SOUTHWESTERN NEWS

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# HARMFUL SIDE EFFECT ELIMINATED FROM IMMUNOTOXIN USED AS CANCER THERAPY

DALLAS – March 12, 2003 – A dangerous side effect of an immunotoxin that selectively kills cancer cells has been successfully eliminated in mice models, according to researchers at UT Southwestern Medical Center at Dallas.

The study evaluated genetically engineered mutations of the immunotoxin with the goal of eradicating the side effect known as vascular leak syndrome (VLS). The condition, which can cause severe weight gain, pulmonary edema and dangerously low blood pressure in humans, occurs when the immunotoxin – made with the enzymatically active A chain of the toxin ricin – damages the layer of endothelial cells that line the blood vessels. The four-year study is online and will be published in a future issue of *Nature Biotechnology*.

Genetically engineered versions of the cancer-fighting immunotoxin were administered to mice with human cancer of the lymphoid cells. Researchers identified one genetically altered form of the immunotoxin that did not cause VLS in mice and also more effectively destroyed cancer cells than earlier generations of the therapy.

Researchers said the finding lays the groundwork for human clinical trials and could facilitate the development of many other therapeutic agents if the elimination of VLS can be duplicated in other immunotoxin families.

"This was the bottleneck of the entire field. It was a broader problem than just our particular immunotoxins," said Dr. Ellen Vitetta, the study's senior author and director of the Cancer Immunobiology Center at UT Southwestern. "Any type of immunotoxin causes vascular leak. Should these findings hold in other families of immunotoxins and cytokines, such as interleukin-2, they might be improved as well."

Immunotoxins are hybrid molecules consisting of antibodies linked to toxins or their subunits. The ricin A chain immunotoxin works by attaching itself selectively to cancer cells. When internalized by the cell, the ricin A chain separates from the tumor-reactive antibody and makes its way into the cytosol, where it enzymatically inhibits protein synthesis, causing the cell to die.

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"It's not perfectly specific to cancer cells, but it is semiselective for cancer cells," said Dr. Joan Smallshaw, postdoctoral researcher in the Cancer Immunobiology Center and lead author of the *Nature Biotechnology* study.

The elimination of VLS in mice caps more than 20 years of research into the use of immunotoxins to treat diseases such as cancer and autoimmune disease. The first clinical trials in humans were initiated in the 1980s. Over the next decade, more than 250 patients at eight clinical sites in four countries were treated with three different immunotoxins produced in the Cancer Immunobiology Center's laboratories. While proving effective in killing tumor cells in patients with Hodgkin's disease and non-Hodgkin's lymphoma, the study also revealed the existence of VLS as a dose-limiting side effect.

"We hope this is the next-to-final phase of a very long journey," Vitetta said. "The final phase will take place in patients. If we've fixed it, we're near the finish line."

Vitetta's work with ricin recently received international attention when she and a team of UT Southwestern researchers developed an experimental vaccine for the deadly toxin as an outgrowth of their cancer-therapy work.

Ricin is easily produced from castor beans. A single ricin molecule inside a cell shuts down protein synthesis, killing the cell. Ricin can be administered in foods and water or sprayed as an aerosol. A small dose can produce flulike symptoms and result in death in a few days.

Other UT Southwestern researchers from the Cancer Immunobiology Center who worked on the study were Dr. Victor Ghetie, professor; Dr. Maria-Ana Ghetie, assistant professor; Linda Trahan, research scientist; and John Fulmer, research associate. Dr. Jose Rizo-Rey, associate professor of biochemistry, also contributed.

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