# Predicting chemotherapy response and tailoring treatments for pancreatic cancer patients

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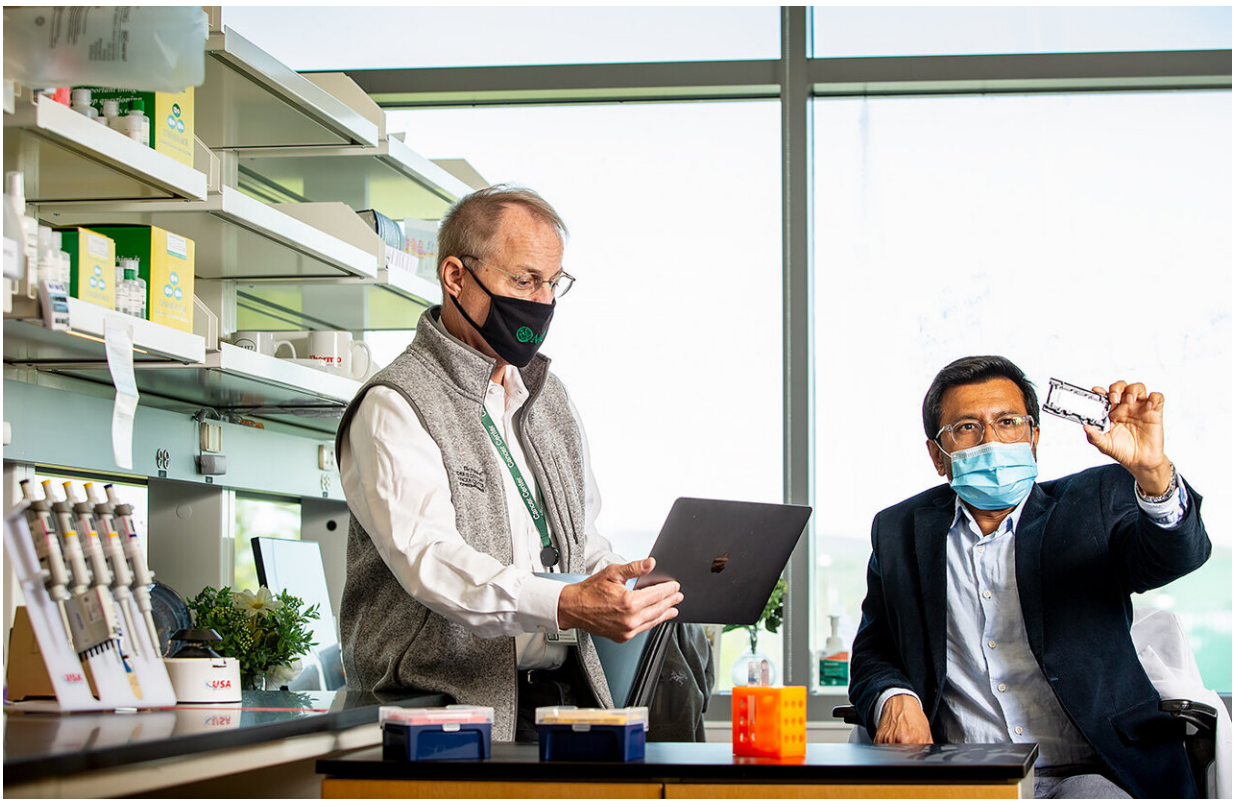

(L-R) Dartmouth and Dartmouth-Hitchcock's Norris Cotton Cancer Center Director Steven D. Leach, MD, and Surajit Dhara, PhD, Senior Research Scientist in the Leach laboratory are about to bring change to the treatment of pancreatic cancer with a novel biomarker technology that predicts chemotherapy response and potential benefit of epigenetic therapy in patients with pancreatic cancer. Credit: Mark Washburn

By 2030, pancreatic ductal adenocarcinoma (PDAC), the most lethal form of pancreatic cancer, is projected to become the second leading cause of cancer-related deaths in the United States. Not only are therapeutic options limited, but nearly half of all PDAC patients who have their tumors removed surgically experience disease recurrence within a year, despite receiving additional chemotherapy. For more advanced stages, only about one-third of patients have a limited response to approved chemotherapy.

A team of researchers led by Dartmouth and Dartmouth-Hitchcock's Norris Cotton Cancer Center (NCCC) Director Steven D. Leach, MD, and Surajit Dhara, Ph.D., Senior Research Scientist in the Leach laboratory, in collaboration with colleagues at Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, are developing the first prognostic and therapeutic epigenetic biomarker for PDAC patients.

Their discoveries will help predict which patients are likely or not likely to benefit from traditional chemotherapy. The likely "responder" patients can be confidently treated with traditional chemotherapy regimens, while the likely "non-responder" patients can be given an alternate regimen—potentially a combination of epigenetic therapy. The technology addresses a pressing clinical need by introducing the first ever epigenetic precision medicine approach to pancreatic cancer, as a means toward better outcomes and quality of life for all patients.

Epigenetic therapy can reactivate expression of the regulatory genes that have been silenced in chemo-resistant tumors and therefore make the tumors responsive to chemotherapy.

The team's work, entitled "Pancreatic cancer prognosis is predicted by an ATAC-array technology for assessing chromatin accessibility," is newly published in *Nature Communications*.

"We have a discovery and an invention emanating from this work," says Dhara. "By investigating all epigenetic elements that regulate genes in PDAC, we discovered that only about 1,092 elements are associated with chemotherapy resistance and early recurrence of this disease. Of those, 723 elements are silenced in chemo-resistant tumors, and are optimally predictive."

To translate this knowledge into the clinic, Leach and Dhara invented a novel technology platform called "ATAC-array" that assesses gene regulatory elements as a means to predict chemotherapy response and the potential benefit of epigenetic therapy in patients with PDAC. The technology is DNA-based and can potentially be performed on fine-needle aspiration specimens collected from tumors at the time of diagnosis.

Although there are nine FDA-approved epigenetic drugs, and more in the pharma pipeline, a fundamental means of distinguishing tumors that would benefit from epigenetic reprogramming therapy is still lacking. "We currently appear to be at the dawn of a new era in which epigenetic reprogramming is poised to become increasingly relied upon to optimize therapeutic effectiveness in multiple tumor types," says Leach. "With this work, we have pioneered a precision epigenetic approach in PDAC, a treatment approach that is now ready to be translated into the clinic."

Leach and Dhara have co-founded Episteme Prognostics, Inc.— a precision medicine company developing therapeutic biomarkers for pancreatic cancer—in order to translate this work directly to the clinic as rapidly as possible.

**More information:** "Pancreatic cancer prognosis is predicted by an ATAC-array technology for assessing chromatin accessibility," *Nature Communications* (2021). DOI: 10.1038/s41467-021-23237-2

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