2020 Call for projects

# Understanding redox homeostasis to improve axonal transport deficits in ALS

**Acronym: Axon ALS**

**Principal Investigator:** Jonathan Gilthorpe

**Grant: 247 000€**

**Duration: three years**

## Summary of the research project

The discovery of *SOD1* as the first ALS-linked gene in 1993 has resulted in a promising potential treatment for SOD1-ALS via antisense oligonucleotide (ASO) therapy. The rationale for lowering *SOD1* expression is to combat the toxic gain of function (GoF) exerted by aggregation of disordered SOD1 - reducing SOD1 protein levels reduces its potential to unfold and aggregate. The rationale is also built upon the assumption that SOD1 function is non-essential in humans. Evidence for this is based mainly on *SOD1* knockout mice, which exhibit peripheral neuropathy but lack an overt ALS phenotype. However, the discovery of children carrying a particular homozygous SOD1 loss of function (LoF) mutation and presenting with progressive neuropathy, but not ALS, points to an important function for human SOD1 that is not understood. A dearth of homozygous carriers with strong SOD1 LoF alleles supports an essential function for human SOD1. Recent impetus has also come from high-throughput CRISPR/Cas9-based screening, showing a vital function of human SOD1 in iPSCs and neurons. Hence, in addition to the toxic GoF caused by SOD1 unfolding and aggregation, SOD1 could contribute to ALS via LoF. This is important to understand, especially in light of therapeutic interventions aimed at lowering SOD1 levels.

This project aims to define the essential function(s) of human SOD1. SOD1 has been found to accumulate on endocytic organelles (EOs) during their retrograde axonal transport in motor neurons. EOs are a key component of the growth factor signaling machinery and our hypothesis is that one crucial function of human SOD1 is in the regulation of EO transport, via redox-mediated signaling. In this project we aim to understand both LoF and GoF effects of SOD1 using novel axonal transport assays in human iPSC-derived models. We will use these assays to determine the interaction of EOs with mitochondria, as the main source of intracellular superoxide in motor neurons. We will quantify the effects of SOD1 LoF, GoF as well as altered antioxidant capacity on axonal transport in order to:

- Understand the relative effects of SOD1 LoF and GoF on axonal transport and motor neuron survival
- Analyse changes in endosomal cargo
- Develop a method for early diagnosis of ALS in patient-specific MNs

## Potential clinical relevance of the research:

For the first time we will establish whether SOD1 LoF and GoF contribute significantly to MN dysfunction via axonal transport. Subsequently, we will gain insights into how LoF and GoF may influence the onset and progression of ALS in either an inter-dependent or independent manner. This knowledge may provide new avenues for treatment of ALS. It will also provide a new conceptual framework to understand the dynamics of the SOD1-ALS phenotype.

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The development of new organelle tracking and interaction algorithms for use in axonal transport assays should offer new avenues for proof of principle testing of new ALS therapeutics.

The study will be conducted by Dr. Jonathan Gilthorpe, Senior Lecturer, Department of Integrative Medical Biology, Umeå University, Sweden.