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August 4, 2022

Sylvester Researcher Leads Novel Pancreatic Cancer Study, Paving Way for Prestigious PanCAN Grant

Jashodeep Datta, M.D., associate member of Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine, led a study recently published in the journal *Oncogene* that helps to explain pancreatic cancer's notorious virulence and resistance to therapy.

This important research describing the high-risk genotype of KRAS-TP53 co-alteration, which is associated with poor outcomes in pancreatic cancer patients, helped pave the way for a two-year, $250,000 career development grant from the Pancreatic Cancer Action Network (PanCAN) to further study what drives these potentially deadly changes at the cellular level.

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Jashodeep Datta, M.D., associate member of Sylvester Comprehensive Cancer Center

The *Oncogene* paper, titled "Distinct mechanisms of innate and adaptive immune regulation underlie poor oncologic outcomes associated with KRAS-TP53 co-alteration in pancreatic cancer," is an impactful publication for the Sylvester Pancreatic Cancer Research Institute (SPCRI), which launched earlier this year.

“This novel research into the mechanisms of innate and adaptive immune regulation associated the KRAS-TP53 co-

alteration, which the majority of pancreatic cancer patients have, will help us to better understand and potentially more effectively treat this deadly cancer," said surgical oncologist and founding SPCRI Director Nipun Merchant, M.D. "This is the goal of the SPCRI – to support innovative research, increase collaborations between scientists and clinicians, and provide more treatment and clinical trial opportunities for patients."

One of the biggest challenges in pancreatic cancer research – even in the era of next-generation sequencing – has been the lack of understanding of what connects the genome of pancreatic cancer cells to its very virulent and therapy-resistant phenotype, according to Dr. Datta.

"The way we approached this question was to take a high-risk genotype, which is this co-alteration between KRAS-TP53, and understand how the transcriptional networks that are encoded and regulated by KRAS and TP53 orchestrate this extremely immunosuppressive and therapeutically resistant phenotype," Dr. Datta said.

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Nipun Merchant, M.D., surgical oncologist and founding director of the SPCRI

To overcome this challenge, Sylvester researchers collaborated with multiple Miller School departments, including public health sciences, biostatistics, and bioinformatics, as well as Sylvester's tumor biology network.

"This paper shows for the first time that the KRAS-TP53 co-alteration, which is a common mutation in gastrointestinal cancers, also results in sustained oncogenic signaling in pancreatic cancer," Dr. Datta said. "We showed in three different independent patient datasets that this KRAS-TP53 co-alteration results in worse survival in patients with pancreatic cancer. And the first dataset that we used was our

own home-grown data – the University of Miami PatientAtlas platform, a system-wide platform that harmonizes next-generation sequencing data that we obtain from our patients in routine practice."

The PatientAtlas platform helped to establish the relationship between a genotype, a high-risk phenotype, and worse clinical outcomes.

"The goal to understand this intersection between the genome and phenotype of pancreatic cancer will result in the development of a molecular signature that can be used to stratify patients in terms of clinical trials, as well as inform patient survival," Dr. Datta said. "The ultimate goal is to use it to develop novel therapies targeting individual elements of this signature to make pancreatic cancer less immunosuppressive."

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Stephen D. Nimer, M.D., director of Sylvester, Oscar de la Renta Endowed Chair in Cancer Research, and executive dean for research at the Miller School

This research helped Dr. Datta secure the prestigious PanCAN grant, an award designed to encourage and support junior faculty to conduct pancreatic cancer research and establish successful career paths in this field, according to PanCAN.

Dr. Datta was one of eight researchers from prestigious cancer centers including Johns Hopkins, Moffitt, and Cedars-Sinai to receive this year's PanCAN Career Development Awards and

Extensions.

“The PanCAN career development award stands out because it is a stepping-stone to research independence,” Dr. Datta said. “The publication of this manuscript set the stage for a better understanding of the innate immune space in pancreatic cancer. My lab studies innate immunity – specifically, why pancreatic cancer hijacks the innate immune system to orchestrate the immunosuppressive crosstalk that happens in the tumor microenvironment.”

Dr. Datta and colleagues found in their research that neutrophils are actually corrupted or hijacked by the tumor microenvironment to become suppressive cells, or neutrophilic myeloid-derived suppressive cells (NMDSCs).

“One of the interesting and novel findings in this manuscript is that tumor necrosis factor (TNF) appears to be a master regulator in the innate immunoregulatory transcription programs that are seen disproportionately in KRAS-TP53 tumors,” Dr. Datta said. “When we investigated this further, we found very compelling evidence that neutrophilic NMDSC-derived TNF appears to be a very strong regulator of both stromal inflammation and T-cell dysfunction, and that is exactly what my grant is going to study,”

Dr. Datta’s novel, collaborative, and impactful research fulfills the mission of the SPCRI and Sylvester, according to Stephen D. Nimer, M.D., director of Sylvester, Oscar de la Renta Endowed Chair in Cancer Research, and executive dean for research at the University of Miami Miller School of Medicine.

“Dr. Jash Datta is one of Sylvester’s exceptional physician-scientists, whose work is already having an important impact

on our understanding of pancreas cancer," said Dr. Nimer. "He will use this prestigious and competitive PanCAN award to advance his research and propel the recently formed SPCRI to make discoveries that change peoples' lives."

Content Type Article