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KILLING MALIGNANT TUMORS BY COAGULATING THEIR BLOOD SUPPLY

DALLAS — January 24, 1997 — By engineering proteins that coagulate the blood that feeds malignant tumors, scientists at UT Southwestern Medical Center at Dallas have succeeded in destroying malignancies in mice. This therapy is expected to be effective on all major cancers, with clinical trials on humans possibly starting within two years.

The study, published in the Jan. 24 issue of the journal *Science,* shows that human coagulant proteins can be targeted to the flat cells lining vessels that deliver blood to the tumors. Cutting off the blood to the tumor kills the cancerous cells by depriving them of oxygen and nutrients, said Dr. Philip Thorpe, UT Southwestern pharmacology professor and holder of the Serena S. Simmons Distinguished Chair in Cancer Immunopharmacology.

"We engineered the tumor to induce a marker on the vessels," said Thorpe, senior researcher on the project conducted at UT Southwestern's Hamon Center for Therapeutic Oncology Research. "Then we took a human coagulant protein, called tissue factor (TF), and targeted it so that blood clots formed in the tumor vessels."

To ensure the protein would not cause coagulation before it reached the tumor, scientists altered the genes for TF. This engineering deleted the part of the molecule that allows it to associate with normal cell membranes.

"That renders our protein soluble so that it can be targeted to the cancer's blood vessels. When it arrives in the tumor vasculature, it sticks to the endothelial cells that line the vessels. This brings the tissue factor into contact with the cell membrane, enabling coagulation to proceed normally, but only in the tumor vessels," Thorpe said. "It's like an on/off switch."

In the study, mice with neuroblastoma tumors that were approximately 2 to 5 percent of their body weight were used. The size of these malignancies would be the equivalent of about two to five pounds in a person.

Within minutes after the mice were treated with the targeted tissue factor molecule, the

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tumor's vessels were blocked by blood clots. By 24 hours, tumor cell death was seen throughout the tumor. At 14 days after therapy began, 38 percent of the mice had only fibrous scar tissue visible where the neuroblastomas had been. In other words, the rodents experienced complete tumor regression.

"What is remarkable about this treatment is that it is so effective on large tumors and appears to be safe," Thorpe said. "We have observed little or no toxicity using this method."

The researchers now are trying to find markers that occur naturally on blood vessels in human tumors so the therapy can be tested clinically. They have two markers that they believe will work. One is a growth factor known as vascular endothelial growth factor or VEGF. Virtually all solid tumors secrete VEGF which binds to its receptor on the endothelial cells. Antibodies against VEGF have been shown to localize specifically to tumor vessels in guinea pigs in research done by Dr. Hal Dvorak and his colleagues at Harvard University Medical School. That work has been verified in Thorpe's laboratory.

"So, we have a good coagulation method, and we have a good method for targeting human tumor vessels," Thorpe said. "We hope to merge those two to produce an effective treatment for cancers in people."

All major types of cancer, including breast, colon, lung and ovary, are expected to respond to the therapy. UT Southwestern already has licensed the technology for this research to Peregrine Pharmaceuticals Inc., which is being acquired by Techniclone International. The companies will market the drugs after testing on humans is completed.

The other scientists involved in this study are UT Southwestern pharmacology postdoctoral fellows and research associates Drs. Xian Ming Huang, Grietje Molema, Steven King and Linda Watkins. Dr. Thomas Edgington at the Scripps Research Institute in La Jolla, Calif., also participated in the work. Molema is now at the Groningen Utrecht Institute for Drug Exploration, University of Groningen, the Netherlands.

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