PROJECT 1

DoS: Rosa Bernardi

Title: *Dissecting the mechanisms of metastasis regulation by the PML gene*

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page: http://research.hsr.it/en/divisions/experimental-oncology/preclinical-models-of-cancer.html

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

Metastasis is the leading cause of cancer-associated mortality. Within breast cancer subtypes, triple-negative breast cancers (TNBCs) are aggressive tumors characterized by high metastasis rates, recurrence to therapy, and poor overall survival (1). Due to elevated genetic complexity and lack of expression of hormone and HER2 receptors, patients with TNBC currently lack tailored therapeutic options. For this reason, a deeper understanding of the molecular circuitry regulating the formation and metastatic dissemination of TNBC is urgently needed to develop new therapies for these patients.

It was recently suggested that one of the defining features of TNBC is activation of the hypoxia-inducible HIF-1a transcription factor, which predominantly promotes metastasis in this tumor context. We have recently demonstrated that the promyelocytic leukemia protein PML, which in most neoplastic contexts acts as a tumor suppressor gene, in TNBC plays oncogenic functions by critically mediating metastatic dissemination downstream HIF-1a (2, 3). Specifically, PML promotes the expression of pro-metastatic target genes of HIF-1a and promotes metastatic features in TNBC cells both in vitro and in vivo. Importantly, inhibition of PML by arsenic trioxide, a compound that is currently used to treat patients with acute promyelocytic leukemia, recapitulates PML silencing in reducing metastasis in TNBC models. Nonetheless, the molecular mechanisms that lead to metastasis regulation by PML are still incompletely understood. Therefore, we plan to perform in depth characterization of the regulation of metastasis by PML in the context of TNCB. Specifically, we will study HIF-1a function, global gene expression profiles and chromatin modifications upon manipulation of PML expression. These studies will be extended to other tumor contexts where PML is similarly upregulated.

Skills to be acquired by the student:

The prospective PhD student will acquire basic cell and molecular biology skills (gene expression manipulation, RNA expression analysis, cell culture, protein complexes analysis) as well as bioinformatics skills for data analysis. In addition, the student will be strongly encouraged to develop independent project management skills, collaborate with other in house and external research units for setting up protocols not available in the laboratory, writing and oral communication skills and independent thinking.

References (max. 3)

1. Bernardi R., Gianni L. (2014) Hallmarks of triple negative breast cancer emerging at last? Cell Res. 24, 904-905.
2. Bernardi R., Pandolfi P. P. (2014) A dialog on the first 20 years of PML research and the next 20 ahead. Front. Oncol. 4, 23.
3. Ponente M, Campanini L, Cuttano R, Piunti A, Delledonne GA, Coltella N, Valsecchi R, Villa A, Cavallaro U, Pattini L, Doglioni C, Bernardi R. (2017) PML promotes metastasis of triple-negative breast cancer through transcriptional regulation of HIF1A target genes. JCI Insight. 2, e87380.