Pancreatic ductal adenocarcinoma (PDAC) is the fourth-leading cause of cancer-related deaths worldwide and one of the most aggressive human malignancies. Although the current model posits that hyper-activation of oncogenic KRAS signaling represents an essential initiating event in PDAC, a substantial fraction of PDAC tumors harbor wild-type KRAS, hinting at the existence of alternative driver events. In this seminar, Dr. Atfi will discuss how to combine human genomics with genetic-engineered mouse models to identify the long sought-after genetic drivers in PDAC patients with normal KRAS signaling.