PROJECT 1

DoS: Dr. Simone Cardaci

Title: Functional and mechanistic understanding of metabolic adaptations and vulnerabilities in solid tumours

Curriculum: Fisiopatologia Cellulare e Molecolare

Link to OSR/UniSR personal page:

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

Cancer figures among the leading cause of morbidity and mortality in the world. This study proposes to advance our understanding of the basic biology of cancer and contribute to clinical benefit by identifying metabolic adaptations and vulnerabilities in tumours, exploitable for therapeutic gain.

Alterations in the acquisition and metabolism of nutrients are recognized as hallmarks of cancer development[1]. Many, if not all, oncogenes and tumour suppressor genes promote a complex metabolic reprogramming in cancer cells through changes in the regulation of expression and activity of enzymes and transporters. These adaptive changes sustain increased capture and synthesis of cellular building blocks, such as sugars, fats, and amino acids, and are necessary for cancer cells to meet the combined biomass and energy demands imposed by uncontrolled cell growth. Furthermore, cancer cells often invade other tissues where blood supply, and the accessibility to oxygen and other nutrients that comes with it, becomes scarce. During these conditions of nutrient stress, many cancer cells may adapt by using other resources to survive. **We aim at generating mechanistic understanding of the metabolic reprogramming of cancer** by using cell biology, functional genomics, and metabolomics-integrated approaches in chemically-induced and genetic mouse models of solid tumours. Tergeting metabolic genes essential for growth of malignant cells, but dispensable in normal counterparts, will disable the proliferative capacity of tumours, thus revealing novel and effective therapeutic strategies for the improved treatment of cancer patients[2].

Genomic analyses of tumours reveal that hemizygous deletions of tumour suppressor genes frequently occur in transformed cells. These aberrations result in loss of several proximal genes, that may not participate to cancer development (passenger deletions), but are potentially essential for cell survival and proliferation. The partial loss of such genes is tolerated, but might render cancer cells highly susceptible to either further inhibition of the remaining allele or the suppression of functionally-related paralogues, thus serving as potential targets for collateral lethality[3]. Driven by this rationale, **we aim at deciphering metabolic vulnerabilities** imposed by partial loss of tumour suppressor genes, by using genomics, transcriptomics and analytical chemistry-combined strategies, thus revealing cancer-selective liabilities exploitable for personalized therapeutic gain.

Skills to be acquired by the student:

The student will develop cutting-edge expertise in a wide range of biochemical, molecular and cellular biology techniques necessary to interrogate biological systems, *in vitro* and *in vivo*, for understanding, functionally and mechanistically, metabolic and signalling processes underlying cancer development and identifying cancer-specific vulnerabilities. In particular, she/he will acquire proficiency in establishment and maintenance of stable and primary cell lines,

retroviral and lentiviral infections, RNA-interference and gene editing techniques (CRISPR/Cas9), metabolomic (liquid chromatography-mass spectrometry) analysis, Western Blotting, flow cytometry and hands-on experience in mouse models of tumours.
Importantly, the student will develop ability in generate original hypotheses, design and conduct experiments to answer novel biological questions, develop new protocols & techniques, analyse and interpret data, advise and assist colleagues technically and analytically with their own projects as well as supervise and train undergraduate students, write and review original papers.

References

1) Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism. ***Cell Metab***. 2016;23:27-47.
2) Cardaci S, et al. Pyruvate carboxylation enables growth of SDH-deficient cells by supporting aspartate biosynthesis. ***Nat Cell Biol***. 2015; 17:1317-26.
3) Nijhawan D, *et al*. Cancer vulnerabilities unveiled by genomic loss. ***Cell***. 2012;150:842-54.