

Neuroblastoma's foes

Researchers seek better, safer treatments for a rare childhood cancer
By Richard Saltus

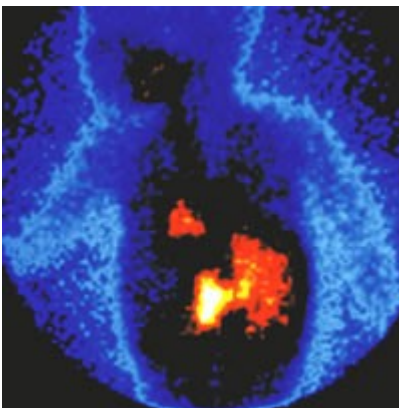


Brent McCreesh has faced neuroblastoma with the help of his family, care team, and inner strength.

Almost always, when a mother takes her feverish and lethargic toddler to the pediatrician, it turns out to be nothing more serious than a common childhood virus. So **Dana McCreesh** of Southport, Conn., wasn't overly worried about her 2-year-old son, **Brent**, when routine blood tests came back abnormal and the doctor referred them to a large teaching hospital 45 minutes away.

It was Sept. 13, 2004. "We had a great life going, and no one in our family had ever been really sick," recalls McCreesh. "At first, I didn't even bother to call my husband, who was at work." But the McCreeshes' "great life" disintegrated when, after several hours of tests including ultrasound and CT imaging, two grim-looking physicians at Yale-New Haven Medical Center broke the news to McCreesh and her husband, Mike, who had just arrived.

"Your son has Stage IV neuroblastoma," the doctors informed them. It was a disease that Dana and **Mike McCreesh** had never heard of, and not surprisingly, as only 600-800 new cases are recorded each year in the United States. Neuroblastoma is a solid tumor of infants and children that starts in nervous system tissue, often in the adrenal glands inside the abdomen. Some infants are born with the cancer, which forms when cells called neuroblasts fail to mature into nerve cells but instead remain undifferentiated and divide uncontrollably to form tumors.



A neuroblastoma tumor on a toddler's kidney, as seen through a scan

Most cases are diagnosed in children under age 5. About 50 percent of neuroblastomas occur in a fast-growing, aggressive form that spreads to lymph nodes and other organs before causing symptoms that lead to diagnosis. Though some types are easily cured with surgery, nationally only about one-third of the highest-risk patients survive longterm.

Hit with this bombshell, the McCreeshes simply refused to believe the doctors' verdict. "I was sure that after more tests, they'd say it was a mistake," Dana McCreesh recalls. A biopsy (tissue removal and exam) of Brent's multiple tumors, however, stripped away that last hope. From that moment forward, the life of the McCreesh family would be consumed by the disease and its complicated care, both in the hospital and at home. They also have a daughter, Madison, 15 months older than Brent, and Dana was pregnant with another daughter, Kira, at the time.

Team of specialists



Suzanne Shusterman, MD, got hooked on neuroblastoma care and research during a fellowship at Children's Hospital of Philadelphia, and joined the Dana-Farber staff to continue working on it.

Patients with advanced neuroblastoma require expert, specialized treatment with surgery, chemotherapy, radiation, and blood stem cell transplants. In New England, a joint Dana-Farber/Children's Hospital Boston (DF/CHB) team cares for an average of 20 to 30 neuroblastoma patients at any given time, most of them participants in clinical trials of new drug combinations and novel anticancer agents.

Lisa Diller, MD, of Dana-Farber, who heads the multidisciplinary program, says the past year has seen a surge of activity. A new physician-researcher who focuses on neuroblastoma, **Suzanne Shusterman, MD**, has joined the program, and several new clinical trials have begun or are being planned. "We also were approved to open a study on survivors," says Diller. "An increasing number of kids are surviving neuroblastoma, and we want to look at what's happening in terms of their growth, hormonal development, bone health, and other concerns." Shusterman, formerly of Children's Hospital of Philadelphia, came to Boston thanks to a fellowship endowed by Friends for Life, a fundraising organization founded by Michael and Denyse Dodd, whose daughter, Isabelle, was successfully treated for neuroblastoma through Dana-Farber/Children's Hospital Cancer Care.

"This work is incredibly rewarding. You help people through the worst times of their life, and a lot of kids are now happy and active and thriving."

—Suzanne Shusterman, MD

Neuroblastoma, according to Shusterman, "scientifically is a curious disease because it has different biological forms. Half the patients will do well with just surgery to remove the tumors. The other half

have very aggressive disease, and many of them are not cured with current treatments." She's studying new approaches for those patients who relapse after their initially successful treatment.

In some cases, it is a blessing of sorts when neuroblastoma causes severe symptoms early on. **Kane Goodman** of Andover, Mass., was only three months old when his mother insisted on a series of tests to find the cause of his constant crying and leg weakness. **Tracy Goodman** says she persisted, even though doctors could find nothing wrong and speculated that he had acid reflux. Finally, a neurologist ordered imaging tests in February 2003 that revealed a neuroblastoma tumor woven around his spinal cord and compressing it, causing the leg weakness that quickly progressed to total paralysis.

Surgeons removed the tumor, and Kane underwent chemotherapy because some of the cancer cells remained, but today he's been cancer-free for nearly three years and is considered a childhood cancer survivor. "The paralysis saved his life," says his mother, though the toddler has yet to recover completely from the spinal cord damage. He wears braces on his legs and uses a wheelchair to get around; he's also mastering the use of a walker. "Day to day I worry less about his cancer coming back."

Doubling the effect



Dana-Farber's Lisa Diller, MD, checks up on neuroblastoma patient Kane Goodman with the support of his mother, Tracy.

As in about half of neuroblastoma patients, Brent McCreesh's cancer caused no diagnosable symptoms until it had spread to several organs and his bone marrow. The doctors at Yale-New Haven moved quickly. They implanted in his chest a flexible rubber catheter, which for the next year would serve as a port for medications, fluids, and blood transfusions, as well as easy access for blood samples.

The opening salvo of treatment was six rounds of combination chemotherapy to shrink the tumors before they were removed during three long operations by **Robert Shamberger, MD**, at Children's Hospital Boston. Back at Yale, Brent underwent 14 days of radiation therapy. Next, the Children's team prepared the *coup de grace*. Brent received a blast of high-dose chemotherapy designed to mop up any surviving cancer cells, and then had an infusion of his own blood stem cells (previously removed and stored) to rebuild his bone marrow. A few weeks later, the chemotherapy and stem cell transplant treatment was repeated, this time accompanied by total-body radiation.

At many U.S. cancer centers, Brent would have received a single stem cell transplant. But the Dana-Farber/Children's Hospital Cancer Care team has been pushing the treatment envelope for several years by adding a second transplant after an additional round of chemotherapy and radiation.

Overall, the "very, very aggressive" double transplant treatment has upped the long-term survival rate

to about 50 percent, says Diller. One child died during therapy, highlighting the tightrope that doctors are walking with current treatments for high-risk neuroblastoma patients. "We are at our limit with conventional chemotherapy, surgery, and radiation," she says. "Fortunately, a lot of new agents are being developed for this disease."

Tactics on trial

To make further gains, physicians will need to move beyond the brute-force assault of toxic drugs and radiation, turning to newer weapons that are more specific and less harmful to the body. Advancing this line of research is where Shusterman puts much of her time and energy. When she joined the Dana-Farber/Children's neuroblastoma program, she also became the principal investigator in Boston for NANT – New Approaches in Neuroblastoma Therapy – a collaboration of 14 universities and children's medical centers carrying out clinical trials of a variety of agents.

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One of the promising avenues being tested is shrinking tumors by choking off their blood supply with antiangiogenesis agents. Two such drugs, temozolomide and thalidomide, have been used in neuroblastoma, and the new angiogenesis inhibitor Avastin is under consideration for testing. A different type of drug, topotecan, prevents breaks in cancer cells' DNA from being repaired, thereby causing the cells to die. It has proved surprisingly effective in relapsed neuroblastoma, and a trial of the drug as a first-line treatment in newly diagnosed patients is being planned.

Another line of attack uses a targeted "search-and-destroy" strategy to deliver radiation directly to neuroblastoma cells. For example, a drug called MIBG is preferentially taken up by neuroblastoma tissue, and four medical centers in the United States are treating the tumors by linking radioactive iodine to MIBG, carrying targeted radiation to the neuroblastoma.

The treatment has few toxic side effects and in some studies has shrunk advanced tumors in 40 percent of relapsed patients. "These are very good results," says Shusterman, adding that more than three-quarters of patients get significant pain relief. She says she hopes the Dana-Farber/Children's program can begin offering the therapy this fall after construction of a special lead-lined treatment room.

Yet another "smart" weapon is an antibody called Hu14.18-IL2 that affixes to neuroblastoma cells and signals the patient's immune system to combat the cancer. A trial of this therapy has recently opened here. And one of the collaborative NANT studies is using cyclophosphamide, a chemotherapy agent, given in almost-constant small doses along with Zometa (zoledronic acid), an antiangiogenic drug that may help prevent a cancer from metastasizing (spreading) to the patient's bones.

A promising future

In September 2005, Brent McCreesh was declared free of cancer. He celebrated Christmas among 12 cousins and other extended family members from whom he'd been virtually cut off; during the chemotherapy and transplants, Brent wasn't allowed to be indoors with other children for 16 months, for fear of infection.

In saving his life, the extremely intense treatments have taken a toll on Brent. He is short – likely to reach a little over 5 feet – and he will be infertile; he also has some hearing loss. Despite the repeated chemo and whole-body radiation that can affect brain function, Brent has shown no signs of learning disabilities. In fact, his intelligence is above normal, a surprising observation in many neuroblastoma

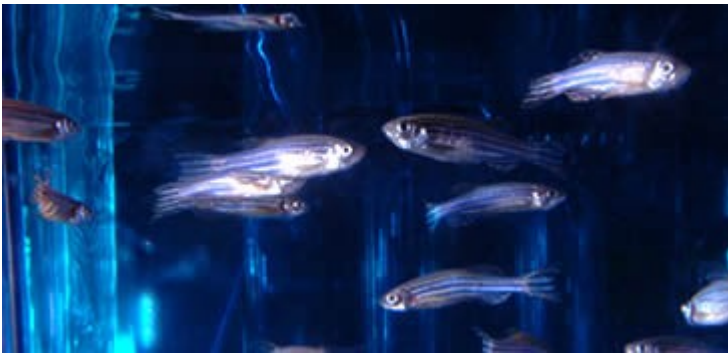
transplant survivors that hasn't been explained, notes Diller.

"Brent is amazing," says Dana McCreesh. "He's happy; he's at nursery school and having play dates." So far, so good. But the McCreeshes are holding their breath: Until three years have passed since Brent's transplants, there's a 50-50 chance of a recurrence. "We hope he enters permanent remission in June 2008," his mother adds.

Despite the daunting prognosis for a large segment of patients, says Shusterman, "This work is incredibly rewarding. You help people through the worst times of their life, and a lot of kids are now happy and active and thriving."

Fish and (gene) chips

By Richard Saltus



Not your average fish: zebrafish help propel neuroblastoma research

Neuroblastoma strikes the very young, not out of some malevolent biological design, but because of genetic damage to the immature nervous system. About 40 percent of neuroblastomas begin before birth, making it the most common cancer in newborns.

In addition to conducting research directly involving patients, Dana-Farber scientists are using powerful new biomedical tools to unravel the roots of neuroblastoma and search for drugs. For example, pediatric oncologists Kimberly Stegmaier, MD, and Todd Golub, MD, of Dana-Farber and the Broad Institute of the Massachusetts Institute of Technology and Harvard University have devised a method of rapidly testing thousands of chemicals and drugs against rare cancers such as neuroblastoma.



Thomas Look, MD, with (left to right) colleagues Jeong-Soo Lee, PhD, Rodney Stewart, PhD, Rani George, MD, PhD, and John Kanki, PhD

The novel strategy uses microarrays ("gene chips") to identify compounds that cause a favorable change in the genetic activity, or "signature," of cancer cells. "Neuroblastoma arises from immature

neural crest cells that have both an inability to mature and an abnormal capacity to proliferate," Stegmaier says. Although researchers have not yet found the molecular targets that cause these cells to differentiate, or specialize – thereby halting the cancerous proliferation – the large-scale testing method can identify compounds that may alter a cancer cell's gene activity to resemble that of a mature cell. "Such a drug might be effective in treating the cancer," she says.

On another front, Thomas Look, MD, of Dana-Farber and Children's Hospital Boston and his colleagues are investigating the genetics of nervous system development in the zebrafish, a small, brightly-striped and nearly transparent animal that reproduces rapidly and which, literally, provides a window on the formation of internal organs and systems.

Jeong-Soo Lee, PhD, a postdoctoral fellow in Look's lab, is creating a zebrafish equivalent of neuroblastoma for genetic research and for testing potential treatments. His strategy in the project, which is supported by a gift from the Durand family, is to insert into zebrafish embryos a cancer-causing oncogene, *MYCN*, that drives the most aggressive and hard-to-treat form of neuroblastoma in humans. Lee is devising a way to activate the gene at the appropriate time so the fish develop neuroblastoma but don't die before they can be studied.



Rodney Stewart and co-workers are studying nerve development in zebrafish for clues to neuroblastoma.

Other investigators are hunting genes involved in embryonic growth of the nervous system. "Some of these genes have already been identified, and we're looking for mutations among neuroblastoma patient samples," says Dana-Farber postdoctoral fellow **Rodney Stewart, PhD**. Colleague **Rani George, MD, PhD**, is using a cutting-edge technique for finding small genetic alterations, called single nucleotide polymorphisms, that might reveal mutations in molecules that regulate nerve-cell growth.

Look's lab also runs tests on most of the neuroblastoma tumors taken from patients in the United States and Australia, to help determine whether these individuals are at low, intermediate, or high risk of cancer recurrence. The results can guide physicians toward the best treatments, says **Lisa Moreau**, supervisor of the DFCI Neuroblastoma Reference Library.