During the last decade, researchers have made tremendous progress in deciphering the biology of cancer, which has made targeted therapies, immunotherapies, and combination chemotherapies possible. These advances have improved the survival rates and the quality of life for people with many different cancers.

“Unfortunately, we haven’t had that,” said Mandar Deepak Muzumdar, MD, a new Assistant Professor of Genetics at Yale who recently left Dana-Farber Cancer Institute to open a lab at Yale’s Cancer Biology Institute. “In the past 10 or 15 years we have learned quite a bit about how pancreatic cancer works, in terms of its genetic features, and how it progresses from early stage to advanced stage, but we haven’t been able to take advantage of this knowledge clinically.”

As a result, pancreatic cancer remains one of the most deadly, with a five-year survival rate of less than 10 percent. Part of the explanation is that the disease rarely shows early symptoms, and there is no reliable way to detect its initial stages. Consequently, the disease often goes undiagnosed until it metastasizes. This year, an estimated 53,000 Americans will die from this cancer.
In his new lab, Dr. Muzumdar will continue his groundbreaking research into the genetic and environmental factors that underlie pancreatic cancer. His discoveries have altered science's understanding of this disease and also identified some promising possibilities for preventing and treating it.

Genetic research into pancreatic cancer starts with mutations of the KRAS gene, which researchers have long suspected drives the disease. “KRAS mutations are found in more than 90 percent of human pancreatic cancers,” explained Dr. Muzumdar, “also in 40 to 50 percent of colon cancers, and 25 to 30 percent of lung cancers. Those are the three leading causes of cancer death in the United States, so there is considerable interest in developing inhibitors of KRAS molecules. But despite our knowledge of KRAS, for more than 30 years we haven’t been able to develop drug inhibitors for it that are effective and reach the clinic.”

To decode the gene’s riddles, and to discern whether KRAS is even the correct target, Dr. Muzumdar has leveraged sophisticated genetic engineering techniques and a murine model that replicates what happens in human pancreatic cancer. “When we induce a KRAS mutation in the pancreas of a mouse,” he said, “the mouse will develop cancer that looks like human pancreatic cancer under a microscope and behaves like it in terms of how it progresses from early to advanced stages, spreads, and responds to chemotherapy.”

Though drugs have failed to inhibit KRAS mutations, Dr. Muzumdar wondered if he could simulate inhibition through genetic engineering, and if so, how that would affect the cancer. He used a new gene-editing tool called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) to completely eliminate KRAS function in pancreatic cancer cells, something never done before.

“To our surprise,” he said, “nearly 50 percent of the cancer cell lines that we profiled could survive that process and generate a subpopulation of pancreatic cancer cells that survived without functional KRAS.” Dr. Muzumdar knew that similar behavior has been observed with the use of targeted inhibitors in other cancers. He used the surviving cancer cell lines to explore the next question: how did these cells evade KRAS inhibition? Once again he was surprised—more than 80 percent of the cell lines used the same escape mechanism.

“And that was true across species,” he said. “Human pancreatic cancer cells and mouse pancreatic cancer cells all escaped in the same fashion. To maintain their growth and survive, they rewire how they signal within themselves, and reactivate some of the same downstream signaling pathways regulated by KRAS. And it turns out that this rewiring is targetable with drugs that are currently in clinical trials, using a PI3K inhibitor.”

Dr. Muzumdar’s discoveries are valuable for the development of drugs that target KRAS mutations. He has shown that simply inhibiting KRAS will likely allow roughly half of pancreatic cancers to evade the drug and survive. To be effective, a therapy must simultaneously inhibit KRAS and block the escape route, probably through a combination of drugs that might include a PI3K inhibitor.

Dr. Muzumdar also has made discoveries about the role played in pancreatic cancer by a tumor suppressor gene named p53, which is known to slow or prevent the growth of many different cancers. But when p53 is lost through mutation or malfunction, cancer cells can proliferate, and p53 loss is observed in about half of all cancers, including more than 75 percent of pancreatic cancers. What has not been well understood is when p53 functions to block the development and progression of disease.

“If we can understand these mechanisms, how normal cells progress to early and then advanced cancer,” said Dr. Muzumdar, “maybe we can intervene to intercept or prevent cancer from ever getting to the advanced stage.”

To investigate these mechanisms, Dr. Muzumdar applied a sophisticated genetic system that he helped design as a medical student. He uses KRAS mutations to create early-stage pancreatic tumors and then genetically engineers some cells to lose p53 and others to maintain it. He labels these cells with different fluorescent markers, which allow him to compare what happens to them over time and thus follow the cancer’s progression from early to late stages.

“That hasn’t been well-established previously,” he said. “We know that cells that have lost p53 eventually go on to advanced stage. Now, because we have a separate fluorescent label for the cells that have retained p53, we can isolate both cell populations at various times and compare them using molecular or biochemical analyses to see the differences between the two. That could give us insight about the cellular features involved in progressing from early to advanced disease. Those features may be proteins that are increased or decreased, proteins that might be the important ones to block with drugs in order to prevent that progression.”

Dr. Muzumdar is also investigating non-genetic factors implicated in pancreatic cancer. One of these is obesity, which puts a person at greater risk of developing the disease and being diagnosed at a more advanced stage, all of which shorten survival. Again, the mechanism behind these links is poorly known.

To explore this, Dr. Muzumdar combined genetic mouse models of obesity and pancreatic cancer. His studies confirmed that obese mice develop pancreatic cancer that progresses rapidly leading to death. Dr. Muzumdar speculates that obesity might alter the immune system in a way that speeds up tumor progression. He is particularly excited by another outcome from the mouse model: he was able to reverse obesity. “If we genetically make mice lose weight very early,” he said, “we can alter how the tumor progresses to advanced disease and completely reverse it. Instead of making mice lose weight, if we interfere with other aspects of obesity such as changes in the immune system or diabetes, perhaps we can recapitulate the reversion of obesity. These pathways might be something we can target to prevent or treat pancreatic cancer.”

Dr. Muzumdar decided to bring his research to Yale to take advantage of the resources and opportunities available at Yale Cancer Center and the Cancer Biology Institute. Another factor was Charles Fuchs, MD, MPH, Director of the Cancer Center and Physician-in-Chief of Smilow Cancer Hospital, who had been Dr. Muzumdar’s division chief and mentor at Dana-Farber. “He was a big driver in choosing Yale,” said Dr. Muzumdar.

Dr. Muzumdar is also looking forward to working with Smilow Cancer Hospital physicians, in the hopes of moving some of his basic research toward the clinic. “I’m also excited to join the group that Mark and Yossi (Mark Lemmon, PhD, FRS, and Joseph Schlesinger, PhD, co-Directors of the Cancer Biology Institute) have brought together at the Cancer Biology Institute,” he said. “It’s such a diverse group of great investigators, all with different expertise, with a focus on combating cancer together.”