PROJECT 1

DoS: GIANVITO MARTINO

Title: Development of an in vitro functional platform to discover new drugs for progressive multiple sclerosis and translation to preclinical animal models

Curriculum: NEUROSCIENCE AND EXPERIMENTAL NEUROLOGY

Link to OSR/UniSR personal page:

http://research.hsr.it/en/institutes/institute-of-experimental-neurology/neuroimmunology.html

Project description (*Number of characters, including spaces*: 2.000 - 3.000): NOW 5000

Multiple sclerosis (MS) is a chronic disabling disorder with strong social impact and economic consequences. The disease is clinically heterogeneous. In the past 20 years new mechanisms and processes involved in the disease have been elucidated and resulted in new therapeutic options for patients carrying the relapsing profile. Valuable options to offer to patients who enter the disabling phase of MS or suffering of early rapid progression are still lacking. During chronicization, neurons whose myelin cover-layer is damaged or missing, present progressively impaired functions and ultimately become atrophic and die.
The goal of the project is to perform *in vitro* functional assays using bioinformatically prioritize drugs (*1*), mainly repurposed, on neuronal cultures and to test the best performing molecules *in vivo* in preclinical animal models with the ultimate aim of translating valuable compounds to the clinic.
The work is part of the efforts of an international network of scientists, with bioinformatic, neurobiological and pharmacological expertises.
The specific tools that will be used in the project are (i) cortical murine and embryonic derived neurons, (ii) neuronal differentiated embryonic-like (i.e. induced pluripotent stem cells, iPSCs) human neural cells from healthy controls and MS subjects as a 'disease-in-a-dish' human validation system and fetal neural precursors; (iii) drug target validation on tissue samples from both murine and MS patients to prove *ex vivo* the validity of the molecular pathway of action of selected compounds; (iv) the *in vivo* neuroinflammatory and demyelinating animal models of experimental autoimmune encephalomyelitis and the toxic cuprizone treatment.(*2, 3*)
The student will directly contribute to the development of functional cellular assays to study the neuroprotective properties of drugs that will be tested on the above mentioned cell types (viability, dendrite length, electrical activity, calcium response, fluorescent voltage-sensitive dye assays). Further, the candidate will be involved in identifying the context specific-"mechanism of action" of those compounds that exploit *in vitro* therapeutic properties. Altered molecular and biochemical targets will be validated on human brain tissues, available through collaborators. Last, the student will assess the therapeutic properties of selected compounds *in vivo* in preclinical models of neurodegeneration.

Skills to be acquired by the student:

- **pose a research question/problem.**
- **examine the range of available modes of inquiry.**
- **identify the appropriate research mode and procedure.**
- **define a sample/population.**
- **identify a data collection strategy .**
- **analyze and interpret data.**
- **draw conclusions from the data.**
- **acquire experimental skills in the context of induced pluripotent stem cells.**
- **write research reports/ paper.**

References (max. 3)

1. D. Himmelstein, Lizee, A., Hessler, C., Brueggeman, L., Chen, S., Hadley, D., Green, A., Khankhanian, P., Baranzini, S. , Rephetio: Repurposing drugs on a hetnet *Thinklab*, (2016).
2. D. De Feo *et al.*, Neural precursor cell-secreted TGF-beta2 redirects inflammatory monocyte-derived cells in CNS autoimmunity. *J Clin Invest* **127**, 3937-3953 (2017).
3. E. e. a. Butti, Neural stem cells of the subventricular zone are dispensable for the remyelination of the corpus callosum after cuprizone injury. *under revision*.