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Researchers uncover novel immune therapy for pancreatic cancer

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Researchers at the University of Pennsylvania's Abramson Cancer Center have discovered a novel way of treating pancreatic cancer by activating the immune system to destroy the cancer's scaffolding. The strategy was tested in a small cohort of patients with advanced pancreatic cancer, several of whose tumors shrank substantially. The team believes their findings – and the novel way in which they uncovered them -- could lead to quicker, less expensive cancer drug development.

The authors call the results, published in the March 25 issue of *Science,* a big surprise. "Until this research, we thought the immune system needed to attack the cancer directly in order to be effective," said senior author Robert H. Vonderheide, MD, DPhil, an associate professor of Medicine in the division of Hematology/Oncology and the Abramson Family Cancer Research Institute. "Now we know that isn't necessarily so. Attacking the dense tissues surrounding the cancer is another approach, similar to attacking a brick wall by dissolving the mortar in the wall. Ultimately, the immune system was able to eat away at this tissue surrounding the cancer, and the tumors fell apart as a result of that assault. These results provide fresh insight to build new immune therapies for cancer."

The current study is part of a unique research model designed to move back and forth between the bench and the bedside, with the investigative team consisting of researchers based in both the laboratory and in the clinic. In the clinical trial led at Penn by Peter O'Dwyer, MD, professor of Hematology/Oncology, and Gregory L. Beatty, MD, PhD, instructor

of Hematology/Oncology, pancreatic cancer patients received standard gemcitabine chemotherapy with an experimental antibody manufactured by Pfizer Corporation. The antibody binds and stimulates a cell surface receptor called CD40, which is a key regulator of T-cell activation. The team initially hypothesized that the CD40 antibodies would turn on the T cells and allow them to attack the tumor.

The treatment appeared to work, with some patients' tumors shrinking substantially and the vast majority of tumors losing metabolic activity after therapy, although all of the responding patients eventually relapsed. When the researchers looked at post-treatment tumor samples, obtained via biopsy or surgical removal, there were no T cells to be seen. Instead, they saw an abundance of another white blood cell known as macrophages.

To understand what was happening in the tissues of these patients, Vonderheide and Beatty and colleagues turned to a mouse model of pancreatic cancer developed several years ago at Penn. Unlike older mouse models that were simplistic models of human disease, new genetically engineered mice develop spontaneous cancers that are very close reproductions of human tumors. "We can perform preclinical trials in these mice with the same principles we use in our patients," Vonderheide says, noting that the team even used a randomization protocol to assign individual mice to different arms of the study.

When the investigators treated mice that developed pancreatic cancer with gemcitabine in combination with CD40 antibodies, the results looked like those of the human trial. Some mouse tumors shrank and were found to be loaded with macrophages but contained few or no T cells. Closer inspection showed that the macrophages were attacking what is known as the tumor stroma, the supporting tissue around the tumor. Pancreatic tumors secrete chemical signals that draw macrophages to the tumor site, but if left to their own devices, these

macrophages would protect the tumor. However, treating the mice (or patients) with CD40 antibodies seemed to flip that system on its head. "It is something of a Trojan horse approach," Vonderheide says. "The tumor is still calling in macrophages, but now we've used the CD40 receptor to re-educate those macrophages to attack – not promote – the tumor."

The researchers believe that the CD40 antibodies also activated T cells in the mice, but the T cells couldn't get into the tumor or its surrounding tissue. "We learned that T cells have a major problem with migration into tumors, and this may be a particular problem for pancreatic cancer," Vonderheide says. "The area surrounding pancreatic cancers is very dense, fibrotic, and hostile. This is one of the main reasons standard therapies for this disease often work so poorly."

The researchers are now working on ways to capitalize on their novel information, testing ways to super-charge the macrophage response and to get the T cells into the tumor microenvironment. Vonderheide thinks his team can speed up clinical research by running pilot trials in the mice to test potential therapeutics. Once they understand responses in the mice, then they can use that information to design better human trials.

"Beyond our specific findings, we think these findings point to a new approach for drug development in cancer -- one where we use state-of-the-art mouse models for preclinical trials to guide which trials we should do next in patients," Vonderheide says. "It should be faster, cheaper and give us a head start in the clinical trials."

Provided by University of Pennsylvania School of Medicine

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