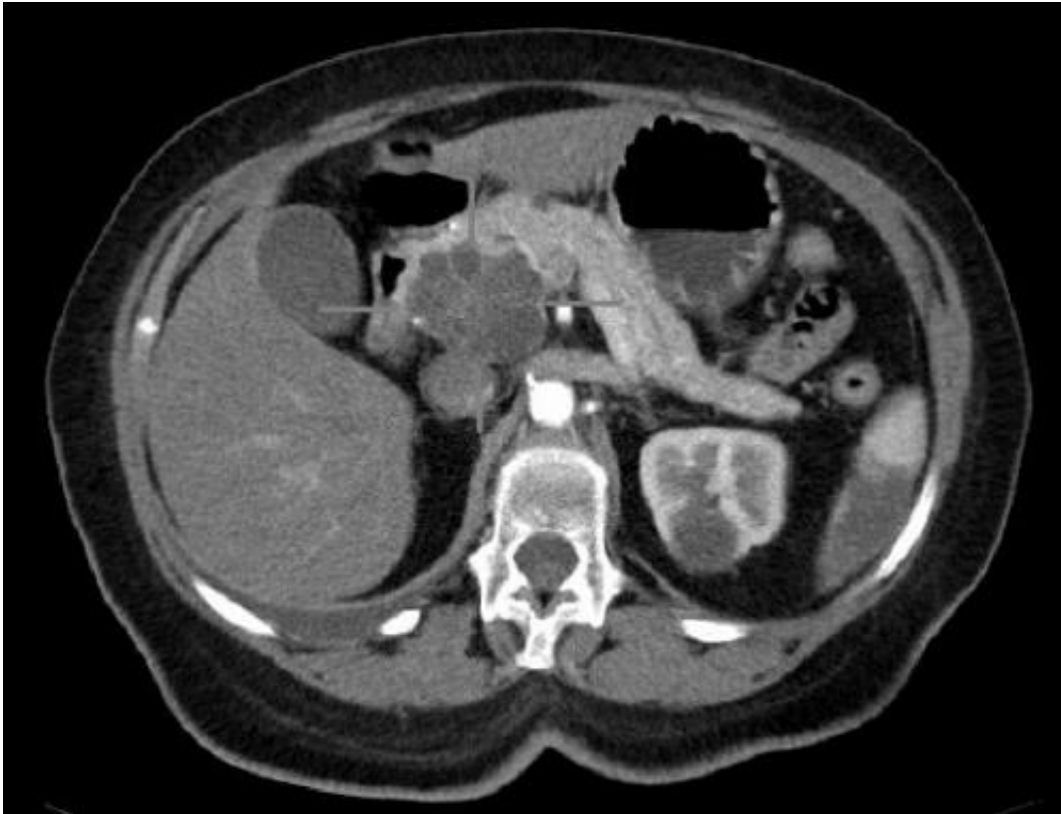


Researchers find a new therapeutic target in pancreatic cancer

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

The development of pancreatic cancer is driven by co-existing mutations in an oncogene involved in controlling cell growth, called KRAS, and in a tumor suppressor gene, called p53. But how these mutations cooperate

to promote cancer is unknown. A new study co-led by Steven Leach, MD, Director of Dartmouth's and Dartmouth-Hitchcock's Norris Cotton Cancer Center (NCCC), uncovers a direct link between these mutations and the mechanism that regulates cell activity, providing insight for future development of therapeutics that could hit this newly found target in pancreatic cancer.

The study is co-led by Leach; Omar Abel-Wahab, MD, Associate Member in the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center (MSKCC); and Luisa Escobar-Hoyos, Ph.D., MSc, Assistant Professor of Therapeutic Radiology at Yale School of Medicine and former post-doc in the Leach laboratory at MSKCC. Dr. Escobar-Hoyos conceived of and performed the work and serves as lead author, while Dr. Leach serves as co-senior author and along with Dr. Abdel-Wahab supervised the work, both while at MSKCC and while at NCCC. "The most commonly mutated [tumor suppressor gene](#) in [cancer](#), p53, dramatically rewires RNA splicing, the fundamental cell mechanism by which RNA is processed before being translated into protein. The rewiring is done in a manner that leads to further activation of the KRAS oncogene, the major 'driver' gene in human [pancreatic cancer](#)," explains Leach.

The team analyzed every known mRNA splice variant encoded by the human genome—more than 200,000 possible sequences, in hundreds of pancreatic cancer patients. Their findings, "Altered RNA Splicing by Mutant p53 Activates Oncogenic RAS Signaling in Pancreatic Cancer" are newly published in *Cancer Cell*. "Our paper shows that a new class of drugs that alter RNA splicing have selective activity against p53-mutant pancreatic cancers," says Leach.

This study shows that there are still fundamental mechanisms to be discovered in cancer that can lead to new treatment strategies. Based on these findings, next steps will be to design clinical trials that will evaluate

these new drugs in patients with pancreatic cancer.

More information: *Cancer Cell* (2020). [DOI: 10.1016/j.ccell.2020.05.010](https://doi.org/10.1016/j.ccell.2020.05.010)

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