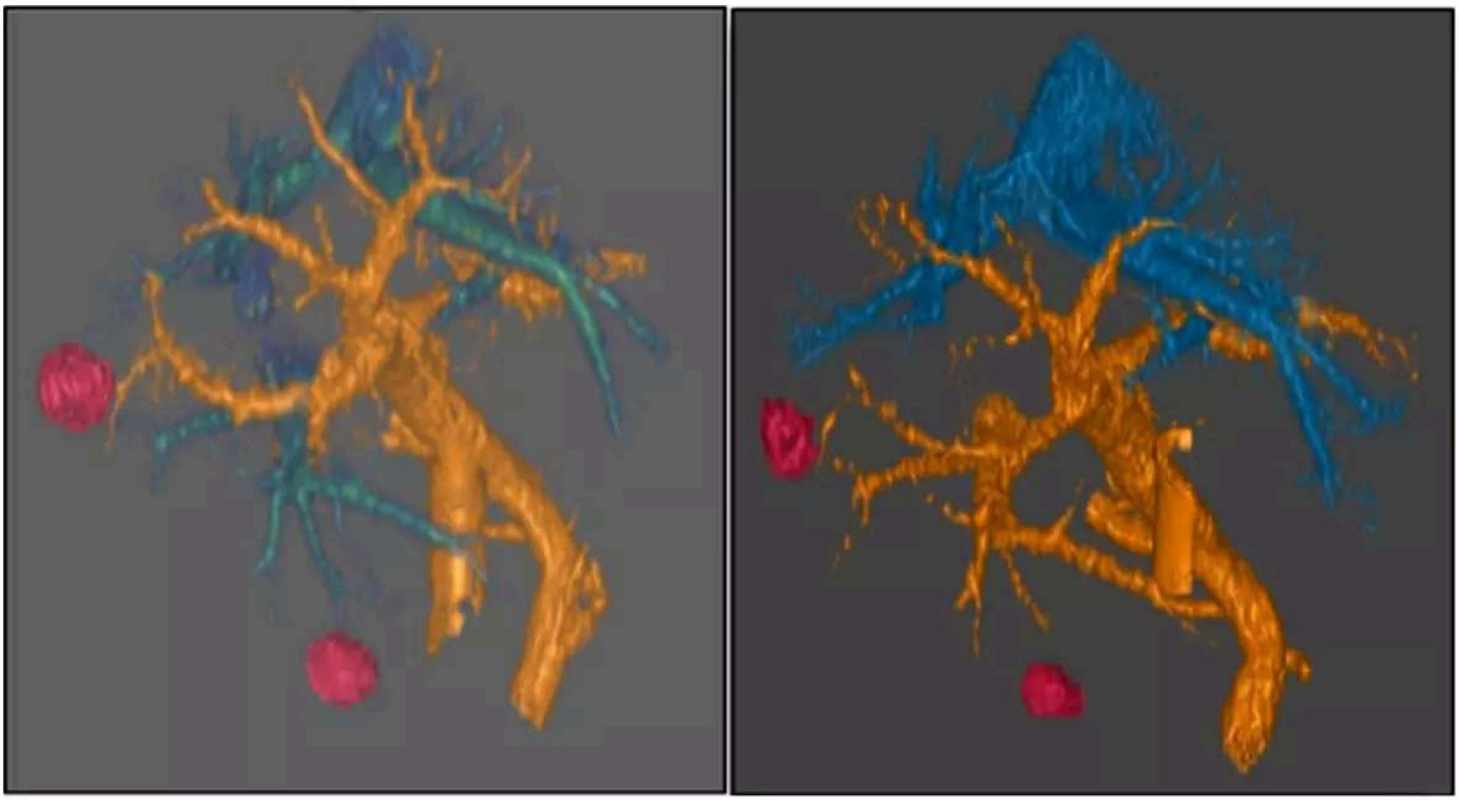
HEALTHCARE & SCIENCE

City of Hope Study Demonstrates Proof of Concept for Targeted New Approach to Treat Pancreatic Cancer



Dr. Mustafa Raoof and team tested an innovative approach on two patients whose pancreatic tumors had resisted earlier treatments. The patients experienced up to a 49% shrinkage in their liver metastases after taking the City of Hope-developed experimental AOH1996 pill twice a day for two months. Overall, the experimental approach was most effective at killing cancer cells with high replication stress. (Photo Credit: Dr. Mustafa Raoof / City of Hope)

By Paul Williams
Contributor

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Scientists Transform Genetic Culprit Behind Treatment Resistance into a Skillful Tool to Use Against Cancer

Researchers at City of Hope have identified a new molecular target for treating pancreatic cancer, according to a new gastroenterology study.

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest human cancers worldwide because it evades most treatments. With few therapeutic options, 90% of these patients don't survive beyond five years. Now an innovative

new approach offers the potential for transforming the genetic culprit behind PDAC's stubborn resistance to treatment into a therapeutic ally.

Led by Mustafa Raoof, M.D., M.S., City of Hope assistant professor of surgery, cancer genetics and epigenetics, scientists focused on transcription-replication conflicts (TRCs), which occur when the mechanisms responsible for gene expression and genome duplication collide. The clash disrupts cells' ability to read and copy genes, leading to replication stress, a frequent phenomenon in pancreatic cancer. The added stress causes cells to make errors copying their DNA, enabling cancer to gain a foothold and spread.

"Transcription-replication conflicts are an important vulnerability of pancreatic cancer," said Dr. Raoof, who served as senior author of the new study. "Our study is the first to confirm proof of concept for whether exploiting this chink in cancer's armor could provide an effective therapeutic target for patients."

In an earlier study, Dr. Raoof and his colleagues had identified high levels of TRCs as a unique weakness in pancreatic cancers that are driven by a common gene mutation. Building upon this research, his team used an experimental drug developed at City of Hope called AOH1996 as a tool to target TRCs and measure clinical responses.

First, the laboratory tested AOH1996 on a mouse model for pancreatic cancer and on small, lab-grown versions of human organs called organoids. The scientists discovered that the drug slowed tumor growth, damaged tumor cells without harming healthy tissue and boosted mouse survival from a median of 14 days to three weeks.

Next, the team tested the approach on two patients whose pancreatic tumors had resisted earlier treatments (NCT05227326). The patients experienced up to a 49% shrinkage in their liver metastases after taking the pill twice a day for two months.

Overall, the experimental approach was most effective at killing cancer cells with high replication stress, a common phenomenon that occurs when the KRAS gene goes awry in 95% of patients with pancreatic cancer.

"While the KRAS mutation has suggested a strong therapeutic target, pinpointing it in human PDAC has been difficult until now," said Dr. Raoof. "With inhibitors to mutant KRAS entering clinical trials, resistance is expected. It's crucial for us to develop new approaches that target dependency on KRAS."

Targeting TRCs enabled the scientists to pinpoint only pancreatic cancer cells that experienced high levels of replication stress.

"Transcription-replication conflicts are more prevalent in cancer cells than normal cells," Dr. Raoof said. "Therapies that interfere with how cells manage their DNA during replication could open up new ways to treat cancer, offering hope for patients who have not benefited from other approaches."

Though excited by the study's early results, Dr. Raoof emphasized caution in interpreting its findings. Due to the trial's small size, scientists will need to pursue larger clinical and biomarker discovery studies to realize the full potential of therapeutic targeting of TRCs.

A respected birthplace for biotech, City of Hope created the technology that led to the development of synthetic human insulin. City of Hope later contributed to the development of "smart" cancer drugs like Herceptin, Rituxan and Avastin.

Information was sourced from BusinessWire. To learn more, contact zlogsdon@coh.org.

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