Vaccine 'reprograms' pancreatic cancers to respond to immunotherapy

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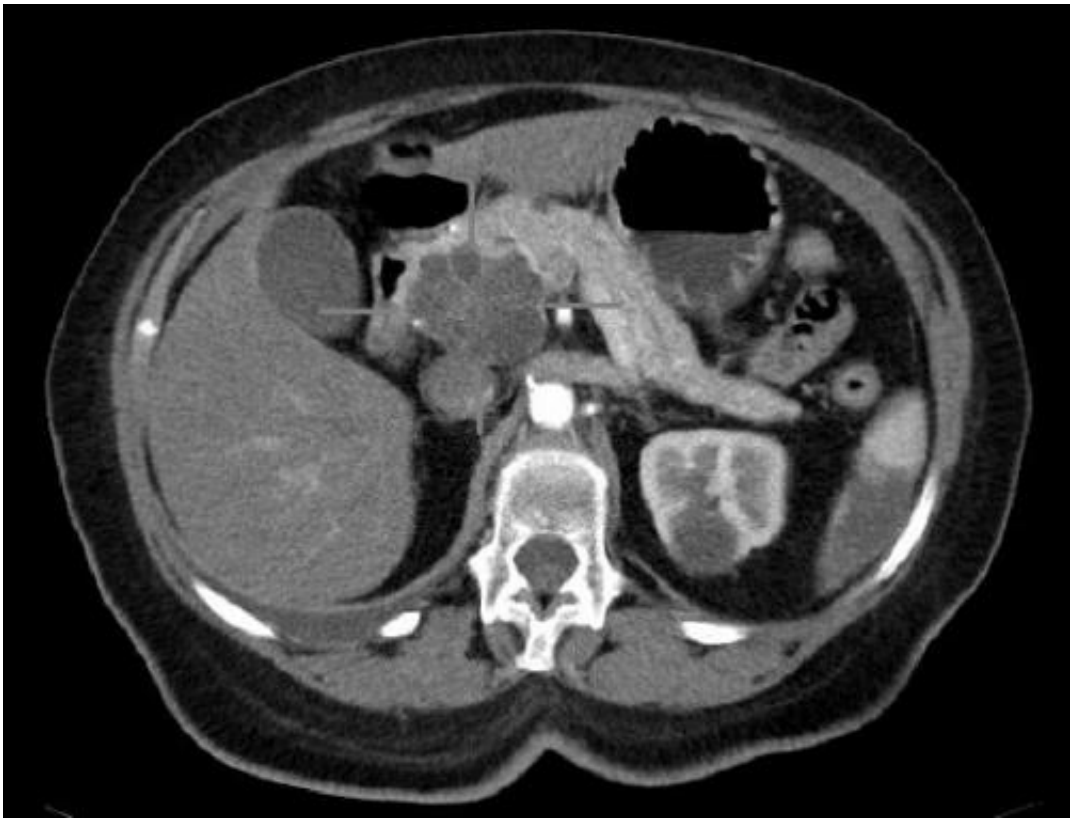

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Researchers at the Johns Hopkins Kimmel Cancer Center have developed and tested a vaccine that triggered the growth of immune cell nodules within pancreatic tumors, essentially reprogramming these

intractable cancers and potentially making them vulnerable to immune-based therapies.

In their study described in the June 18 issue of *Cancer Immunology Research*, the Johns Hopkins team tested the vaccine in 39 people with pancreatic ductal adenocarcinomas (PDAC), the most common form of pancreatic cancer. The disease becomes resistant to standard chemotherapies and is particularly lethal, with fewer than 5 percent of patients surviving five years after their diagnosis.

PDACs do not typically trigger an immune response against the cancer cells that comprise, but with the help of a vaccine developed by Johns Hopkins researcher Elizabeth Jaffee, M.D., the scientists were able to "reprogram" tumors to include cancer-fighting immune system T cells.

The vaccine, known as GVAX, consists of irradiated tumor cells that have been modified to recruit immune cells to a patient's tumor. The researchers tested GVAX in combination with an immune modulator drug called cyclophosphamide, which targets a type of immune cell, called Tregs, that typically suppresses the immune response of certain T cells that destroy cancer.

The reprogramming is designed to make the tumors more vulnerable to other immune-modulating drugs that have been useful in fighting other cancers, said Jaffee, The Dana and Albert "Cubby" Broccoli Professor of Oncology at the Johns Hopkins University School of Medicine.

Jaffee and colleague, Lei Zheng, M.D., say the vaccine could potentially convert many types of tumors to a state where immunotherapies can have a much larger impact.

For example, Jaffee says, in certain melanomas, "we've tested immunotherapies that target T cells and have found a 10-30 percent

response in cancers that naturally have the ability to trigger immune system responses, but there are few options for the other 70 percent of patients who barely or never respond to immunotherapies."

The researchers found that the vaccine created structures called tertiary lymphoid aggregates within the patients' tumor, structures that help regulate immune cell activation and movement. The aggregates, which appeared in 33 of the 39 patients treated with the vaccine, had surprisingly well-organized structures that do not typically appear in these types of tumors naturally, said Zheng, an assistant professor of oncology and surgery at the Johns Hopkins University School of Medicine. "This suggests that there has been significant reprogramming of lymphocyte structures within the tumor."

The aggregates could "really shift the immunologic balance within a tumor, setting up an environment to activate good T cells to fight the cancer, by tamping down Tregs," Jaffee said, "and such T cells would be educated to recognize the cancer proteins in that specific tumor environment."

The vaccine and the resulting lymphoid aggregates boosted the activity of several molecular mechanisms that, like Tregs, inhibit cancer-fighting immune cells. That may sound like a bad thing, but it actually provides many new potential targets within the tumor for immune-modulating drugs, Zheng explained.

The researchers' next study in PDAC patients will test a combination of GVAX and an antibody to PD-1, one of the immune-suppressing molecules that became more active after vaccination. "We think combinations of immune therapies will have the biggest impact," he says.

Provided by Johns Hopkins University School of Medicine