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Protein identified as potential druggable target for pancreatic cancer

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A protein known as arginine methyltransferase 1 (PRMT1) may be a potential therapeutic target for pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, and one of the most deadliest with a less than 10 percent, five-year survival rate. PRMT1 is involved in a number of genetic processes including gene transcription, DNA repair and signaling.

"Our study has identified and validated for the first time an arginine methyltransferase as a novel genetic vulnerability in PDAC," said Giulio Draetta, M.D., Ph.D., professor of Genomic Medicine and director of Institute for Applied Cancer Science (IACS) at The University of Texas MD Anderson Cancer Center. "These findings strongly suggest a role for PRMT1 in PDAC development and illuminate a path toward the development of therapies for patients in desperate need of innovative solutions."

Results from the study will be reported April 3 at the annual meeting of the American Association for Cancer Research in Washington, D.C.

Various treatment regimens have failed to improve PDAC patient survival, driving the critical need for finding druggable targets essential for tumor maintenance. Draetta's team developed an in vivo platform called Patient-based In vivo Lethality to Optimize Treatment (PILOT), a technology enabling systemic identification of tumor vulnerabilities in patient-derived tumors. Through PILOT, they discovered novel epigenetic drivers in PDAC, including PRMT1 in tumors that harbor

KRAS mutations on the background of p53. KRAS and p53 are genes often associated with cancer.

"Through this assessment of epigenetic regulators, we identified PRMT1 as a top scoring 'hit' in these patient-derived tumors," said Virginia Giuliani, Ph.D., senior research scientist, IACS. "This novel dependency was subsequently validated in multiple patient-derived pancreas models."

The team confirmed that genetic "knockdown" of PRMT1 significantly impaired PDAC cell growth in vitro through use of genetic editing tools, including CRISPR and small hairpin RNA (shRNA). This correlated with a global reduction in arginine methylation, which controls multiple cellular processes, including DNA replication and DNA repair.

"We also confirmed a role in PDAC tumor maintenance as inhibition of PRMT1 in patient-derived mouse models significantly inhibited tumor growth and extended survival," said Giuliani. "These data suggest that small molecule inhibition of PRMT1 could be an impactful therapeutic strategy in pancreas cancer."

The teams at MD Anderson's and Center for Co-Clinical Trials are using the PILOT platform to investigate novel vulnerabilities across tumor subtypes with the aim of identifying targets for therapeutic development. PRMT1 is one of several epigenetic dependencies that have been identified using this approach.

Provided by University of Texas M. D. Anderson Cancer Center