PROJECT 1

DoS: Prof. Francesco De Cobelli

Title: ***INVESTIGATION OF BIOMARKERS OF TREATMENT RESPONSE: IMPACT OF LOCO-REGIONAL THERAPIES ON TUMOR MICROENVIRONMENT AND IMMUNOGENICITY***

Curriculum: Experimental and Clinical Medicine

Residency Program: Radiology

Link to OSR/UniSR personal page:

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

Primary and metastatic cancers of lung, liver and kidney account for the vast majority of cancer-related deaths and represent a large part of the world-wide cancer burden. Therapeutic strategies for these tumors are based on stage, localization, tumor progression and changes in the microenvironment. Curative treatments are generally surgical, yet alternatives for patients unfit for surgery include thermal ablation, embolization and other local treatments with varying long-term efficacy according to the underlying disease. Advanced stage disease generally requires systemic chemotherapy alone or in conjunction with locoregional approaches. In the liver, site of primary and/or metastatic disease, embolization procedures such as chemoembolization (TACE), or radioembolization (TARE), are frequently employed for tumor control. Prognosis of non-curable disease in all these tumor types is dismal both in terms of OS and PFS, as is the high rate of recurrence, likely due to the presence of undiagnosed micro-metastases left untreated.

Immunotherapy has emerged as an alternative to conventional cancer treatments based on the ability to stimulate host immune response against tumor antigens. However, while its clinical application has demonstrated effectiveness in particularly immunogenic cancers, the peculiar adaptive immune tolerance of liver tissue makes this approach challenging. In addition, primary and metastatic tumor micro-environments exhibit different mechanisms of immune regulation (1) (2).

In the past few years, literature has supported the role of locoregional therapy (ablation, TACE and TARE) in promoting immunogenic cell death by means of oncolysis (3). Differently from surgery, the locally treated tumor tissue is left in place and release of tumor-associated antigens (TAAs) and danger-associated molecular peptides (DAMPs) originating from dead or dying cancer cells promote the activation of APCs and anti-tumor $CD8^{+}$T cells. Data suggest that a combination of systemic immunotherapy with local treatment may significantly improve prognosis (3). Immunomodulating drugs may amplify the induced local immune response and trigger a systemic antitumor response, also affecting distant disease (abscopal effect). Results of these combined approaches are promising but questions remain regarding the description of TAAs and local immune regulatory pathways in metastatic and primary disease and the best timing of different therapeutic schemes

There is therefore the need to identify biomarkers which could define or predict response to local and/or systemic treatment based on tumoral microenvironment.

The aim is to investigate these aspects by means of:

- The study of the primary and metastatic tumor microenvironment pre- and post- local treatment in tissue samples with immunohistochemistry;
- Evaluation of circulating lymphocytic population pre- and post-treatment:
- Evaluation of treatment response on target and non-target lesions to account for abscopal effect.

Skills to be acquired by the student:

In order to conduct an investigative study in Experimental and Clinical Medicine, the PhD candidate will learn how to organize a structured database, how to collect data, how to correctly analyze them and how to interpret and correlate results of the investigation to draw conclusions. He will also acquire expertise in statistical analysis, bioinformatics and interpretation of imaging- and non-imaging-based biomarkers. Moreover, the PhD candidate will learn how to write research reports/paper and will be encouraged to improve oral communication skills and independent thinking.

References (max. 3)

1. Keenan BP, Fong L, Kelley RK. Immunotherapy in hepatocellular carcinoma: The complex interface between inflammation, fibrosis, and the immune response. .J. Immunother. Cancer.; 2019;7.
2. Matar P, Alaniz L, Rozados V, et al. Immunotherapy for liver tumors: Present status and future prospects. .J. Biomed. Sci.; 2009;16.
3. Kepp O, Marabelle A, Zitvogel L, Kroemer G. Oncolysis without viruses — inducing systemic anticancer immune responses with local therapies. .Nat. Rev. Clin. Oncol.; 2020;17:49–64.