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Antibody hinders growth of Gleevec-resistant gastrointestinal tumors in lab tests

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An antibody that binds to a molecule on the surface of a rare but deadly tumor of the gastrointestinal tract inhibits the growth of the cancer cells in mice, according to researchers at the Stanford University School of Medicine.

The effect remains even when the cancer cells have become resistant to other treatments, and the findings may one day provide a glimmer of hope for people with the cancer, known as gastrointestinal stromal tumor , or GIST. The scientists hope to move into human clinical trials of the antibody within two years.

The antibody's target is a receptor called KIT, which is often mutated in patients with the cancer. When mutated, KIT sends a continuous stream of messages into the cell urging it to grow uncontrollably. The Stanford researchers found that the antibody reduces the amount of KIT on the surface of the cancer cells and stimulates immune cells called macrophages to kill the rogue cells.

Currently, people with GIST are often treated first with surgery and then with the drug imatinib, marketed as Gleevec - a small molecule that also targets KIT. The treatment, which was approved for GIST in 2002, has been remarkably successful: It has increased the average survival time of many people with advanced disease from about 18 months to about five years. It was the first targeted small molecule inhibitor that proved effective against a solid tumor, but its effect is temporary.

"Gleevec, or imatinib, marked a paradigm shift in our understanding about cancer treatment and sparked much additional research into these inhibitors," said Matt van de Rijn, MD, PhD, professor of pathology. "However, a new mutation almost always occurs over time in KIT that renders the tumor insensitive to the drug. We've found that treatment of these resistant cells with an antibody targeting KIT slows the growth of human GIST cells in cell culture and in animals, and increases their chances of being removed by the immune system."

The researchers believe it may be possible that the anti-KIT antibody treatment could be used as an alternative to, or even in combination with, imatinib or other small-molecule or antibody-based therapies to provide better control of the cancer.

"We're moving from an era in which, historically, patients are often treated with a single agent or class of agents into a time when tumors might be treated with more than one approach from the moment of diagnosis," said van de Rijn.

He is a co-senior author of the study, which will be published online Feb. 4 in the *Proceedings of the National Academy of Sciences*. Irving Weissman, MD, director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, is the other co-senior author. Former graduate student Badreddin Edris, PhD, postdoctoral scholar Stephen Willingham, PhD, and graduate student Kipp Weiskopf share first authorship of the paper. Weissman is also a member of Stanford's Cancer Institute.

About 3,000 to 6,000 people per year are diagnosed with GIST in the United States. Seventy to 80 percent of these cancers have what's called an activating mutation in the cell surface receptor called KIT. This mutation causes the receptor to bombard the cells with the signal to proliferate and drives tumor growth. Although imantinib binds to KIT

and inactivates its signaling - resulting in the temporary control of the disease in about 80 percent of cases - the receptor will nearly always develop a new mutation that renders it resistant to the small molecule.

Researchers in the van de Rijn and Weissman labs used cancer cell lines isolated from three patients with GIST for their study: Two were from patients whose tumors had become resistant to imatinib, and one was from a patient whose tumor was still sensitive to the treatment. They also used a cancer cell line from a patient with an unrelated cancer, called a leiomyosarcoma, as a control.

When they treated the cancer cells in a laboratory dish with the anti-KIT antibody, called SR1, the researchers found that the GIST tumor cells grew significantly more slowly than did the control cancer cells, regardless of their sensitivity or resistance to imatinib. When they investigated more closely, they found that the tumor cells exposed to the anti-KIT antibody expressed less KIT on their surface than did untreated cells. Furthermore, all three of the antibody-treated GIST cell lines were significantly more likely to be enveloped and destroyed by a type of immune cell called a macrophage than were untreated or control cancer cells.

To confirm their findings, the researchers genetically engineered the three GIST tumor cell lines to express proteins that emit colored light under certain conditions. This allowed them to track the growth and location of the cells in living laboratory animals over time. They injected the engineered cells into the abdominal cavities of mice, waited two weeks for the cancer cells to become established and then treated the animals with the anti-KIT antibody.

"Although the tumors from the imatinib-resistant cell lines continued to grow, their growth rate was reduced by about 10-fold when compared to that observed in untreated animals," said van de Rijn.

The researchers are now planning to investigate whether a combination treatment of anti-KIT plus imatinib, or anti-KIT plus an antibody that targets a cell-surface molecule called CD47 previously identified in Weissman's laboratory, will further inhibit tumor growth. (Anti-CD47 treatment has been shown to block a "don't eat me" signal expressed by many types of cancer cells that protects them against macrophages.)

Coupling anti-CD47 with another treatment such as anti-KIT that appears to enhance the engulfment of the cancer cells by macrophages may provide a synergistic effect against the tumor, the researchers believe. A similar approach was shown to cure aggressive non-Hodgkin's lymphoma in mice in Weissman's lab in 2010.

Provided by Stanford University Medical Center

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