PROJECT 1

DoS: Massimo Falconi

Title: Precision Medicine for Pancreatic Cancer by Studying Changes in Blood Biomarkers Over Time

Curriculum: Basic and Applied Immunology and Oncology

Residency Program: General Surgery

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Link to OSR/UniSR personal page: https://research.hsr.it/en/divisions/experimental-oncology/pancreas-translational-and-clinical-unit.html

Project description (*Number of characters, including spaces*: 2.000 - 3.000):

Pancreatic cancer (PDAC) is the 4th leading cause of cancer mortality in the USA with a dismal 5-year survival rate of 8%. Late stage at diagnosis is one of the reasons for its high mortality rate. Recurrence after surgery is also very high and contributes to the mortality rate.

At present, diagnosis and recurrence depend upon radiological imaging, EUS-endoscopy and serum measurement of Ca19.9. However, they are costly and invasive techniques, whilst Ca19.9 may have false positive results and is not expressed in about 10-20% of the population.

Liquid biopsies (LB)(i.e. circulating tumor cells, CTCs, or DNA, RNA, extracellular vesicles or proteins released by tumor cells) are increasingly being investigated in different cancers as a noninvasive method for diagnosis, prognosis, response to therapy and follow up. Insofar, the use of LB in PDAC for these purposes has been very limited. The existing studies analyzed few patients and are fraught with low sensitivity, due to technical limitations. Within the frame of an international collaboration with the Johns Hopkins University, USA, we plan to exploit the ISET platform, which is based on the isolation by size of epithelial tumor cells, thus overcoming the main limitation of the current CTC isolation technologies, relying on the identification of EPCAM expression on the CTC surface. ISET platform has been shown to greatly increase the sensitivity of CTC isolation, as compared to the only currently FDA-approved method for the isolation (CellSearch) based on EPCAM expression on CTC surface which is often downregulated for the ongoing epithelial-to-mesenchimal transition.

Aim of the study is to comprehensively investigate the role of LB for the diagnosis and clinical management of patients with PDAC. The presence of CTCs, their count and characteristics, will be measured in patients with resectable PDAC at various time points: before neoadjuvant chemo/radiotherapy, pre- and postoperatively, after adjuvant chemo/radiotherapy, every 3 months for the first 2 years, every 6 months up to 4 years and once a year from then on.

Importantly, we envision to comprehensively characterize the isolated cells, assessing their biological features with approaches as diverse as immunofluorescence, laser capture microscopy, and genetic analysis. Specifically, we will determine the mutational status of ctDNA and CTCs by a targeted next-generation sequencing (NGS) approach and compare\contrast the sequencing results obtained from primary tumor tissue.

Data acquired from blood biomarkers will be correlated with tumoral behavior, local aggressiveness and metastasis, resection margins, response to neoadjuvant and adjuvant therapy, recurrence, progression free survival and overall survival.

Skills to be acquired by the student: Besides the acquisitions of molecular and cellular biology expertise, we envision that the student engaged in this project will acquire expertise in isolating CTCs, generating libraries for NGS sequencing, and a basic and robust knowledge on the bioinformatic tools required to analyze genomic data.

References (max. 3)

Opportunities and challenges for pancreatic circulating tumor cells – Nagrath et al., Gastroenterology 2016; 151:412-426

Clinical applications of circulating tumor DNA and circulating tumor cells in pancreatic cancer – Riva et al., Molecular Oncology 10 (2016) 481-493

Circulating tumor and invasive cell gene expression profile predicts treatment response and survival in pancreatic adenocarcinoma – Yu et al., Cancers 2018, 10, 467