PROJECT 1

DoS: **Simone Cenci**

Title: **Dissecting a novel mitochondrial vulnerability against multiple myeloma.**

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

Link to OSR/UniSR personal page: https://research.hsr.it/en/divisions/genetics-and-cell-biology/age-related-diseases.html

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

Mitochondria are increasingly recognized as powerful signalling hubs capable of conferring heightened cellular fitness and resistance by orchestrating potent stress-adaptive strategies that support proliferation and survival, beyond their established bioenergetic role. Owing to deregulated growth, cancer cells may rely on mitochondrial functions more than normal counterparts, offering unprecedented therapeutic opportunities, as witnessed by the recent repurposing of FDA-approved mitochondria-active agents against tumors. 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. We thus hypothesized MM to be exquisitely reliant on mitochondria. 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, supported by AIRC and the International Myeloma Society, 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 (*Number of characters, including spaces*: max 600):

- Assessment of gene/protein expression and functional characterization of homeostatic pathways
- Morpho-functional characterization of mitochondrial function
- Genetic and pharmacologic manipulation of stress responses
- Genetic engineering and targeted mutagenesis
- Assessment of myeloma development in suitable mouse *in vivo* models
- Molecular (qRT-PCR, FACS, IB), imaging (IF, TEM, IHC) and functional (proliferation, energy metabolism, apoptosis) analyses of myeloma cell lines
- Critical data analysis
- Experimental design
- Critical presentation of data (internal seminars, nat'l and int'l meetings)

References

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.