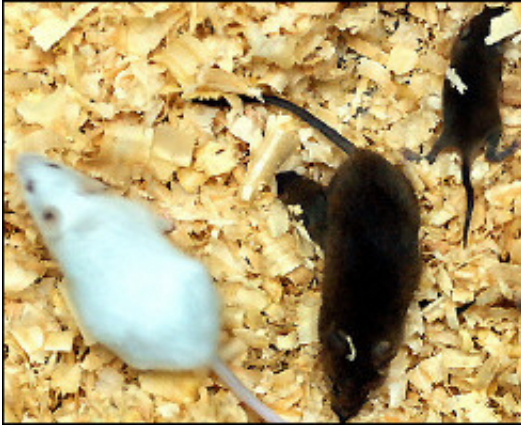


# Genetically modified cells attack tumors

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## **St. Jude researchers show genetically modified stem cells in the nervous system actively seek out even tiny tumors**

Mice with neuroblastoma tumors have been successfully treated with genetically modified cells that sought out the cancer cells and activated a chemotherapy drug directly at those sites, according to investigators at St. Jude Children's Research Hospital and their colleagues at City of Hope National Medical Center (Duarte, Calif.) and the University of British Columbia (Vancouver, Canada). Neuroblastoma is a solid tumor that arises in the part of the nervous system outside the brain.

The researchers also showed that the modified cells migrated to tumors regardless of how small the tumors were or where they were located in the body. A report on this work appears in the Dec. 20 issue of the Web-

based journal PLoS ONE.

The study is the first to provide evidence that such cells, called neural stem-progenitor cells (NSPCs), can be used to target solid tumors that have metastasized (spread from their original site), according to the researchers. During normal development NSPCs give rise to all the various types of cells in the brain.

Moreover, since the drug, called CPT-11 (irinotecan), is already used to treat cancers, doctors and scientists already know how the drug behaves in humans. That knowledge should make it easier to translate these laboratory findings to the clinic, the researchers said.

The ability to target tumors with CPT-11 suggests that this technique could let clinicians treat tumors in humans more effectively while avoiding side effects caused by damage to normal cells. The success with neuroblastoma also suggests this technique might improve the treatment of other solid tumors that metastasize, such as colon and prostate cancer.

This homing ability is especially important in the case of high-risk neuroblastoma because even very small tumors that survive after an initially successful treatment often generate more cancer cells that spread and become unresponsive to treatment, said Mary Danks, Ph.D., associate member of Molecular Pharmacology at St. Jude. Therefore, the study holds special promise for children with high-risk neuroblastoma because as many as 80 percent of these patients relapse with chemotherapy-resistant metastatic cancer. Neuroblastoma is considered high risk if the tumors have certain genetic mutations or have already spread when the cancer is diagnosed.

"Clinicians are limited in how aggressively they can treat these children because the chemotherapy drugs produce harsh side effects and therefore must be administered at reduced levels," Danks said. "But by

targeting tumor cells while avoiding normal cells, doctors could treat the neuroblastoma aggressively while minimizing side effects." Danks is senior author of the PLoS ONE report.

The researchers based their new treatment on work previously reported that showed certain NSPCs have a natural tendency to seek out damaged or cancerous areas in the brain.

In the current study, the researchers first injected into mice that had neuroblastoma large numbers of NSPCs that had been genetically modified to carry a drug-activating enzyme called rabbit carboxylesterase (rCE). The NSPCs traveled to the tumors and used the gene to produce rCE. Three days later the team injected the CPT-11 into the mice. The drug dispersed throughout the mice but was activated by rCE selectively at the neuroblastoma tumors. The researchers used the rabbit form of this enzyme because it activates CPT-11 much more efficiently than the human version, Danks said. This activation is essential to treatment because the activated form is up to 1,000 times more active than CPT-11.

While half of a group of 10 mice that received only CPT-11 survived for six months, all 10 mice treated with both the modified NSPCs and CPT-11 survived for more than six months.

"There is a real need for new treatments for neuroblastoma that target tumor cells while having minimal side effects," said Karen S. Aboody, M.D., assistant professor in the Division of Hematology and Hematopoietic Cell Transplantation at City of Hope. "The use of NSPCs carrying the gene for rCE might fill that need." Aboody is first author of the PLoS ONE report.

Source: St. Jude Children's Research Hospital

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