New discoveries offer first new hope in three decades for lethal pediatric brain tumor

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A pediatric brain tumor that causes gruesome suffering is finally yielding its secrets. For the first time, scientists at the Stanford University School of Medicine have cultured human cells from this cancer, Diffuse Intrinsic Pontine Glioma, and used those cells to create an animal model of the disease. Their discoveries will facilitate research on new treatments for DIPG, a tumor of school-aged children that is now almost universally fatal.

The advances come thanks to the parents of young cancer victims, who donated their deceased children's brain tumors for research in the hopes of sparing other families the pain they had experienced. Because of its location in the brain stem, this cancer is rarely biopsied, so scientists have had few previous opportunities to examine the tumors.

A diagnosis of DIPG is "a death sentence for kids," said John Jewett, whose son Dylan died of DIPG in 2009 at age 5. "No parent should have to hear that, but doctors can't study the disease unless somebody makes a donation." John and his wife, Danah, were the first parents to donate their child's tumor to the Stanford team.

"These donations open up the world in terms of being able to study this tumor, understand the biology behind its growth and develop therapies," said Michelle Monje, MD, PhD, an instructor in neurology and neurological sciences at Stanford who is the primary author of the new study, which will be published online Feb. 28 in Proceedings of the National Academy of Sciences.

The Stanford team's findings include new insight into molecular signals that prompt the cancer to grow. The signals could be good targets for anti-tumor drugs.

"So little is known about this disease," said Philip Beachy, PhD, professor of developmental biology and senior author of the study. "This work has the potential of moving us a huge step forward, particularly with the identification of a specific pathway important in the biology of the tumor, which could serve as a therapeutic target."

Treatment advances for DIPG have been stagnant for 35 years, said Monje, who treats DIPG patients at Lucile Packard Children's Hospital, where she was Dylan Jewett's doctor. The cancer primarily affects children ages 5 to 9, striking 200 to 400 children per year in the United States and killing quickly. Radiation therapy offers temporary remission, but patients soon relapse; just one victim in 100 survives five years. No effective chemotherapy drugs exist, and, because the malignant cells entwine themselves with healthy cells in a region of the brain stem essential for life, surgery is impossible. The disease takes away control of basic body functions such as talking, swallowing and moving one's eyes or limbs, but leaves victims aware of what is happening as their condition declines.

"It's horrific," Monje said.

The researchers began their investigation by focusing on a specific molecular signaling pathway, known as the Hedgehog pathway, that they thought might be driving development of DIPG cells. The Hedgehog pathway has already been shown to play a role in the growth of several other kinds of brain tumor. The team's early experiments supported the idea that the Hedgehog pathway is part of the pathology of DIPG, suggesting that it would be a good target for drugs.

As part of their work, the scientists isolated DIPG tumor cells from brain tissue of two young DIPG victims and grew the cells in the lab. Other institutions have attempted to grow similar primary tissue cultures, but the Stanford team is the first to succeed, thanks in large part to the expertise of Siddhartha "Sid" Mitra, PhD, a postdoctoral research scholar in neurosurgery.

The researchers' experiments also included introducing human DIPG cells to the brains of healthy mice, which revealed that the cancer cells would form DIPG-like tumors. They plan to use this xenograft model to perform further studies of DIPG biology and to conduct early stage tests of potential drugs.

"Just having this model makes possible a real attack on the problem," Beachy said.

Several pharmaceutical companies are currently developing drugs to inhibit the Hedgehog signaling pathway, and two drugs already approved by the FDA for other purposes have been found to have anti-Hedgehog activity. Such drugs will form the basis for the Stanford team's upcoming research on DIPG therapies in the mouse model and in children with the disease.

For the families who donated their children's tumors to the Stanford research, the gift provides an opportunity to have some good come from a terrible personal tragedy. For Dylan Jewett's parents, grieving the loss of a little boy who had loved pretending to be a superhero, hugging his baby brother and building tracks for his Thomas the Tank Engine train, the donation seemed like the only thing to do.

"We couldn't think not to," said Danah Jewett of her family's decision to give Dylan's tumor for research. "Our options were to try and help, or to let him die in vain. Now we feel like his story lives on."