ANN-MARGARET HEDGES

A rousing game of thumb wrestling between Torrey Sandlund, MD, and Ricky Mahar always has the same outcome: a victory for Ricky. Thanks to the A-T clinic at St. Jude, patients with ataxia-telangiectasia now have a better chance to vanquish cancer.

two thumbs up

By Elizabeth Jane Walker

St. Jude opens the world's first clinic specifically designed for patients who have cancer and a rare genetic disorder called ataxia-telangiectasia.

Every time Ricky Mahar goes to a checkup at St. Jude Children's Research Hospital, he challenges his doctor to a wrestling match.

And every time, Ricky wins.

Torrey Sandlund, MD, is quick to concede that 8-year-old Ricky is the undisputed thumb-wrestling champion. Each week, Ricky anticipates the moment when he can clasp hands with Sandlund for a game of dueling digits.

"Ricky loves to thumb-wrestle, and he has beaten me every time," Sandlund says. "But we have staring contests, too, where we stare at each other and see who laughs first. I win those; he always laughs first. So we are each undefeated in our respective areas of competition."

The camaraderie and affection between physician and patient have grown since September 2002, when Ricky traveled from New York to enroll in a new protocol, or scientific treatment plan, at St. Jude. Earlier that month, Ricky learned that he had non-Hodgkin lymphoma, a cancer of the lymphatic system. Because Ricky also has a disorder called ataxia-telangiectasia (A-T), his body would not tolerate traditional cancer treatment. So doctors at Johns Hopkins Hospital in Baltimore, Maryland, suggested that Ricky travel to St. Jude, which houses the world's only clinic specifically designed for A-T patients who have cancer.

The one-two punch

Children with ataxia-telangiectasia (pronounced A-TACK-see-uh Teh-LAN-jick-TAY-sha) have a rare, inherited neurological disorder. "Ataxia" refers to a loss of muscle control caused by degeneration of the cerebellum, the part of the brain that controls motor function. Children with this condition become increasingly clumsy, and their speech becomes slurred. Gradually, they lose their ability to write, talk and walk. Because their muscle control progressively diminishes, most A-T patients are wheelchair bound by age 10 and rarely live beyond their teens. Although they have normal intelligence, they have trouble reading because of jerky eye movements. Children with A-T also develop "telangiectasia," or tiny red spider veins in their eyes and on exposed areas of the skin.

Tim and Lisa Mahar vividly recall the day a doctor told them that Ricky had A-T, a disease that afflicts about 500 children in the United States. "The doctor had never had a patient with A-T before," Lisa says. "When he was giving us the diagnosis and telling us about it, he had a book in front of him, reading to us about it. He pretty much told us, 'This is what he has. There's no treatment; there's no cure; end of story.'"

The couple soon learned that their son's risk of developing a malignancy could be as high as 30 percent. Their worst fears were realized when

Ricky developed non-Hodgkin lymphoma. "We were completely shocked, because we knew that this could happen, but we didn't think it would happen this soon," recalls Tim.

Sandlund says a cancer diagnosis is the crowning blow to most parents of A-T patients. "These families are already stressed to the max, going through far more than most of us could ever imagine," he says. "They're watching their kids little by little losing ground. Then, on top of that, they find out that their kids have cancer. It's like a one-two punch."

Fighting back

Because children with A-T are extremely sensitive to radiation and cancer-fighting drugs, they do not respond well to traditional cancer therapy. Until recently, a diagnosis of cancer in a child with A-T meant a bleak prognosis.

"A lot of doctors thought that if A-T patients were sensitive to radiation, then they were also sensitive to everything else. So they wouldn't treat the children, and they'd die of the cancer. Or they'd treat them very mildly," says Michael Kastan, MD, PhD, chair of St. Jude Hematology-Oncology.

Kastan has been studying DNA damage in A-T patients for more than a decade. Using what he learned in the lab, he began designing treatment plans that he thought patients could tolerate. Physicians around the world began calling him for suggestions about treating their A-T patients who had cancer. "I would give them advice based on my experience with the few patients I had seen," Kastan explains. "I would say, 'please keep me informed about how they do—what toxicities you see, and what responses you get, so that I can continue to modify the advice I give." But the busy physicians rarely called back. The frustrated researcher then hit upon a solution. What if St. Jude created a cancer clinic just for A-T patients—a central location where research and treatment could occur simultaneously?

That's exactly what happened in autumn of 2002. "We're willing to take any patients in the world who have A-T and get cancer," Kastan says. "St. Jude opened this clinic because there was a need for it. If we don't do it, no one's going to, and treatment would continue to go as it's been going—a patient here, a patient there, and no one getting enough experience to know how to improve therapies." The St. Jude specialists share what they learn with hospitals around the globe; that means children who have A-T and cancer can come to St. Jude for treatment or stay in their hometowns. If they choose the latter option, their doctors will work closely with the investigators at St. Jude.

With a team of St. Jude researchers and clinicians united with a common goal, children who have A-T and cancer now have a better chance for survival, observes Kastan. "I can't think of a disease that's more devastating than A-T," he says, "but we can cure the cancer in a significant number of these patients and hopefully let them live for many more years."

Building on success

Long before the new clinic opened, Kastan and Sandlund began developing the protocol for children with A-T. They knew that the clinic's patients would have unique problems that must be addressed. With a hypersensitivity to ionizing radiation, these patients must avoid radiation therapy and drugs that produce similar effects. Because A-T patients have trouble tolerating one of the cornerstone drugs used in lymphoma treatment, the investigators built in protective measures to eliminate those problems. As Kastan and Sandlund developed the protocol, they modified therapy to adjust for other challenges as well.

The A-T protocol combines several existing St. Jude treatment plans. Each is modified to account for the unique toxic effects experienced by A-T patients. The investigators included treatment plans for such diseases as high- and low-risk acute lymphoblastic leukemia, large-cell lymphoma, Burkitt's lymphoma, lymphoblastic lymphoma, Hodgkin disease and non-Hodgkin lymphoma. Pooling their expertise, Kastan, Sandlund and colleagues from departments across the institution spent two years writing the protocol. "Basically, the best chance for curing cancer in children with A-T is based on strategies that we know work in children who don't have this condition," Sandlund says. "This multidisciplinary effort is for a very small number of patients, but why should they receive any less of an effort to cure their cancer than people who have much more common cancers?"

Sandlund says the investigators hope to learn much more about the kinds of cancers that children with A-T develop. The researchers also study blood samples from A-T patients for DNA breakage, in an effort to see if these patients are more sensitive than other people to chemotherapy.

"The academic questions are important," says Sandlund, "but frankly, the most important purpose of this protocol is to provide the best therapy we can come up with for these kids."

ANN-MARGARET HEDGES

Michael Kastan, MD, PhD (at right), chair of St. Jude Hematology-Oncology, and Christopher Bakkenist, PhD, also of Hematology-Oncology, have discovered a process that helps cells in the body respond to DNA damage. The researchers expect that the discovery will lead to exciting new therapeutic approaches and prevention methods.

Scrutinizing genes

Scientists in Kastan's laboratory at St. Jude investigate how cells respond to stresses such as DNA damage. Although some DNA-damaging agents can cause gene mutations, cell death or cancer, others—such as chemotherapy and radiation therapy—are used to cure cancer. So researchers are interested in understanding exactly how cells respond when their DNA is altered. If scientists can learn to manipulate the cell's response to DNA damage, they might be able to create ways to prevent cancer or to make therapies more effective.

The gene that is mutated in ataxia-telangiectasia is called *ATM*. Children have a one-in-four chance of having A-T if both of their parents carry the faulty gene. Cells from children with ataxia-telangiectasia lack the ATM protein, which leaves them extremely sensitive to radiation. Kastan and his colleagues are trying to identify a drug that will inhibit that protein. By inhibiting ATM, they may be able to make all tumor cells more sensitive to radiation. If an ATM inhibitor were given during radiation therapy for a brain tumor, for instance, the radiation would be much more potent.

The ATM protein is a kinase, an enzyme that signals to other proteins by modifying them. ATM adds a phosphate molecule to the other proteins in a process called phosphorylation. Several years ago, Kastan discovered that the *ATM* gene phosphorylates the tumor-suppressor gene *p53*, the most commonly mutated gene in human cancer. Scientists in Kastan's lab have also identified eight other proteins that are modified by ATM. All eight play roles in causing different kinds of cancer.

Kastan and Christopher Bakkenist, PhD, of Hematology-Oncology recently discovered a process that helps cells in the body respond to DNA damage. The researchers found that such damage activates ATM almost immediately. The ATM enzyme leaps into action, phosphorylating other proteins that play important roles in cancer prevention. If this process does not occur, then the cell cannot respond to radiation; that is what happens to children with A-T, who lack the ATM protein.

Understanding this novel biochemical process lays the groundwork for learning how to manipulate it, Kastan says. "This is a really big breakthrough, because it's the first step in everything that happens to the cell when it's been damaged," he explains. "It's a unique mechanism for an enzyme. Out of this research, we're hoping to find a way to activate these pathways without damaging the DNA. We expect that this discovery will lead to new therapeutic approaches and prevention methods."

Everyone's a winner

Today, Sandlund is decked out in a jaunty Sponge Bob Square Pants necktie, a gift from Ricky, who is an aficionado of the underwater cartoon. Ricky dutifully admires the necktie, but his primary focus is on the inevitable thumb-wrestling match and an imminent homecoming. The boy has no idea that his departure marks the culmination of years of planning and research; he is unaware that his involvement in St. Jude research may help save the lives of other patients like himself. No, Ricky is much more concerned with chalking up another victory against his arch-rival and best buddy.

"I'm really going to miss Ricky and his family when they go home," Sandlund says, "but it'll be nice to know that they're going home because he has done well. If Ricky was the only kid we ever treated, I would still say this protocol—and all the time we have invested in it—would have been worth it."

Ricky has won once again.●