PROJECT 1

DoS: **Simone Cenci**

Title: **Characterizing and targeting unprecedented mitochondrial vulnerabilities against multiple myeloma.**

Curriculum: **Basic and Applied Immunology and Oncology**

Link to OSR/UniSR personal page: www.hsr.it/research/organization/divisions-centers/division-of-genetics-and-cell-biology/simone-cenci

Project description (*Number of characters*, *including spaces*: 2-3,000):

Mitochondria are unique, highly integrated hubs capable of transducing different types of stress into potent adaptive responses that increase cellular fitness, healthspan and lifespan. The resulting concept of *mitohormesis* is a new paradigm in age-related diseases, with the notable exception of cancer, where virtually nothing is known on stress-adaptive mitochondrial responses that may disclose new targetable cancer vulnerabilities. The emerging knowledge that tumors rely more than previously thought on mitochondria and suffer more mitochondrial stress than normal counterparts urges to investigate mitochondrial functions and related vulnerabilities in cancer to disclose novel therapeutic avenues.

Multiple myeloma is a still incurable age-onset plasma cell malignancy that spreads in the hematopoietic skeleton causing fatal end-organ damage. Owing to intensive immunoglobulin production, myeloma cells are heavily reliant on pathways ensuring protein homeostasis. Moreover, in keeping with high proteosynthetic and metabolic activity, they are characterized by abundant mitochondria, resistance to mitochondrial apoptosis and significant exposure to mitochondrial stressors. Finally, our preliminary evidence identifies specific mitochondrial proteins that are distinctively expressed in human myelomas and essential for myeloma cell viability, thereby defining novel mitochondrial vulnerabilities for therapeutic manipulation.

A pioneering project is available to characterize and challenge a novel mitochondrial vulnerability in multiple myeloma. The project will aim at:

1) dissecting the molecular function of the identified mitochondrial circuit, combining targeted biochemistry with unbiased proteomics and gene expression studies in a panel of well characterized multiple myeloma cell lines;
2) characterizing the functional connection of the identified vulnerability with myeloma cell fitness and survival, through genetic and pharmacologic manipulation of candidate targets in myeloma cells;
3) testing the relevance and therapeutic value of the mechanisms identified in suitable, already available *ex vivo* culture and *in vivo* pre-clinical myeloma models.

The project is expected to discover new molecular mechanisms ensuring myeloma cell survival and to identify novel therapeutic targets. The knowledge generated in this cancer model will be disseminated to enable rapid translation to other cancers, primary and metastatic, likely or known to experience significant mitochondrial stress.

Skills to be acquired by the student:

- Assessment of gene and protein expression of homeostatic, stress adaptive pathways
- Functional characterization of homeostatic, stress adaptive pathways
- Morpho-functional characterization of mitochondrial function
- Genetic and pharmacologic manipulation of stress responses
- Genetic engineering and targeted mutagenesis of cancer cell lines
- Assessment of myeloma development in suitable mouse *in vivo* models
- Molecular (qRT-PCR, cytofluorimetry, immunoblotting), imaging (immunofluorescence, electron microscopy, immunohistochemistry) and functional (proliferation, energy metabolism, apoptosis) analyses of myeloma cell lines and primary myeloma samples
- Critical analysis of experimental data
- Design of primary and alternative experimental strategies
- Critical presentation of data in internal seminars and at national and international meetings

References (max. 3)

Deng P, Haynes CM. *Mitochondrial dysfunction in cancer: Potential roles of ATF5 and the mitochondrial UPR*. **Semin Cancer Biol. 2017**; 47:43-49

Oliva L, Orfanelli U, Resnati M, Raimondi A, Orsi A, Milan E, Palladini G, Milani P, Cerruti F, Cascio P, Casarini S, Rognoni P, Touvier T, Marcatti M, Ciceri F, Mangiacavalli S, Corso A, Merlini G, Cenci S. The amyloidogenic light chain is a stressor that sensitizes plasma cells to proteasome inhibitor toxicity. **Blood 2017**; 129(15):2132-2142

Fucci C, Resnati M, Riva E, Perini T, Ruggieri E, Orfanelli U, Paradiso F, Cremasco F, Raimondi A, Pasqualetto E, Nuvolone M, Rampoldi L, Cenci S∗, Milan E∗. *The Interaction of the Tumor Suppressor FAM46C with p62 and FNDC3 Proteins Integrates Protein and Secretory Homeostasis.* **Cell Rep. 2020**;32(12):108162.