gastroenterologists, radiologists and pathologists, all of whom specialize in pancreatic cancer.

In addition to state-of-the-art multidisciplinary care, the clinic boasts a cadre of very capable gastroenterologists who are able to perform a multitude of difficult diagnostic and therapeutic endoscopic procedures. Nursing, nutrition, social work and medical genetics support are also available for patients and their families, as well as detailed educational materials.

The Multidisciplinary Pancreatic Cancer Clinic provides:

• Diagnostic testing completed quickly, with same day procedures available
• Expertise in diagnostic procedures (such as endoscopic retrograde cholangiopancreatography)
• Availability of interventional radiologists for biopsies
• Specialized CT scan and endoscopic ultrasound procedures for diagnosis and staging
• Novel therapeutic approaches for pancreatic cancer treatment

The Blue Cross and Blue Shield Association named the U-M Health System a Blue Distinction Center for Complex and Rare Cancers, which includes pancreatic cancer.

TO REFER YOUR PATIENTS to the Multidisciplinary Pancreatic Cancer Clinic call M-LINE at 800-962-3555

KEY POINTS

• Pancreatic cancer is an aggressive and deadly form of cancer that is difficult to treat because it doesn’t respond well to chemotherapy or radiation.

• U-M researchers identified a gene that is expressed on average 20 times more in pancreatic cancer cells than in normal pancreatic cells.

• Identifying and targeting these specific cells is a big step toward potential new drug and therapies for this disease.

• The Multidisciplinary Pancreatic Cancer Clinic provides quick and expert diagnostic testing, that involves interventional radiologists for biopsies, specialized CT scan and endoscopic ultrasound procedures for diagnosis.

CLINICAL CARE UPDATE

Venous Health Program

Jim Froehlich, M.D., M.P.H.
Director, Venous Health Program

In September 2008, the Office of the U.S. Surgeon General announced a Call to Action to focus attention on venous thrombosis as a serious public health threat.

As part of U-M’s response, the U-M Cardiovascular Center launched the Venous Health Program. Jim Froehlich, M.D., director of the program, and his team of multidisciplinary experts treat several venous diseases, including Venous Thromboembolism (VTE), Varicose Veins and Chronic Venous Insufficiency, and Complex Venous Management.

One of the program’s goals is to help referring physicians take the guesswork out of choosing the right specialist for their venous disease patients by offering a complete range of management and treatment services in a central location. Another objective is to bring the latest research findings in venous disease to patients and their physicians for the most advanced bench-to-bedside care. Ongoing studies expand knowledge on the subject of venous disease including causes, treatments and new agents. The Venous Health Program can treat everything from mild cosmetic problems to disabling, limb-threatening conditions.

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therapy for pain for 10 years. The Phase I clinical trial, funded by the Swedish biotechnology company Diamyd Medical, is the culmination of many years of research conducted by Fink and his wife, Marina Mata, M.D., also a U-M professor of neurology.

“This is a clear example of translational research,” Fink says. “We began making the virus in the laboratory, we spent many years testing it in animals and now we are bringing it to people who may benefit.”

Twelve patients with cancer pain are participating in the Phase I clinical trial, the first step in the FDA’s drug approval process.

**Treatment Tomorrow: Conquering Pain with Vectors**

Bringing gene therapy to the marketplace will take time. The Phase I clinical trial will be finished by next year, when Fink hopes to begin Phase II with a larger group of patients.

“I’ve relied tremendously on institutional resources to move from the lab to the human trial,” Fink says. “The Michigan Institute for Clinical and Health Research and Cancer Center Clinical Trials Office have provided invaluable advice and support. It’s one thing to conduct experiments in a lab and another thing entirely to enroll patients in a study.”

In March, Fink presented a proposal to test a similar HSV vector carrying a different gene to treat pain from nerve damage in patients with diabetes. The presentation was at the public review meeting of the NIH Recombinant DNA Advisory Committee in Bethesda, Md.

**FOR MORE INFORMATION**
call M-LINE at 800-962-3555 or visit http://www.med.umich.edu/neurology/mata-fink_lab/projects/humantrial.html