UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title

Lysosomal regeneration as therapeutic strategy in Hereditary Spastic Paraplegia

2)Abstract (max 500 words)

Background Hereditary spastic paraplegia (HSPs) is a group of neurodegenerative disorders characterized by progressive spasticity and weakness in the lower limbs, due to retrograde axonal degeneration of the corticospinal tracts. The high level of genetic heterogeneity with more than 80 SPG (Spastic Paraplegia) genes being identified corresponds to relatively less mechanistic pathways leading to HSP and includes axonal transport, endoplasmic reticulum morphogenesis and function, mitochondrial regulation, myelination, lipid and sterol metabolism, vesicle and endosomal trafficking, lysosomal function and autophagy. Despite the increasing understanding of disease mechanisms, to date, HSP remain incurable conditions and palliative care and rehabilitative programs are the only available treatments for patients.

Rationale Our recent results on preclinical *in vivo* and *in vitro* models, showed that lysosome enlargement and autophagic lysosomal reformation (ALR) defects are common phenotypes to a subgroup of SPG models (SPG4, SPG11 and SPG15, SPG31). Based on that, we recently performed the first combined *in vitro/in vivo* pharmacological screening in SPG15 models demonstrating that lysosomes are a key pharmacological target to rescue the SPG15 phenotype and that rescuing ALR is a good therapeutic strategy for this HSP form and for those associated with ALR defects. We also identified a small effective bioactive molecule with a great biological effect on lysosomal regeneration and locomotion activity. However, no clinical trials are registered for this compound and it has never been tested for tolerability and efficacy and needs to be further investigated.

Aims We selected alternative compounds (already in clinical trials) with promising potential in activating the lysosomal regeneration process. This project aims to i) characterize the efficacy of these compounds in our *in vitro* and *in vivo* preclinical HSP models: a deep analysis at molecular, cellular, tissue and behavioral level will help to dissect the effect of these compounds on endo- lysosomal system, lysosomal regeneration and locomotor deficit; ii) understand their pharmacological mechanisms; iii) generate new derivatives to improve the pharmacokinetic properties and efficacy. This will be a step forward in the pharmacological manipulation of the endo-lysosomal system, useful also for other HSP conditions.

Expected results/outputs

At the end of this analysis we will obtain a comprehensive understanding of the mechanism and therapeutic potential of these compounds for repositioning purpose in clinical trial for HSP.