PROJECT 1

DoS: **Prof. Stefano Cascinu**

Title: **Analysis of the activity of novel radiosensitizers and systemic treatments in pancreatic adenocarcinoma: a road map to improve the outcome in locally advanced disease.**

Curriculum: **Experimental and Clinical Medicine**

Link to OSR/UniSR personal page: https://www.unisr.it/docenti/c/cascinu-stefano

The Project will be funded by a third-party sponsor as project-based fellowship.

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

At least one third of patients with pancreatic adenocarcinoma (PDAC) present at diagnosis with locally advanced disease (LAPC), which is challenging to treat. Indeed, the majority of LAPC patients have occult micrometastatic disease and there is uniform agreement that patients with good performance status should receive upfront systemic chemotherapy, which is mainly based on regimens tested and approved in the metastatic setting [1]. Although multidrug chemotherapy regimens can yield disease control in most of LAPC patients, responses are not long-lasting and second-line and/or maintenance treatments offering a similar disease control are lacking. Concomitant chemo-radiotherapy (CT-RT), usually including fluoropyrimidine or gemcitabine, can play a role as consolidative treatment after induction chemotherapy, especially to increase local control rate [1]. Nevertheless, the impact of CT-RT on overall and progression-free survival remains controversial. [1]
Novel radiosensitizers and systemic compounds (e.g. antibody-drug conjugates) have shown promising activity for the treatment of solid tumors [2,3].

In this scenario, we believe that addressing the unmet need of LAPC treatment entails acting on two fronts: 1) enhancing radiotherapy activity through the association with different radiosensitizers, in order to achieve better local disease control; 2) improving micrometastatic disease control by new systemic therapeutic approaches, especially for the maintenance and/or second-line treatment setting.

In order to pursue these objectives, the present project will be based on three tasks:

- Task 1 (preclinical): A. To investigate the radiosensitizing effect of different antitumoral agents, including alkylating compounds (temozolomide) and DNA Damage Repair Inhibitors, either alone or in combinations, on different PDAC cell lines receiving photons irradiation. Capecitabine plus irradiation will serve as benchmark treatment. B. To assess the cytotoxic activity of novel compounds, especially focusing on antibody-drug conjugates, on PDAC cells. Cytotoxic assays, cell cycle, apoptosis and DNA damage analyses will be performed. Moreover, molecular profiling of tested cell lines will guide the identification of predictive biomarkers.
- Task 2 (translational): Concurrently to Task 1 analyses, cyto-histological and peripheral blood samples will be collected from patients with LAPC undergoing systemic and/or chemo-radiotherapy. Analyses of the molecular biomarkers identified with Task 1 will be performed in these samples and correlated with collected clinical-pathological data, together with TC and PET images to be analyzed for radiomic profile, in order to find markers of local versus systemic failure.

- Task 3 (clinical): Based on the results of Task 1 and 2, a clinical trial will be designed for LAPC, including radiotherapy in combination with the most active radiosensitizer and/or systemic therapy based on the most active novel compound identified.

Skills to be acquired by the student:

The PhD student will acquire specific skills related to the three tasks of the project, as follow:

- Task 1: The student will work with PDAC cell lines treated with different antitumoral agents, either alone or in combination with photons irradiation, performing the aforementioned analyses and learning how to interpret data on cytotoxic activity and their correlation with the molecular profile of PDAC cells.

- Task 2: The student will first learn how to collect clinical-pathological data and how to organize and manage a structured database. Secondly, he/she will acquire skills in data analysis and interpretation, performing correlations between clinical-pathological and mutational characteristics of patients and their survival outcomes and drawing conclusions from the results obtained. This involves the acquisition of expertise in statistical analysis and bioinformatics.

- Task 3: The student will learn how to design a clinical trial, capable to address the unmet clinical need of LAPC treatment on the basis of the results of Task 1 and 2 analyses.

Concurrently, the PhD student will learn how to write research reports/papers and will also be encouraged to improve his/her oral communication skills, by taking part in poster and oral presentation sessions in meetings and conferences focusing on the topic of the investigation.

References (max. 3)

1. White RR, Murphy JD, Martin RCG. The Landmark Series: Locally Advanced Pancreatic Cancer and Ablative Therapy Options. Ann Surg Oncol 2021. doi: 10.1245/s10434-021-09662-z. Epub ahead of print.

2. Reda M, Bagley AF, Zaidan HY, Yantasee W. Augmenting the therapeutic window of radiotherapy: A perspective on molecularly targeted therapies and nanomaterials. Radiother Oncol 2020;150: 225-235.

3. Liu J, Pandya P, Afshar S. Therapeutic Advances in Oncology. Int J Mol Sci 2021;22(4):2008.