PROJECT 1

DoS: **Simone Cenci**

Title: **Role in aging pathophysiology of an unprecedented proteostatic control of mitochondrial homeostasis**

Curriculum: Cellular and Molecular Biology

Residency Program: Internal Medicine

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):

Aging is the universal progressive multi-organ functional decline that predisposes to age-dependent diseases (including neurodegenerative, cardiovascular, metabolic disorders, cancer, and geriatric syndromes), resulting in disability and death. The extraordinary expansion of the aging population urges to develop effective strategies against age-related diseases by advancing our understanding of aging. Among the established hallmarks of the aging process, loss of protein homeostasis and mitochondrial dysfunction are two fundamental cell-intrinsic drivers of aging whose interconnection is underexplored. Through unbiased proteomics and mechanistic *in vitro* and *in vivo* studies, we have identified an unprecedented intracellular crosstalk whereby protein homeostasis controls mitochondrial structure and function, involving the pro-longevity eumetazoan adapter protein, SQSTM1/p62. This previously unsuspected level of integration across distinct cellular compartments opens a new area of investigation that promises to disclose new molecular circuits underlying aging pathophysiology.
To leverage this framework, we deployed a multidisciplinary approach designed to dissect novel mechanisms that promote aging and age-related tissue damage. The scientist in charge will also test the pathophysiologic significance and anti-aging therapeutic potential of the newly defined circuits integrating *in vitro*, *ex vivo* and *in vivo* approaches, including: primary cells from aged animal and human individuals; already available *ad-hoc* engineered cellular and animal systems, including knock-out and knock-in genetic mouse models; and state-of-the-art comprehensive geriatric assessment in elderly patients, entailing a unique cohort of individuals bearing proteostasis-relevant *SQSTM1* mutations.
This pioneering project is expected to further the knowledge of the fundamental bases of aging and age-related diseases and may translate into new strategies to improve healthy aging.

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
- Genetic and pharmacologic manipulation of stress responses
- Genetic engineering and targeted mutagenesis of cancer cell lines
- Assessment of mitochondrial function, cellular fitness and tissue pathophysiologic aging features in dedicated mouse *in vivo* models

- Molecular (qRT-PCR, cytofluorimetry, immunoblotting), imaging (immunofluorescence, electron microscopy, immunohistochemistry) and functional (proliferation, energy metabolism, apoptosis) cellular analyses
- 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)

Lopez-Otin C, Blasco MA, Partridge L et al. *The hallmarks of aging.* **Cell 2013**; 153:1194-1217

Sun N, Youle RJ, Finkel T. *The mitochondrial basis of aging.* **Mol Cell 2016**; 61:654-666

Bitto A, Lerner CA, Nacarelli T et al. p62/SQSTM1 at the interface of aging, autophagy, and disease. **AGE 2014**; 36:1123-1137