Small change makes cancer vaccine more effective in animal tests

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Jefferson researchers developing a cancer vaccine to prevent recurrences of gastric, pancreatic, esophageal and colon cancers have added a component that would make the vaccine more effective. The change

makes the vaccine less prone to being cleared by the immune system before it can generate immunity against the tumor components. The preclinical studies pave the way for a phase II clinical trial opening to patients this fall.

"Our data show strong immune responses in mice that might otherwise clear the vaccine, and suggests this approach will be more effective in the human trials we are starting shortly," says Adam Snook, Ph.D., assistant professor in the Department of Pharmacology and Experimental Therapeutics and researcher at the NCI-Designated Sidney Kimmel Cancer Center (SKCC)—Jefferson Health, a top ranked cancer center.

The research was published in *Journal of ImmunoTherapy of Cancer* on August 20, 2020.

Many vaccine targets, such as a tumor antigen or circulating virus, are introduced to the immune system through a "broker,"—a safe negotiator of immunity. That broker introduces the vaccine components to the immune system, triggering a strong immune reaction needed for immunity, while protecting a person from the original threat—the cancer or disease-causing virus. Many vaccines, including some COVID-19 candidate vaccines, are often built using a strain of adenovirus as that broker or carrier.

Adenovirus is a common choice for vaccine development because of its safety profile and its generally strong and two-pronged immune reaction—both important characteristics for lasting immunity. But because adenoviruses also cause the common cold, many people have existing antibodies against the virus, and would clear away any adenovirus-based vaccine before it has a chance to act. New research from Dr. Snook's laboratory shows that introducing a component of a less common adenovirus strain can make the vaccine more effective and

less likely to be cleared by existing antibodies.

Rather than using a new carrier or broker, which would have triggered a restart in the clinical trials process, the investigators tweaked the existing vaccine based on commonly used serotype called adenovirus 5, or Ad5. To this, they added the spike protein of a rare adenovirus serotype Ad35 to create a hybrid vaccine Ad5.F35.

Dr. Snook and colleagues first showed that the Ad5.F35 cancer vaccine produced a comparable immune response to the original Ad5 vaccine in animal models of colorectal cancer. Similar to the Ad5, the vaccine with the F35 component added showed no toxicity in non-tumor tissue.

The researchers also showed that the Ad5.F35 vaccine was resistant to clearance by antibodies produced by mice exposed to Ad5. They also showed that the sera of colorectal cancer patients with Ad5 antibodies was not able to neutralize the vaccine.

"We speculate that based on these data, more than 90% of patients should produce a clinically meaningful immune response to the new version of the vaccine, whereas we would only expect about 50% to respond to the first version," says Dr. Snook.

The phase II clinical trial aims to enroll 100 patients with gastric, pancreatic, esophageal or colon cancers who have been treated with first-line therapy and are in remission. Eligible patients will have undergone standard first-line therapy, usually surgery and chemo or radiation therapy, with no evidence of disease.

"This cancer vaccine is really designed to help the body keep the cancer from coming back," says Babar Bashir, MD, assistance professor of medical oncology at Jefferson and researcher with the SKCC, who is the clinical leader on the trial. "It's not powered to remove large tumor

burden. But recurrence is a major problem for each of these cancers, and being able to reduce the chance of recurrence can translate to major improvements in a patient's longevity."

"This work is the latest advance in what is a larger effort at the Sidney Kimmel Cancer Center at Jefferson to develop effective cancer vaccines. We are so proud of the laboratory and clinical teams, who ensure that discoveries are fast-tracked to the clinic, and provide our patients in Philadelphia access to the most advanced form of cancer care," said Karen E. Knudsen, Ph.D., EVP of Oncology Services at Jefferson Health and Enterprise Director of the Sidney Kimmel Cancer Center.

More information: John C Flickinger Jr et al, Chimeric Ad5.F35 vector evades anti-adenovirus serotype 5 neutralization opposing GUCY2C-targeted antitumor immunity, *Journal for ImmunoTherapy of Cancer* (2020). DOI: 10.1136/jitc-2020-001046

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