PROJECT 1

DoS: LUCA MUZIO

Title: **M**itophagy and autophagy in the **I**schemic brain: a New avenue to foster **NE**uroprotection (MINE)

Curriculum: NEN

Link to OSR/UniSR personal page: http://www.unisr.it/medicina-chirurgia/ddr-internazionale-in-medicina-molecolare/luca-muzio/

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

Stroke accounts for 70-85% of cerebrovascular diseases, costing to the European economy more than €38 billion [1]. Local loss of blood supply during ischemia affects oxygen and glucose delivery, promotes anaerobic glycolysis associated with H+ increase and tissue acidification. The energetic collapse jeopardizes gradient and membrane polarization causing release of glutamate, which binds to ionotropic receptors and promotes intracellular Ca2+ flux. H+ dependent Acid Sensing Ion Channels (ASICs) activation further sustains calcium overload, leading to mitochondria dysfunctions, swelling and then to neuronal death [2]. Patient functional recovery is largely dependent on what happens to cells adjacent to the stroke core (penumbra). Neurons of the peri-ischemic area suffer of endoplasmic reticulum stress that triggers autophagy/mitophagy as seen in human[3] and rodent brains. Those are important tissue reprogramming events, but they act as a double-edged sword. On one side, autophagy is a protective reaction providing a source of energy upon nutrient deprivation. On the other, under acidosis/excitotoxic conditions, excessive autophagy leads to neuronal cell death. Likewise, mitophagy is beneficial in transient focal ischemia while its inhibition increases the infarct volume. Current pharmacological modulators have limited specificity and the identification of new therapeutic tools is an appealing area of investigation to rescue dying neurons in the penumbra. Aim of this study is thus to identify new modulators of autophagy and mitophagy for treating ischemic stroke. We propose to 1) perform a drug screening on human induced pluripotent stem cells (hiPSC)-derived neurons looking for autophagy and mitophagy modulators; 2) validate our findings in aged hiPSC-derived neurons; 3) apply the best leads in experimental stroke to reduce disability and mortality in aged mice.

Skills to be acquired by the student:

Cell reprogramming, biochemistry, cell biology, HTS screening

References (max. 3)

1 Chen, R. L., Balami, J. S., Esiri, M. M., Chen, L. K. & Buchan, A. M. Ischemic stroke in the elderly: an overview of evidence. *Nat Rev Neurol* **6**, 256-265, doi:10.1038/nrneurol.2010.36 (2010).

2 Pignataro, G., Simon, R. P. & Xiong, Z. G. Prolonged activation of ASIC1a and the time window for neuroprotection in cerebral ischaemia. *Brain* **130**, 151-158, doi:10.1093/brain/awl325 (2007).

3 Frugier, T. *et al.* Evidence for the recruitment of autophagic vesicles in human brain after stroke. *Neurochem Int* **96**, 62-68, doi:10.1016/j.neuint.2016.02.016 (2016).