PROJECT 1

DoS: Rossella Galli

Title: **Validating advanced MRI features as surrogate biomarkers of the molecular subgroups of glioblastoma by exploiting patient-specific cancer stem cell (CSC)-based animal models.**

Curriculum: *Experimental and Clinical Medicine*

Residency Program: Neurosurgery

Link to OSR/UniSR personal page:
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Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):
Distinct molecular subgroups are now acknowledged to exist for most types of tumors. As such, patient subgroup status is expected to become an integral component of clinical trials, by enabling the use of treatment protocols that are rationally tailored towards each subgroup of the disease. This notion applies also to glioblastoma (GBM), the deadliest brain tumor in adults. To date, distinct GBM molecular subgroups have been identified by the presence of specific molecular alterations, with the proneural (PN) and mesenchymal (MES) subclasses correlating with better and worse prognosis, respectively [1]. In the last decade, others and we reported that cancer stem cells (CSCs), isolated from patients' GBM specimens by the NeuroSphere Assay (NSA), give rise to valuable experimental xenografts that closely reproduce the malignant nature of the tumor [2], and, most remarkably, preserve subgroup-specific features [3].

As not all GBM patients are eligible for surgical intervention, which is required for reliable histologic and molecular diagnosis, it is essential to implement methodologies to define non-invasively the tumor molecular status.

To this end, we will exploit subgroup-specific CSC-induced animal models of GBM to validate novel diagnostic, prognostic and predictive biomarkers, identified via advanced (a) MRI. Selected patients will be subjected to a preoperative MRI examination on a 3T scanner and the imaging features obtained from conventional and aMRI will be correlated with the molecular status of the patient (Neuroradiology Dept. OSR). The same patients will undergo surgery (Neurosurgery Dept. OSR) by using a multiple sampling approach that might help in resolving tumor heterogeneity. Post-surgery samples will be then collected and exploited for the establishment of patient-specific CSC lines that will be used to generate orthotopic xenografts. Tumor-bearing animals will be analyzed, by the same conventional and aMRI protocols used in patients, on a 7T scanner (Experimental Imaging Center OSR). MRI features will be correlated with the patient's molecular subtype and with pathological tumor features such as tumor cellularity, vascularization and invasiveness. In the end, the correlation of MRI features derived from GBM patients with those from CSC-derived xenografts that retain subgroup-specific molecular and pathological characteristics may improve our understanding of GBM biology and, at the same time, may offer the opportunity for stratifying prognosis and for non-invasively selecting patients, who may be candidates for specific treatments, such as anti-angiogenic and molecular targeted therapies.

Skills to be acquired by the student:

The student will be directly involved in most of the tasks of the project. Besides the acquisition of both molecular and cellular biology techniques as well as *in vivo* methodologies related to cancer stem cell establishment, characterization and utilization in different experimental settings, the student will have the opportunity to interact with neuro-surgeons during the intervention that will lead to tumor tissue procurement as well as with neuro-radiologists to implement and integrate the analysis of pre-clinical imaging data.

References (max. 3)

1. Phillips, H.S., et al., Cancer Cell, 2006. 9(3): p. 157-73.

2. Galli, R., et al., Cancer Res, 2004. 64(19): p. 7011-21.

3. Narayanan., et al., Cell Death Differ, 2018 : epub.