**PROGETTO**

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| **Supervisore**: | Colnaghi Luca |
| Titolo/*Title*: | New insights into NEDAMSS, an incurable regressive neurodevelopmental syndrome |
| *Curriculum*: | Neuroscienze e Neurologia Sperimentale |

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| Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento: | https://research.hsr.it/en/divisions/neuroscience/luca-colnaghi.html |

**Descrizione del progetto (max 3.000 caratteri spazi inclusi)**

**Background/gap of knowledge**

Recently identified as a novel regressive neurological disorder, Neurodevelopmental Disorder with Regression, Abnormal Movements, Loss of Speech, and Seizures (NEDAMSS) stems from mutations in the gene encoding the IRF2BPL protein (1-4). This gene encodes for a protein poorly characterized with intrinsically disordered domains, ubiquitin ligase activity, and transcriptional regulation function. Due to this lack of knowledge, the mechanisms underlying its association with NEDAMSS, and potential therapeutic avenues for this condition remain unclear. Therefore, this Ph.D. project proposal seeks to elucidate the fundamental mechanisms of IRF2BPL function and the dysfunction linked to NEDAMSS, to identify potential novel therapeutic targets.

**Rationale and hypothesis**

In preliminary experiments, we found that IRF2BPL is SUMOylated, can interact with several chaperones, can form organized complexes mediated by the intrinsically disordered regions, and can display specific biochemical behaviors that are altered by pathogenic mutations. All these are features that are shared by several other proteins involved in neurological disorders (5-6). Therefore, the aim of the project is to dissect all these preliminary findings to shed new light on the molecular mechanisms of NEDAMSS.

**Objectives and specific aims**

Leveraging the expertise of the lab and using multidisciplinary approaches including *in vitro* approaches, microscopy, primary neuronal cultures, and zebrafish studies, we will study:

i) What is the role of SUMOylation on the transcriptional activity of IRF2BPL?

ii) How do patient-derived mutations dysregulate the biochemical behavior of IRF2BPL?

iii) Can pharmacological modulation of IRF2BPL SUMOylation alter IRF2BPL pathological behavior in both primary neurons and animal models such as zebrafish?

**Expected outcomes**

This work will shed new light on the molecular pathogenesis of NEDAMSS uncovering how NEDAMSS-related mutations may cause disease by disrupting or altering the physiological roles of IRF2BPL. Moreover, it will identify regulatory mechanisms of IRF2BPL function (e.g.: SUMOylation and protein folding pathways) that may represent attractive therapeutic targets for NEDAMSS, which is yet an untreatable disorder.

**Competenze che deve acquisire lo studente** (Max 600 caratteri spazi inclusi):

The student during the training period will have to acquire independence in the planning, execution, and analysis of experiments. Emphasis will be applied to the critical analysis of results. From a practical point of view, the student will learn to work with mammalian cells, primary mouse neurons, and genetic manipulation of the zebrafish animal model. The student will also learn to master laboratory routine techniques such as western blotting, microscopy (confocal and SIM-super resolution microscopy), and molecular biology and biochemistry approaches and protocols.

**Bibliografia** (max. 15)

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