

Obesity has long been identified as a risk factor for pancreatic cancer, but how to leverage that knowledge for prevention and treatment has been elusive. Mandar Deepak Muzumdar, MD, is in the process of changing that.

Dr. Muzumdar has uncovered hormonal activity associated with obesity that creates targets for drug development. He was lead author of a paper published in the journal *Cell* in May 2020 that revealed the role of the peptide hormone cholecystokinin (CCK)—made within the pancreas itself—in accelerating tumor progression in pancreatic ductal adenocarcinoma in mice. Dr. Muzumdar’s discovery raises the possibility of more effective drugs in the battle against pancreatic cancer—as well as a new promising strategy of employing endocrinology and genetics in concert to explore the mechanisms driving obesity-related cancers.

The paper is the result of intensive work since his arrival at Yale Cancer Center three years ago. But its genesis stretches back more than a decade to when Dr. Muzumdar was a medical student at Stanford. “On my clinical oncology rotation, one of the things that was impressed upon me was to learn the risk factors of different cancer types,” he said. “It never quite made sense why it would matter, because at that point the patient had already been diagnosed with cancer. It was not clear that knowing the risk factors would really change their treatment.”

As his studies continued, obesity was getting increasing attention as a risk factor in pancreatic and other cancers. But there was scant knowledge about exactly how obesity was contributing to malignancies. “I conceived this project to study this in more tractable animal models that would allow us to understand causal relationships between obesity and

cancer, and then hopefully understand mechanisms. In the last few years of my research fellowship before coming to Yale, I developed a mouse model to study this phenomenon. I was fortunate to go where the science led us and to find collaborators to help us here at Yale to really dive deep.”

“We also had a very diverse array of trainees who were involved in the project. I think training the next generation of scientists in cancer biology is really important. I take pride in the fact that we were able to involve so many trainees to make important discoveries,” he said.

His work showed that tumor progression could be slowed or stopped in mice with precancerous tumors if they lost weight. Unfortunately, since pancreatic cancer is typically diagnosed in advanced stages in humans, that finding does not point to a treatment option. But Dr. Muzumdar said that the information will be important for doctors to use in counseling weight loss for patients who may be at high-risk for pancreatic cancer.

Late diagnosis is one of the reasons that pancreatic cancer has a higher mortality rate than most. “I think I was drawn to this primarily because it remains a challenging disease,” Dr. Muzumdar said. “I was also drawn because I was personally impacted by gastrointestinal cancer, with my father who passed away from duodenal cancer.”

Dr. Muzumdar is an Assistant Professor of Medicine (Medical Oncology) and Genetics. He expected the KRAS gene, which has mutations in more than 90 percent of pancreatic cancer patients, to loom large in his investigations. “A few years ago, we tried to test whether KRAS was a good target in pancreatic cancer. Instead of drugs, which weren’t available,

we used genetic tools to eliminate KRAS in pancreatic cancer cells, and through these studies we found that over half of the pancreatic cancer cell lines that we eliminated KRAS in could survive nevertheless.”

This led him to think about looking “beyond the gene” to other activity within the pancreas and ultimately to CCK. The investigation reinforced Dr. Muzumdar’s belief in “team science” as endocrinology became important in his own work. He is the leader of the Yale Pancreatic Cancer Collaborative (see feature article), which aims to help scientists from various disciplines work together to accelerate discovery around better prevention and treatment.

“There is no single lab that can do everything. Every lab has its expertise, and there’s relationships that are required between basic scientists, translational researchers, and clinicians to effectively take advantage of the basic science and bring it to the clinic,” he said. Collaboration also helped him validate critical findings in this investigation. “We were able to validate findings, for example, from our animal models in human biospecimens. We were able to profile for these hormonal factors in human specimens and validate that they were present where we thought they would be.” Based on these findings, Dr. Muzumdar believes that targeting CCK or other hormones made within the pancreas may become an important strategy in pancreatic cancer prevention or even treatment. He was recently awarded a 2021 Damon Runyon-Rachleff Innovation Award from the Damon Runyon Cancer Research Foundation and will continue to “understand that fundamental biology of pancreatic cancer in hopes of informing better ways of preventing and treating the disease.”

Mandar Deepak Muzumdar, MD

Curiosity and Collaboration Work Together to Solve a Cancer Mystery