Defining the Cancer Stem Cell Niche

Principal Investigator:

- Tuomas Tammela, MD, PhD – Memorial Sloan Kettering Cancer Center

Co-Principal Investigators:

- Lukas Dow, PhD – Weill Cornell Medicine
- Dana Pe'er, PhD – Memorial Sloan Kettering Cancer Center

Abstract: Lung, pancreatic and colon adenocarcinomas are common and lethal cancers. Despite improvements in chemotherapy regimens and the advent of immunotherapies, advanced-stage adenocarcinomas remain largely incurable. One explanation for the failure of therapies in these cancers is the cellular heterogeneity that exists within tumors, enabling subpopulations of cells to survive treatment and repopulate the tumor. We and others have identified subsets of cancer cells, sometimes termed cancer stem-like cells (CSCs), that have increased capacity for selfrenewal and may contribute significantly to cellular heterogeneity in tumors. In normal tissues, stem cells are defined as having the capacity to self-renew while also producing differentiated cells. The decision to divide or differentiate is primarily dictated by extrinsic factors, which, together with the cells that produce them, comprise a niche that provides highly localized cues to stem cells. Recent work by us and others suggests that the adenocarcinoma CSC phenotype is driven by WNT-producing niches similar to normal stem cell compartments. Thus, targeting WNT is an attractive approach to eliminate CSCs in tumors, but has significant toxicities. We propose to identify the molecular mechanisms that drive the niche cell fate in lung, pancreatic and colon adenocarcinomas, as well as functionally interrogate the role the niche plays in tumor growth and maintenance. To do this, we will take advantage of single-cell approaches, genetically engineered mouse models and novel niche cell labeling/ablation systems that we have developed. Mechanisms controlling niche and CSC fates may translate into conceptually novel cancer therapies enabling tissue-specific elimination of cancer stem-like states.