

# The role of Miro and PKC signalling in axonal transport defects in amyotrophic lateral sclerosis.

<https://www.neurodegenerationresearch.eu/survey/the-role-of-miro-and-pkc-signalling-in-axonal-transport-defects-in-amyotrophic-lateral-sclerosis/>

## Principal Investigators

Dr K De Vos

## Institution

University of Sheffield

## Contact information of lead PI Country

United Kingdom

## Title of project or programme

The role of Miro and PKC signalling in axonal transport defects in amyotrophic lateral sclerosis.

## Source of funding information

MRC

## Total sum awarded (Euro)

€ 573,168

## Start date of award

01/03/2013

## Total duration of award in years

3.0

## The project/programme is most relevant to:

Motor neurone diseases

## Keywords

### Research Abstract

Amyotrophic lateral sclerosis (ALS) is a lethal motor neuron disorder without a cure. Impaired axonal transport is one of the earliest pathological features observed in ALS models, suggesting that transport defects might be a primary cause of ALS. We showed that mutations in SOD1 and

VAPB that cause familial ALS inhibit anterograde but not retrograde axonal transport of mitochondria. The mitochondrial kinesin-1 receptor Miro regulates anterograde transport of mitochondria in response to calcium and mitochondrial damage. Furthermore, several groups including us have shown a role for phosphorylation in regulation of the transport process. We hypothesise that inhibition of anterograde mitochondrial axonal transport by a calcium/Miro and kinase-dependent pathway is a primary cause of motor neuron death in ALS and a potential therapeutic target. The specific objectives are: (1) To determine if a calcium/Miro signalling pathway underlies the mitochondrial axonal transport deficit in ALS. We will evaluate if a calcium insensitive mutant Miro can restore the transport deficit in mitochondrial transport assays. (2) To investigate the involvement of kinase signalling. We will test kinase inhibitors for their effect on axonal transport in mitochondrial transport assays. (3) To establish if axonal transport defects are a primary cause of cell death in ALS. We will restore axonal transport of mitochondria using a calcium insensitive Miro mutant or kinase inhibitors in motor neurons expressing ALS mutant proteins and monitor motor neuron survival. Summarised, this research will increase our understanding of the mechanisms underlying defective mitochondrial transport and motor neuron death in ALS, and will establish if restoration of axonal transport has therapeutic potential. Furthermore, the results obtained here are likely to be transferable to other neurodegenerative diseases that involve axonal transport defects, including Alzheimer's and Parkinson's disease.

### **Lay Summary**

**Further information available at:**

#### **Types:**

Investments > €500k

#### **Member States:**

United Kingdom

#### **Diseases:**

Motor neurone diseases

#### **Years:**

2016

#### **Database Categories:**

N/A

#### **Database Tags:**

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