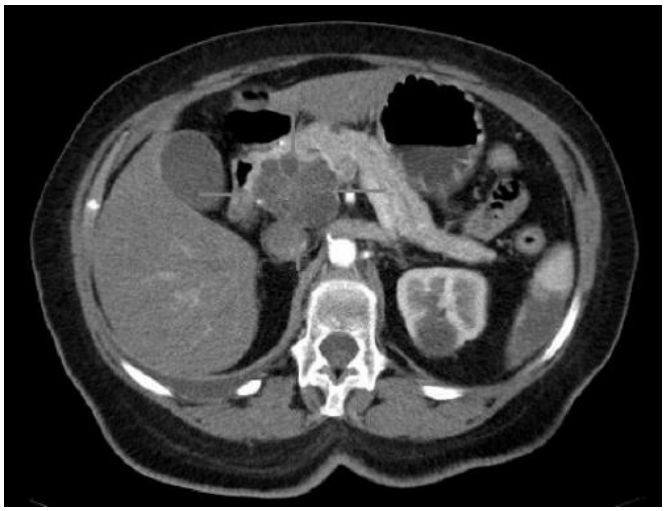
Preclinical study: Three-step treatment strategy for pancreatic cancer

11 July 2022



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

Research led by investigators at Cedars-Sinai Cancer and Johns Hopkins University have discovered a novel three-step treatment that disrupts the pancreatic tumor microenvironment in laboratory mice.

The preclinical study, published in the journal *Gastroenterology*, focuses on a trio of drugs that prevented cancer metastasis; the spread of disease to other parts of the body. The preclinical study also is the first to identify synergistic effects of targeting both inside the cell and the tumor microenvironment outside of the cells.

"These three drugs, used in combination in a laboratory setting, prevented disease metastasis," said Arsen Osipov, MD, program lead in the Pancreatic Cancer Multidisciplinary Clinic and Precision Medicine Program at Cedars-Sinai Cancer and senior and corresponding author of the study. "By focusing on the difficult-to-treat tumor microenvironment, we were able to amplify an immune response while simultaneously attacking cancerous cells."

The three-step combinatorial strategy combined an anti-PD-1 immunotherapy antibody and a protein known as FAKi with a novel pathway called CXCR4. This combination destroyed the tumor's outer microenvironment, attacked the tumor itself, and bolstered the immune system of the laboratory mice.

"The combined therapy prevented disease metastasis and extended life," said Osipov, also a medical oncologist and researcher in the Gastrointestinal Research Group at the Samuel Oschin Cancer Center. "This is an important step for a disease that is extremely challenging to treat and has very low survival rates."

The tumor microenvironment in pancreatic ductal adenocarcinoma—the most common form of pancreatic cancer—has long been resistant to therapeutics, including immunotherapy.

Pancreas tumors tend to be aggressive and often become resistant to traditional treatments like chemotherapy. While immunotherapies have proven successful in many other forms of cancer—like melanoma and lung cancer—benefits have been limited in pancreatic cancer.

This difficulty to treat the disease has made pancreatic cancer one of the deadliest cancers, with a five-year survival rate of just 11%.

More than 62,000 Americans are expected to be diagnosed with pancreatic cancer in 2022. By the year 2030, pancreatic cancer is expected to become the second-leading cause of cancer-related death in the United States.

"Our teams of investigators are exploring novel

methods to target the tumor microenvironment with the hope of improving survival and treatment options for patients," said Dan Theodorescu, MD, Ph.D., director of Cedars-Sinai Cancer and the PHASE ONE Foundation Distinguished Chair. "This innovative research study emphasizes how simultaneously targeting both intracellular and extracellular components of the microenvironment may improve an immunotherapy response."

As a next step, Osipov and team plan to develop a clinical trial to further explore the treatment potential of the CXCR4 pathway.

More information: Alex B. Blair et al, Dual stromal targeting sensitizes pancreatic adenocarcinoma for anti-PD-1 therapy, *Gastroenterology* (2022). DOI: 10.1053/j.gastro.2022.06.027

Provided by Cedars-Sinai Medical Center