UT SOUTHWESTERN MEDICAL CENTER NEWS

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Cancer requires support from immune system to develop, UT Southwestern researchers report

DALLAS – Oct. 30, 2008 – Tumors that grow around nerves in a rare genetic disease need cooperation from cells from the immune system in order to grow, reports a team of scientists, including researchers from UT Southwestern Medical Center.

Treating mice with a drug that attacks the immune cells – not the tumor – greatly reduced the size and metabolism of the tumors, the scientists reported. A clinical trial of the treatment in humans has begun.

"It was not the tumor being treated, but its environment," said Dr. Luis Parada, chairman of developmental biology at UT Southwestern and co-senior author of the study, which appears in the Oct. 31 issue of the journal *Cell*. "This insight has led to a very promising therapy of a previously untreatable tumor.

"This is the first time a mouse model has been used to gain insight into a cancer that could not be derived from patient studies," said Dr. Parada, director of the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration.

The researchers were studying tumors called plexiform neurofibromas, which occur around peripheral nerves. In humans, they occur as part of a genetic disease called neurofibromatosis-1. About 25 percent to 40 percent of people with the disease develop the tumors, which are generally benign but can grow large enough to cause disfigurement or disability and can sometimes become malignant.

These tumors are complex structures that include many different types of cells, particularly Schwann cells, which provide a fatty coating that makes nerve cells electrically efficient, and mast cells.

Because of their complexity, plexiform neurofibromas are difficult to remove surgically, and there is currently no cure for them.

Neurofibromatosis-1 is caused by a mutation in a single gene called *Nf1*. About 250,000 people in the U.S., Europe and Japan have this mutation. The mutation is dominant, meaning that

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people with one normal gene and one mutated gene develop the disease.

The UT Southwestern researchers had previously found in mice that plexiform neurofibromas develop from Schwann cells that have two mutated copies of *Nf1*. In addition, they discovered that even before a plexiform neurofibroma begins to form around a nerve, mast cells migrate into the area.

In the current study, the scientists used genetically engineered mice to confirm first that the animals need two mutated copies of *Nf1* in their Schwann cells to develop neurofibromas, which the rest of their cells can still have one normal and one mutant *Nf1* gene.

In addition, a bone marrow transplant from normal mice with two normal *Nf1* genes prevented 90 percent of the engineered mice from developing neurofibromas, confirming that even with two mutated genes in the Schwann cells, a mutated copy must also be present in other cells. Bone marrow is the source of mast cells, blood cells and many other types of cells that circulate through blood vessels.

The researchers then focused on the role of mast cells in tumor formation, particularly a molecule on the cells' surface called c-kit, which controls many functions, including migration and proliferation.

The mice engineered to develop tumors were given the drug imatinib mesylate, also known as Gleevec. The drug, known to inhibit c-kit, currently is used to treat chronic myelogenous leukemia and other cancers.

Positron emission tomography scans showed that Gleevec halved the metabolic activity of the tumors, while later examination confirmed that the tumors were much smaller than in placebo-treated mice.

"We found there was a requirement from the immune system to interact with the tumor for the tumor to grow," Dr. Parada said. "When mast cells are blocked, the tumor cannot grow."

During the course of these experiments, the researchers learned about a girl who had a large neurofibroma that could not be removed surgically because too many blood vessels were involved. Because Gleevec is already approved for other conditions, the girl's doctor treated her under "compassionate use" guidelines.

The girl's tumor shrank by 70 percent with no apparent side effects during the first three months of a six-month treatment under "compassionate use" regulations. The mass has remained dormant in the six months afterward, the researchers reported.

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While this was only a single case, it was consistent with the one-year study of the tumor and its action in mice, Dr. Parada said, and the child's treatment was tailored to reflect the findings from the animal study.

A phase 2 clinical trial of this treatment in people with neurofibromatosis has been approved and is under way.

Dr. Parada cautioned, however, that further research is needed. A single human case, while encouraging, is not enough to prove the long-term effectiveness of the treatment, and Gleevec might be exerting other actions in addition to inhibiting mast cells.

Other UT Southwestern researchers involved in the study were Dr. Yuan Zhu, former instructor of developmental biology, and Dr. Dennis Burns, professor of pathology. Researchers from Indiana University School of Medicine, including co-senior author Dr. D. Wade Clapp, also participated.

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