

## Researcher Profile: Venu Pillarisetty, MD



Dr. Venu Pillarisetty

### Understanding the immune response to cancer as the first step to immunotherapy

Pancreatic cancer (PC) is a devastating disease that strikes 45,000 Americans each year. It has low 5-year survival rates—just 14% for those diagnosed at the earliest stage, according to the [American Cancer Society](#)—and the only potentially curative therapy for PC is surgical resection; however, only

about 20% of patients with PC are candidates for surgery and long-term survival after surgery is rare. There are many potential reasons why PC has such a dramatically worse prognosis than other gastrointestinal malignancies. These range from intrinsic properties of the cancer cells arising from specific genetic mutations, to cell-cell interactions within the tumor that increase the cancer cells' propensity for invasion and metastasis. The latter concept focuses on the tumor microenvironment, which includes interactions between cancer cells and immune cells.

Immune surveillance for cancer has long been recognized as an important aspect of the body's defense system. Recent successes with various immunotherapy modalities have brought this field to the forefront of cancer therapy, and the [Seattle Cancer Care Alliance's \(SCCA\)](#) research partner, [Fred Hutchinson Cancer Research Center \(FHCRC\)](#), was selected in 2012 by the [National Cancer Institute \(NCI\)](#) to be the Central Operating and Statistical Center of its newly formed [Cancer Immunotherapy Trials Network \(CITN\)](#). Yet despite the efficacy of immune-activating agents in such disparate diseases as melanoma and non-small cell lung cancer, similar therapies in PC have thus far proven ineffective. The reason for this lack of response in PC remains unclear; however, there are suggestions from mouse models and human studies for how successful immunotherapies may be developed for PC.

In addition to his clinical work at the SCCA's Pancreatic Cancer Specialty Clinic (PCSC), [Venu Pillarisetty, MD](#), Assistant Professor in the Division of General Surgery, has spent the past five years studying the immune response to PC, working under the guidance of Cassian Yee, MD and Stanley Riddell, MD at FHCRC, and more recently with Ian Nicholas "Nick" Crispe, PhD, Professor in the Department of Pathology, to dissect the T cell infiltrate in human PC. Dr. Pillarisetty's work has uncovered some features of the T cell response to PC, including the surprising fact that there is a large infiltrate of memory T cells expressing

surface markers indicative of prior activation. These cells would normally be expected to provide some element of immunity to the cancer, but it is likely that they are being suppressed by smaller populations of immunosuppressive macrophages and regulatory T cells that are also present in the tumor.

Based upon these initial data, Dr. Pillarisetty is working with Dr. Crispe to define the role of chemokines, which are chemical signals produced by cells to attract other specific cell types, in creating cancer-specific immunosuppression in PC. Clearly identifying the molecules responsible for recruiting immunosuppressive cells to the PC tumor microenvironment has great potential as many of these molecular interactions can readily be blocked for therapeutic gain. Additionally, Dr. Pillarisetty is working with the CITN to bring to the clinic novel early-phase immunotherapy aimed at altering the T cell repertoire in PC patients.



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In addition to his work with PC, Dr. Pillarisetty has also recently begun a project in collaboration with Seth Pollack, MD, an Assistant Member of FHCRC, to study immune targeting of desmoid tumors (DT). DT can arise in virtually any part of the body and may lead to regional tissue destruction, and while they lack the ability to metastasize, they frequently significantly impact patients' quality of life. DT have been found to have an immune infiltrate consisting of macrophages and lymphocytes, however little is known about the specific cellular components of the adaptive immune cell population. With the support of \$80,000 in funding from the SCCA Sarcoma Program, Dr. Pillarisetty and his team will work to characterize the immune infiltrates in DT, determine if DT express cancer testis antigens that can be targeted in immunotherapy, and finally test whether DT infiltrating lymphocytes can be expanded for adoptive immunotherapy.