Try, try again

When a homegrown cancer therapy didn’t work as anticipated, U researchers went back to the lab to find—and solve—the problem

Hope was high as University of Minnesota scientists and physicians tested a therapy designed to fight off deadly brain tumors during a 2012 clinical trial. In most cases, the immunotherapy—which was developed at the U and trains a person’s own immune system to fight off disease—performed admirably to prolong adults’ and children’s lives by preventing their tumors from returning. But the progress was short-lived when the tumors eventually came roaring back.

The team’s curiosity about what went wrong led to an important discovery of a little-known protein called CD200. Turns out it plays a leading role in suppressing the immune system and perpetuating brain cancer. Such findings by researchers Christopher Moertel, M.D., and Michael Olin, Ph.D., hold the potential to make the next big breakthrough in brain cancer treatment.

The clinical–scientific pair aims to launch a human clinical study later this year that would test a new cancer immunotherapy based on their CD200 discoveries. They are building on the successes they’ve had treating dogs that have similar naturally occurring brain tumors, prolonging their lives from typically just weeks after diagnosis to more than a year and a half.

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“I think we can probably show a similar difference in humans,” says Moertel, a pediatric neuro-oncologist at University of Minnesota Masonic Children’s Hospital and holder of the Kenneth and Betty Jayne Dahlberg Endowed Professorship in Pediatric Brain Tumor Research.

Learning from failure

Brain tumors are often aggressive, wily, and difficult or impossible to treat. Brain cancer is the second-most common form of cancer in children and the leading cause of cancer-related deaths in children.

Masonic Cancer Center members Olin and Moertel are driven to make a difference in treating this devastating disease. Olin’s mother died from it, and Moertel has watched countless children struggle—and fail—to beat it.

After the unsuccessful brain tumor clinical trial in 2012, Olin went on a quest to find out why this therapy, which seemed to have so much potential, didn’t work. He found himself comparing blood samples that were taken weekly from study participants. A neuro-immunologist and assistant professor of pediatric hematology/oncology, Olin focused on changes in proteins in the blood, evaluating an alphabetical list of proteins one by one when he noticed slight changes in CD200 levels.

Patients who didn’t respond to the immunotherapy at all had sky-high CD200 levels. Those who responded well to the therapy had low CD200 levels initially but high levels when the tumors returned.

“It was our theory that CD200 was important and the reason the tumors returned,” Moertel says. “It turns out that CD200 is an important immunosuppressant agent that tumors make to escape discovery by the immune system.”

Though there had been some scientific interest in CD200’s abilities to shut down the immune system, research in this area hadn’t made much progress. When the U of M team began doing experiments, Olin found that blocking CD200 in mice made their brain tumors disappear. Blocking CD200 also killed human tumor cells in a petri dish.

Finding this promising, Olin began analyzing CD200 more closely and got even better news. Not only does blocking CD200 keep tumors at bay, it also has the ability to transform from bad cop to good cop. Olin found that chains of amino acids called peptides turn on the protein’s unique activation receptors, which then overpower the CD200 protein, transforming it from perpetuating cancer to fighting it.

Moertel and Olin partnered with Liz Pluhar, D.V.M., Ph.D., a professor of veterinary clinical services at the University, to evaluate their CD200 theory on dogs that develop brain tumors. Canine and human brain tumors are very similar, as are the canine and human immune systems. The partnership has both improved care for dogs that have brain tumors and served as a productive trial run for the human version of the therapy.

In fact, using a new form of the therapy with a CD200 blocker has extended some dogs’ lives to more than 500 days, when typically their brain tumors would have killed them in weeks.

“We’ve seen some fantastic results,” Olin says.
The team now is working to bring these discoveries to humans via a series of new clinical studies.

Getting there will still take significant effort, including toxicity testing, approval from the U.S. Food and Drug Administration, and funding. The work has benefited greatly from federal research grants and philanthropic support, such as that from the Dahlberg Family Foundation and significant donations from Bob and Corinne Ferris, Children’s Cancer Research Fund (CCRF), CCRF’s Dr. Daniel G. Carey Brain Tumor Research Fund, the American Brain Tumor Association, Randy Shaver Cancer Research and Community Fund, Humor to Fight the Tumor, and Love Your Melon.

“We have a long list of people who have made a significant contribution to this work and helped us move the research along,” says Moertel, who has worked in pediatric oncology for nearly 30 years. “Before we were taking baby steps. This work is a big leap.”

Because this research is inherently expensive, Moertel and Olin spun out a company from the University called OX2 Therapeutics to create an avenue for venture capital investments. They see the promise of their work in fighting brain cancer and want to help patients as quickly as possible while also expanding the anti-CD200 immunotherapy model to other cancers.

“This will be a rock star for breast cancer and melanoma as well,” Olin says. “If we give the inhibitor to mice modeling human breast cancer, they have an 80 percent survival rate.”

It’s part of the team’s shared vision and lifelong goal of stopping cancer in its tracks.

“We want to cure brain tumors. That’s why I do my job,” Moertel says. “When I look at kids every single day who don’t have a cure for their disease, it’s heartbreaking. I want to find an answer.”

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**Putting together the pieces for autism spectrum disorder**

1 in 68

Estimated number of children who have some form of autism, according to the Centers for Disease Control and Prevention

2

Earliest age that autism spectrum disorder (ASD) can typically be diagnosed

4

Average age that ASD is actually diagnosed

80

Percent accuracy using magnetic resonance imaging (MRI) to predict which infants would later be diagnosed with ASD, in infants who have older siblings with the disorder

89

Percent accuracy using MRI to predict which babies would not receive an ASD diagnosis

50,000

Families affected by ASD being recruited to the nationwide SPARK study, aimed at finding the genes responsible for the cluster of neurodevelopmental disorders

100+

Genes that likely play a role in ASD

“With $1 million raised so far, the team is close to being ready to launch the first Phase I clinical trial. For more information about this research or how to support it, contact Jen Foss at 612-626-5276 or foss@umn.edu.”

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*This research highlights the best of contemporary science. It’s collaborative and informed by technology and multiple areas of expertise, with the common goal of helping families.*

—Jed Elison, Ph.D., of the U of M’s Institute of Child Development and Department of Pediatrics
Philanthropy advances a doctor’s efforts to promote wider newborn screening for cytomegalovirus, one of the most common causes of disability in children

Combining legislative advocacy with in-depth research and education efforts, Mark R. Schleiss, M.D., and his team are determined to stop a health threat that has been allowed to run rampant for far too long: cytomegalovirus (CMV).

“Cytomegalovirus causes more disabilities than any other infectious disease in children,” says Schleiss, a professor of pediatrics and codirector of the University of Minnesota’s Center for Infectious Diseases and Microbiology Translational Research. These disabilities can include deafness, cerebral palsy, developmental delays, and seizure disorders.

Research shows that babies born to women who become infected with CMV for the first time during pregnancy are the most likely to develop disabilities. Mothers can pass the virus to their babies in utero through the placenta.

Particularly for expectant mothers with toddlers at home, CMV is all too easy to contract. Since CMV is transmitted through bodily fluids such as saliva from a sloppy kiss, pregnant mothers with young children who attend daycare are at a high risk of becoming infected. Premature and underweight babies also are extremely susceptible to CMV.

A type of herpes virus, CMV ends up infecting most of the world’s population eventually, Schleiss notes. “Most people in human history have been infected with CMV,” he says. And once you’re infected, the virus stays with you for life. Throughout a person’s life, the virus can be reactivated by triggers such as stress, sleep deprivation, and malnutrition.

But somehow, this harmful and prevalent virus has managed to fly under the medical radar for decades, even though CMV affects babies more often than Down syndrome, fetal alcohol syndrome, and neural tube defects combined, says Schleiss.

Schleiss and his team think CMV deserves all the attention it can get. They’re advocating to make CMV screening standard in Minnesota for the infants who don’t pass their newborn hearing test. (Some states have already done this.) The effort is supported by a three-year Community Health Impact in Pediatrics grant from the Vikings Children’s Fund, a longtime partner of the U’s Department of Pediatrics.

“I am enormously grateful for their support,” he says.

By identifying the babies affected by CMV very shortly after birth, Schleiss says, the medical team could offer antiviral drugs to minimize the developmental and neurological problems the virus can cause.

Schleiss’ lab also is developing a vaccine strategy that could protect a woman from CMV in her childbearing years, to be administered before she becomes pregnant. The vaccine would thereby guard her baby from infection and CMV-related disability.

Schleiss radiates energy and passion for his work. “We are really excited about what the future holds,” he says. “If we can change practice in Minnesota, wouldn’t that be exciting?”

Support this work today at give.umn.edu/giveto/cmv.
Toward the end of her battle with Ewing sarcoma, 5-year-old Zoya Wajahat got a visit from an adult friend who attends her family’s mosque. The friend is “very involved in fundraisers and charity, always doing good things,” explains Zoya’s mother, Mariam Siddiqui. She brought one of Zoya’s favorite sandwiches, and the two chatted and played together.

“The friend texted me later that day, after she left,” Siddiqui recalls. “She said, ‘Zoya gave me $20. She took it out of her red envelope [of spending money; it contained $26 total] and she said, please put this in the charity box for me.’

“She asked me, ‘what do you want me to do with this money? Doesn’t she want it for something?’ I said, ‘no, it’s OK.’ Of course, Zoya didn’t mention this to me.”

That was Zoya: giving and teaching to the end of her young life—and beyond. In her final few days, she fretted to her grandmother about her mother’s fatigue. “She said, ‘Naano, let my mom sleep because she is very tired.”’ Siddiqui recalls. “She couldn’t sleep herself, but she wanted me to sleep.”

So it’s fitting that the initiative her mother, father, and sister started, the Zoya Palliative Care Memorial Fund for University of Minnesota Masonic Children’s Hospital, has inspired compassion and generosity in donors around the globe—from Minnesota to Pakistan, Australia, Dubai, and England. Their quest to improve care for dying children and their families grew out of Zoya’s pronouncement that she wanted to be a nurse because, she said, “I know how much it hurts when they put a needle in my port. I will make sure that no child will hurt anymore.”

Through her diagnosis, chemotherapy, surgery, a bone marrow transplant, and radiation, Zoya’s spirit—her joy and loving energy—helped sustain her family, and it has continued to guide them since her death in April 2015. Siddiqui, her husband, Wajahat Khalil, and their older daughter, Maria, now 13, say their journey with Zoya made them “witness to grace” and deepened their sense of purpose. One day, Maria wants to become a doctor like her parents; she’s interested in pediatric oncology.

“To witness the dignity of how she left us—I pray that other parents don’t have to go through this, but it gives you deep clarity about what we are doing here,” says Khalil. Their mission, he says, is to help educate physicians, nurses, social workers, chaplains, and others who care for terminally ill kids about seeing the bigger picture of healing.

“Healing can be understanding and appreciating death,” he says.

Naomi Goloff, M.D., the lead pediatric palliative care clinician for University of Minnesota Health, agrees. “Most people don’t want to hear about children who are dying. But just because it’s difficult doesn’t mean [that quality care] is needed any less,” she says. “There are patients you can cure, and that’s wonderful. But when kids can’t be cured, you can still help bring healing.”

The Zoya fund will support teaching future providers how to give “open, honest, compassionate, family-centered care” to dying kids and their families.

“This,” says Khalil, “will be Zoya’s gift.”

Make a gift to the Zoya Palliative Care Memorial Fund at crowdfund.umn.edu/zoyafund.

Photo courtesy of Wajahat Khalil
After being treated for ‘innumerable’ tumors on her liver, a baby girl and her family look forward to the joys of an ordinary life.

Not even the sniffles can slow down little Willow Flaherty. She and her identical twin sister, Hazel, are babbling happily and showing off their new crawling skills. It’s a delightfully ordinary scene for the two, who got off to a rocky start—especially Willow.

Had she been born just a few years ago, her future might have been grim. The tiny red dots that appeared all over Willow’s body soon after she was born mirrored tumors that covered her liver, and had she not been treated swiftly, she might have faced a liver transplant, or worse.

The Flaherty twins were born six weeks premature and spent their first two weeks in the neonatal intensive care unit at University of Minnesota Masonic Children’s Hospital. After they came home, their parents, Courtney and Jim Flaherty, began noticing little spots on Willow’s hands and belly.

These small spots were infantile hemangiomas: small vascular tumors that can be harmless, but when more than five appear on a newborn’s skin, it’s a clue that there may be hemangiomas on the liver as well.

Untreated, liver hemangiomas can lead to serious complications—thyroid dysfunction, heart failure, or even death. University of Minnesota Health pediatric dermatologist Sheilagh Maguiness, M.D., an expert on vascular lesions, was aware of the potential consequences and ordered an abdominal ultrasound. Indeed, the care team found “innumerable” tumors on Willow’s liver.

Maguiness recommended starting Willow on propranolol, a medication that, a decade ago, was accidentally found to dramatically shrink hemangiomas. At the time, the Flahertys didn’t fully grasp what a dangerous bullet they were dodging.

“Thank goodness [Maguiness] did a really good job of downplaying how bad it could have been,” Courtney Flaherty says. “She helped keep me calm.”

The medication, a liquid Willow took three times daily, yielded almost immediate results with negligible side effects; within two months, her liver hemangiomas were almost gone.

In March, the twins’ parents celebrated more than the girls’ first birthday: Willow also took her last dose of propranolol.

Maguiness, an assistant professor of dermatology at the U who is studying the co-occurrence of infantile hemangiomas with other birthmarks, emphasizes the importance of raising awareness among pediatricians about infantile hemangiomas, especially when they are large, on the head and neck, or many. She calls propranolol’s effectiveness in treating all types of hemangiomas “game-changing.”

“Before propranolol, mortality was as high as 28 percent with diffuse liver hemangiomas,” says Maguiness, who codirects the interdisciplinary Vascular Lesions Clinic at the U. “Now, with regular screening and appropriate therapy, there are no deaths. It’s a story with a very happy ending.”
Kirk Ramin, M.D., is one of those doctors who makes each pregnant woman he treats feel like she is his only patient. His calm and comforting manner, exquisite skill in maternal and fetal medicine, and nearly round-the-clock dedication helped many women through stressful, high-risk pregnancies.

Kari Berman is one of those women. After struggling for years with infertility, including about a dozen miscarriages, Berman got pregnant and endured numerous complications before she went into labor at 19 weeks. Ramin tended to her through 4.5 months of complete bedrest until she delivered healthy twins at 36 weeks.

“He was very calming and reassuring, and I always felt like things were under control if he was around,” says Berman. “His level of dedication was staggering.”

A nationally recognized maternal-fetal medicine specialist—who also maintained a prolific research profile as a professor of obstetrics, gynecology, and women’s health at the University and created the first maternal-fetal medicine fellowship program in Minnesota—Ramin reluctantly relinquished his teaching and clinical duties at the University last April for health reasons.

“Kirk has had a tremendous impact because of his commitment to patient care and rapport with referring physicians who trusted him to continue their patients’ care,” says Daniel Landers, M.D., director of the U’s maternal-fetal medicine division. “His practice was always cutting-edge with best practices, so patients, residents, and fellows learned from that. He was a dedicated teacher and talented clinician.”

Berman is forever grateful for Ramin and his skill. “By virtue of his incredible care and medical prowess, he allowed me to leave the hospital with two healthy babies,” she says. “I often say that he saved my kids’ lives, but he also saved mine.”

In Ramin’s honor, his colleagues have established the Kirk D. Ramin Endowment Fund to support training and continued education of pregnancy-related care providers at the University of Minnesota. Make a gift at crowdfund.umn.edu/DrRaminFund.

Save the date: Champions for Children Celebrity Golf Classic

Monday, June 26
Windsong Farm Golf Club, Independence, Minn.

Hosts Kyle Rudolph of the Minnesota Vikings and Jason Zucker of the Minnesota Wild are helping us drive toward $1 million raised through the annual Champions for Children Celebrity Golf Classic.

Proceeds from this year’s tournament benefit Kyle Rudolph’s End Zone at University of Minnesota Masonic Children’s Hospital, a place for children and teens to relax, play, and socialize with other kids who know what it’s like to be in the hospital.

Learn more at give.umn.edu/events/champions.

Join honorary chairs Tom and Tori Ostlund in celebrating the next-generation geniuses of medicine and winemaking at the two-day WineFest No. 22—to be held May 12 and 13 at the Renaissance Minneapolis Hotel, The Depot. Enjoy unparalleled wines, delectable gourmet fare, intriguing auction items, and memorable entertainment, all while advancing innovative pediatric research at U of M Masonic Children’s Hospital.

Get the details and buy your tickets atthewinefest.org.

WineFest No. 22 art: “State of Grace” by Meranda Turbak
Chasing down cancer

Get geared up and join our quest to defeat cancer. Chainbreaker is a cycling event and celebration supporting collaborative, lifesaving cancer research at University of Minnesota Masonic Children’s Hospital and the Masonic Cancer Center, University of Minnesota.

The event is modeled after the successful Pelotonia event at the Ohio State University, which raised more than $24 million last year.

Choose a ride that matches your skill level, including one-day rides of 25, 50, or 100 miles and a two-day ride of 180 miles. The cycling and entertainment experience is August 11, 12, and 13.

Register to ride and learn more at chainbreakerride.org. Or to sign up your company as a team or volunteer group, contact Elizabeth Patty at 612-625-6136 or patty@umn.edu.