Researchers say decoy shows promise as cancer-fighter in novel phase 0 trial

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(Medical Xpress) -- A critical protein that had been deemed "undruggable" can be effectively targeted by using a decoy to fool the body into a cancer-fighting response, according to researchers at the University of Pittsburgh Cancer Institute (UPCI) and the University of Pittsburgh School of Medicine. In a report in the August issue of *Cancer Discovery*, they showed the decoy was successful in a phase 0 study, an uncommon but useful preface to the commencement of standard human trials.

Activation and increased signaling of a protein known as Signal Transducer and Activator of Transcription 3 (STAT3) has been identified in many cancers and is associated with poor prognosis, said senior author Jennifer Grandis, M.D., professor of otolaryngology and pharmacology and chemical biology, Pitt School of Medicine, and director of the Head and Neck Program at the University of Pittsburgh Cancer Institute (UPCI). Transcription factors such as STAT3 regulate the activity, or expression, of other genes; in adult tissues, STAT3 triggers the production of other proteins that promote the growth and survival of cancer cells.

"Lab experiments have shown that inhibiting STAT3 activity or function limits the proliferation and survival of a variety of cancer cell lines," she explained. "But the drugs that have been tested in patients are not selective for STAT3 and haven't been effective."

So her research team tried an unusual approach: they fooled the STAT3

protein into binding to a harmless decoy that they engineered, rather than the real gene sequence that would have initiated the production of cancer-promoting proteins. Preclinical experiments showed that the strategy was tolerated well and didn't produce toxic side effects.

To further justify clinical development, the team conducted a phase 0 study to see if the decoy would work in humans. First, they took biopsies of head and neck cancers in 30 patients who were having surgery to remove the tumors. At the start of the operation, the tumors were injected with either the decoy or a salt-water placebo. After surgery, about four hours after injection, the cancerous tissue that had been taken out of each patient was biopsied again. Tests were conducted in the specimens to determine the activity of genes regulated by STAT3.

"We found reduced expression of the STAT3 target genes in tumors that had been treated with the decoy compared to those that got a placebo injection and to pre-treatment samples," Dr. Grandis said. "This indicates we were able to selectively inhibit STAT3, which is a significant step forward."

The researchers also developed a version of the decoy that could be injected into the bloodstream, which inhibited tumor growth in a mouse model of head and neck cancer.

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