Study finds more effective approach against ovarian cancer

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In a recent issue of Cancer Research, Daniel J. Powell, Jr., PhD, a research assistant professor of Pathology and Laboratory Medicine and Obstetrics and Gynecology at the Perelman School of Medicine at the University of Pennsylvania, showed for the first time that engineered human T cells can eradicate deadly human ovarian cancer in immune-deficient mice. Ovarian cancer is the most lethal reproductive cancer for women, with one-fifth of women diagnosed with advanced disease surviving five years. Nearly all ovarian cancers (90%) are characterized by their expression of a distinct cell-surface protein called alpha-folate receptor, which can be a target for engineered T cells.

In a past clinical study, first generation engineered T cells did not shrink tumors in women with ovarian cancer because the T cells did not persist in the patients. The new second generation technology developed in the current study overcomes the limitations of the first generation approach. Here, second generation T cells shrank tumors; whereas, T cells engineered using first generation technology did not.

The alpha-folate receptor is expressed on the surface of ovarian cancer cells and has a high affinity for folic acid, a vitamin which helps "feed" the cancer cells, and represents an "Achilles' Heel" for cancer researchers to target.

"We anticipate the opening of a genetically modified T cell clinical trial in the next few months for women with recurrent ovarian cancer," says Powell. "Targeting the alpha-folate receptor is an opportunity for

widespread clinical application."

Until now, human T cells engineered to express an antibody fragment specific for the alpha-folate receptor protein have shown anti-tumor activity against epithelial cancers in the lab, but not in the clinic due to their inability to persist and home to tumors in the human body. The modified T cells used in this study express an engineered fusion protein – called a chimeric antigen receptor — that combines the specificity of an antibody with the T cell signaling portions from two different proteins that stimulate the immune system to recognize ovarian cancer cells. These added signaling protein pieces give the engineered T cells the extra survival signals they need to do their job.

Two Birds, One Stone T Cells

The double-barreled cells are engineered to multiply, survive, recognize, and kill ovarian tumors. The modified T cells are expanded for two weeks in the lab, and then tested for reactivity by exposing them to human ovarian cancer cells to see if they destroy the cancer cells. Researchers also test for effectiveness by measuring cytokine production by the T cells, a sign of inflammation produced by the engineered T cells when killing cancer cells.

The new second generation engineered cells were successful in many ways. They were resistant to cancer-induced cell death: Fewer new T cells died when exposed to cancer cells, compared to the older technology. The new T cells also multiply better and survive; therefore their numbers increase over time in test-tube experiments and in the mouse model.

A clinical trial using these T cells is pending with George Coukos, MD, Director of the Ovarian Cancer Research Center at Penn and the trial's principal investigator. Penn is the only study site identified to date.

Investigators aim to recruit up to 21 patients with advanced recurrent ovarian cancer whose tumors express the alpha-folate receptor.

"This technology represents a promising advancement for the treatment of women with ovarian cancer," Powell says, "But we will continue to work around the clock to improve this approach using other costimulatory portions and antibody-like proteins to make this the most powerful and safe approach for the treatment of the greatest number of women with this horrible disease."

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