Deficits in axonal transport as a target for pharmacological intervention in ALS

Acronym : ALS-GO !

Principal Investigator: Giampetro Schiavo

Grant: 117 000€

Duration: 18 mois

Summary of the research project

Deficits in axonal transport are a common feature of several neurodegenerative conditions including Amyotrophic Lateral Sclerosis (ALS). We have previously demonstrated that alterations in the axonal transport of signalling endosomes and mitochondria occur in the pre-symptomatic stages of ALS, suggesting a pivotal role of deficits in axonal transport in ALS onset and/or disease progression. Thus, the identification of small molecules that ameliorate axonal transport deficits is a potential therapeutic strategy for ALS, as well as other neurodegenerative diseases.

Using chemical screens in mouse ES cell-derived motor neurons, we recently identified novel small molecules which are able to restore the deficits in axonal transport observed in $SOD1^{G93A}$ motor neurons. In particular, one of these compounds (E4) has been described to specifically target insulin-like growth factor 1 receptor (IGF-1R).

The first aim of this proposal is to validate IGF-1R as the biological target of compound E4 by assessing the role of this receptor tyrosine kinase in the regulation of axonal transport in wild type and ALS motor neurons. We will use primary motor neurons from $SOD1^{G93A}$ mice as well as motor neurons differentiated from human inducible pluripotent stem cells (hiPSC) isolated from ALS patients to perform pharmacological experiments with established inhibitors of IGF-1R as well as with compound E4 identified in our screen. Moreover, we will assess the impact of IGF-1R down-regulation by shRNA on the axonal transport of signalling endosomes and other organelles.

In the second aim of this project, compound E4 will be tested for its ability to restore axonal transport *in vivo* in $SOD1^{G93A}$ mice and other selected ALS models by intravital microscopy. If these studies confirm that E4 restores axonal transport deficits in mouse models of ALS, we will test the ability compound E4 to modify disease progression in $SOD1^{G93A}$ mice.

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Relevant research articles for this project are:

- Bercsenyi K, Schmieg N, Bryson JB, Wallace M, Caccin P, Golding M, Zanotti G, Greensmith L, Nischt R and **Schiavo G** (2014) Nidogens are therapeutic targets for the prevention of tetanus. *Science,* **346**, 1118-23
- Terenzio M, Golding M, Russell MRG, Wicher K, Rosewell I, Spencer-Dene B, Ish-Horowicz D and **Schiavo G** (2014) Bicaudal-D1 regulates the intracellular sorting and signalling of neurotrophin receptors. *EMBO J,* **33**, 1582-98.
- Wang Y, Chakravarty P, Ranes M, Kelly GP, Brooks PJ, Neilan E, Stewart A, **Schiavo G** and Svejstrup JQ (2014) Dysregulation of gene expression as the cause of Cockayne syndrome neurologic disease, *Proc Natl Acad Sci U S A*, **111**, 14454-9.
- Terenzio M, Golding M and **Schiavo G** (2014) siRNA screen of ES cell-derived motor neurons identifies novel regulators of neurotrophin receptor trafficking. *Frontiers Cell Neurobiol,* **8**, 140.