Medical Xpress

RIP1 Kinase identified as promising therapeutic target in pancreatic cancer

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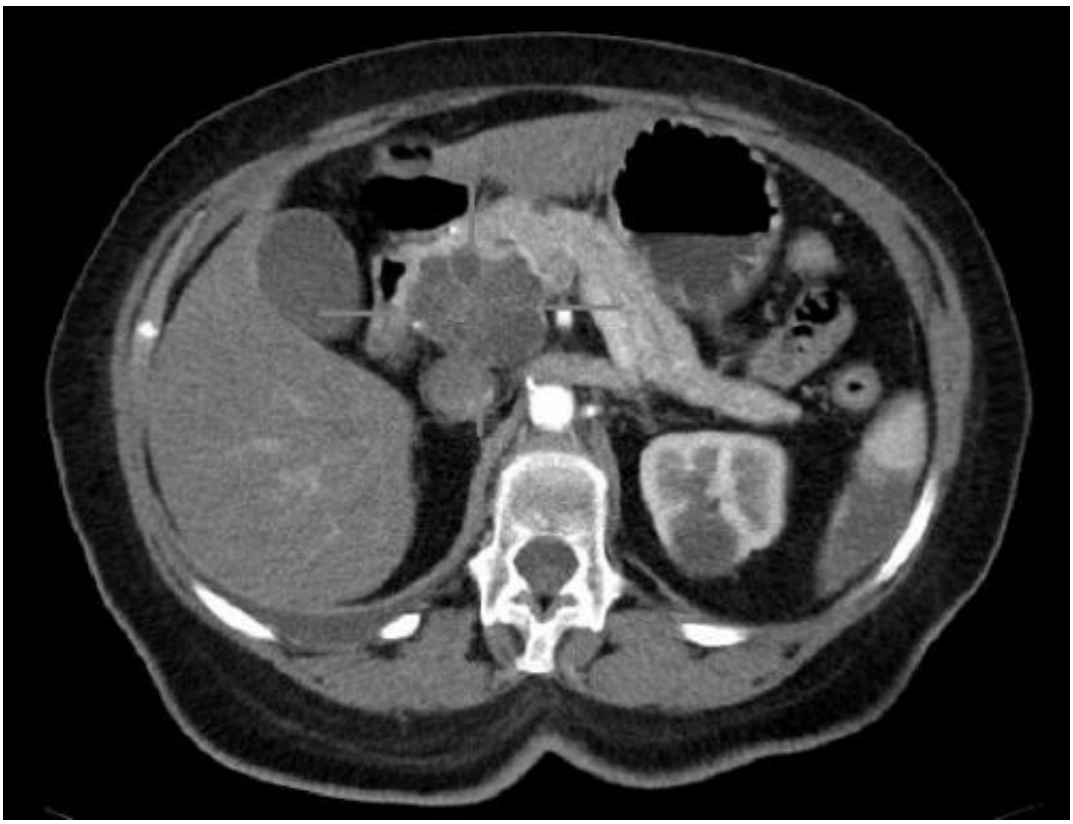

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

An experimental drug may be effective against a deadly form of pancreatic cancer when used in combination with other immune-boosting therapies, according to a cover study publishing online Nov. 12

in *Cancer Cell*.

The findings revolve around the immune system, which attacks foreign organisms like bacteria while leaving the body's own cells alone. To spare normal cells, the system uses "checkpoint" sensors to turn off immune cells when they receive the right signal. The body recognizes tumors as abnormal, but cancer cells inappropriately flip the checkpoint "off switch" to avert immune attack.

The current results in mice and lab-grown human tumor cells showed that the study drug, called GSK547, helps another drug class called checkpoint inhibitors to mount a more aggressive attack against tumor cells seeking to evade notice. The GSK547 combo doubled survival to 50 days in mice with pancreatic ductal adenocarcinoma while similar mice given only checkpoint inhibitors lived 25 days.

The study was performed by scientists at NYU School of Medicine and its Perlmutter Cancer Center in collaboration with scientists at GlaxoSmithKline, the manufacturer of the drug being developed. Moreover, the company expects to launch a Phase I clinical trial in November using a version of the new drug meant for safe testing in humans and named GSK095.

"Our results support the potential effectiveness of blocking a signaling pathway in pancreatic ductal adenocarcinoma in a way that potently complements existing treatments," says George Miller, MD, the H.L. Pachter Professor at NYU Langone Health and Perlmutter. "If clinical trials prove successful, this could be really promising for many people with end-stage disease," says Miller, who also serves as vice chair for research in the Department of Surgery at NYU Langone.

Miller, the co-senior study investigator and a hepatobiliary surgeon, says GSK547 and GSK095 work by blocking the action of an enzyme called

receptor-interacting serine/threonine-protein kinase 1, or RIP1. This enzyme regulates immune cells called macrophages that home in on tumors, but then "decide" to become a cell type that suppresses the immune response based on signals given off by cancer cells.

Miller adds that such macrophages in pancreatic ductal adenocarcinoma cannot turn on "killer" T cells, which would normally attack cancer cells.

Specifically, the new study found in laboratory tests of human pancreatic cancer cells that treatment with the RIP1-inhibiting GSK547 brought about a doubling of killer T cell activation and a fivefold decrease in the macrophage-influenced T cell type that suppresses the immune system.

Pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer, which strikes over 50,000 Americans annually and kills nearly the same number, says Miller. Current treatment options, he says, are few and focus on pain relief, or surgery and radiation therapy to prolong life.

Previous attempts at harnessing the immune system to increase killer T cell counts have failed, probably Miller says, because there have been too few of the cells needed to attack the cancer, with tumors continuing to grow and spread. Miller says his team has not seen this problem with GSK547, which operates "upstream" in the immune system, before T cell activation, and as a "master regulator."

Drugs used in combination with GSK547 were a PD1 inhibitor, a checkpoint-blocking therapy that prevents cancer cells from evading the immune system, and an ICOS activator that helps prime the immune system's T cells to identify cancer cells and target them for attack.

"Our approach is designed to turn 'cold' tumors that evade the immune system into 'hot' tumors, which the system can target," says study co-first

author Wei Wang, MD, a postdoctoral fellow in the Department of Surgery at NYU Langone and Perlmutter. "Ultimately, we hope that our future research will reveal that RIP1 kinase inhibition can be applied to several cancers that are resistant to checkpoint inhibition."

The upcoming Phase I clinical trial on the study drug will use GSK095, which is taken as a twice-a-day pill for as long as it is tolerated with no disease progression. The study will measure the side effects of the drug candidate along with its ability to treat cancer. The RIP1-kinase inhibiting drug will be tested alone, and, in a separate set of patients, in combination with pembrolizumab, a checkpoint inhibitor. The study is listed on the National Institutes of Health's website at https://clinicaltrials.gov/ct2/show/NCT03681951 and will be led by study co-investigator Deirdre Cohen, MD, an assistant professor in the Department of Medicine at NYU Langone and Perlmutter. Funding support for the trial will be provided by GlaxoSmithKline. The Perlmutter Cancer Center is one of eight cancer centers participating in GlaxoSmithKline's Oncology Clinical and Translational Consortium.

Provided by NYU Langone Health

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