PROJECT 1

DoS: Prof. Carlo Tacchetti

Title: Translation rewiring determines triple-negative breast cancer aggressiveness: unraveling its role in metabolism and immune niche composition

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page:

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

Metastasis is the leading cause of carcinoma-related mortality. While the options for metastatic disease treatment remain unsatisfactory, the contribution of non-genetic mechanisms generating phenotypic heterogeneity and refractoriness to conventional therapies is becoming recognised.
Our analysis of pan-cancer databases reveals that in breast cancer, the deadliest cancer for women worldwide, a translation rewiring signature predicts poor patient survival. The highest translation reprogramming levels are found in triple-negative breast cancer (TNBC), the most aggressive molecular subtype.
Showing that translation reprogramming, a mechanism that allows a rapid and reversible response to acute microenvironmental stresses, is sufficient to trigger cancer invasiveness, rewire the metabolism, and determine the composition of the immune infiltrate, leads us to suggest translational regulation as an emerging hallmark of cancer, and a possible new therapeutic target.

Based on our previous results (1-3) we plan to address the hypothesis-driven theory the the stress-response signalling cascade pivoted by the peIF2a/ATF4 axis determines cancer aggressiveness modulating more than one aspect of the cancer cell biology.

Thus, targeting the translation machinery might represent an alternative therapy strategy to limit the capacity of cells to survive stresses in the intratumour microenvironment or during metastatic dissemination.
In this Study we will utilise multiple approaches to dissect the protein translation mechanisms taking place in TNBC cell reprogramming.

To expose new targetable vulnerabilities, the PhD Student will answer the following key questions:

1) What are the key events triggered by stress-induced translation reprogramming that lead to survival, drug resistance and metastasis?
The PhD student will select and analyse the data obtained by Next Generation Sequencing (RNA-seq and Ribo-seq) highlighting the genes/pathways involved in triple-negative breast cancer aggressiveness.
Of particular interest will be the genes involved in lipid metabolism, stemness and cancer-immune system communication;

2) What is the role of the immune microenvironment and which are the mechanisms dictating the interplay between infiltrating immune cells and stressed tumour cells?
The PhD student will co-culture stressed TNBC cells with components of the innate immune response and utilize imaging and biochemical tools to determine the key player of their crosstalk.

Our project aims to address these questions to propose a new therapeutic window for metastatic cancer, identifying and validating new targets, and to develop or reposition drugs for metastatic disease treatment.

Skills to be acquired by the student:

The Student will acquire:

1- Technical skills

- 3D culture set-up, validation, screening
- Biochemistry and molecular biology basic and advanced techniques
- CRISPR/Cas9 based editing, transfection, retroviral and lentiviral infection
- Basic and advanced imaging techniques

2- Critical analysis of literature, data interpretation, short- and long-term experimental planning

3- Abstracts, manuscripts, dissertation scientific writing

4- Independent thinking as well as teamwork approach

References (max. 3)

1- Falletta, P., L. Sanchez-Del-Campo, J. Chauhan, M. Effern, A. Kenyon, C.J. Kershaw, R. Siddaway, R. Lisle, R. Freter, M.J. Daniels, X. Lu, T. Tuting, M. Middleton, F.M. Buffa, A.E. Willis, G. Pavitt, Z.A. Ronai, T. Sauka-Spengler, M. Holzel, and C.R. Goding. 2017. Translation reprogramming is an evolutionarily conserved driver of phenotypic plasticity and therapeutic resistance in melanoma. Genes Dev 31:18-33.

2- Garcia-Jimenez, C., and C.R. Goding. 2019. Starvation and Pseudo-Starvation as Drivers of Cancer Metastasis through Translation Reprogramming. Cell Metab 29:254-267.

3- Vivas-García, Y., P. Falletta, J. Liebing, P. Louphrasitthiphol, Y. Feng, J. Chauhan, D.A. Scott, N. Glodde, A. Chocarro-Calvo, S. Bonham, A.L. Osterman, R. Fischer, Z. Ronai, C. García-Jiménez, M. Hölzel, C.R. Goding. Lineage-Restricted Regulation of SCD and Fatty Acid Saturation by MITF Controls Melanoma Phenotypic Plasticity. Mol Cell Jan 2;77(1):120-137.e9.

PROJECT 2 (optional)

DoS: _____

Title: _____

Curriculum: _____

Link to OSR/UniSR personal page:

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

Skills to be acquired by the student:

References (max. 3)