



RAB10 AS A NOVEL TARGET TO MANIPULATE AXONAL TRANSPORT OF NEUROTROPHIC SIGNALLING ENDOSOMES.

Oscar Marcelo Lazo^{1,2} and Giampietro Schiavo^{1,2,3}

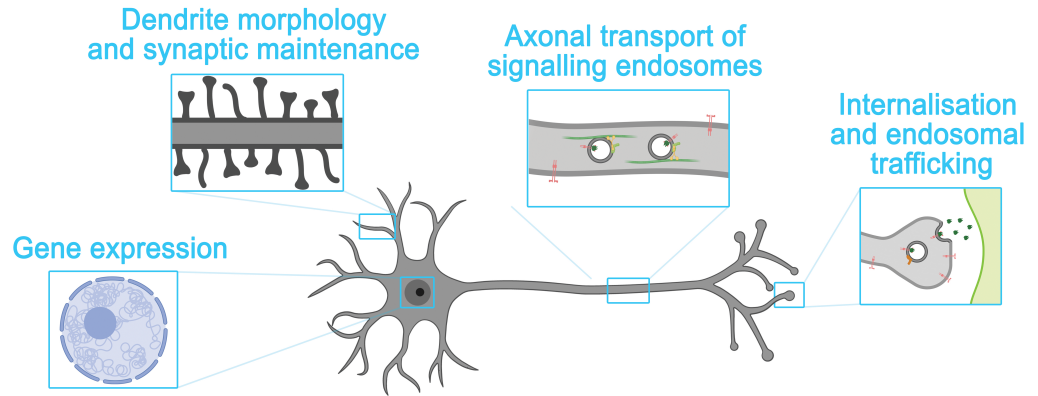
¹ Department of Neuromuscular Diseases,
² UK Dementia Research Institute at UCL,
³ Discoveries Centre for Regenerative and Precision Medicine at UCL,
 Queen Square Institute of Neurology, University College London, United Kingdom.



1. Why targeting axonal transport of neurotrophic receptors?

Deficits on the **availability** of neurotrophic factors, **internalisation** of receptors, **sorting** and **axonal transport** of signalling endosomes, as well as **dendritic atrophy** and changes in **gene expression** are common features to several neurodegenerative conditions, including Alzheimer's disease.

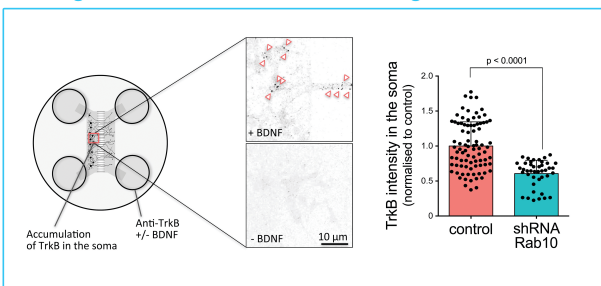
Since neurotrophic factors are secreted by the neuronal targets and **required retrograde propagation along the axon** to impact on neuronal survival and function, we propose that therapeutic targets must be **critical nodes regulating both neurotrophic signalling and trafficking** to effectively rescue neuronal function.



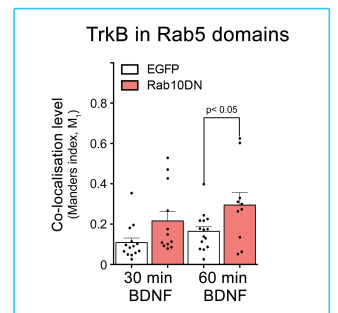
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2. Rab10 as a novel regulator of TrkB sorting to retrograde axonal transport.

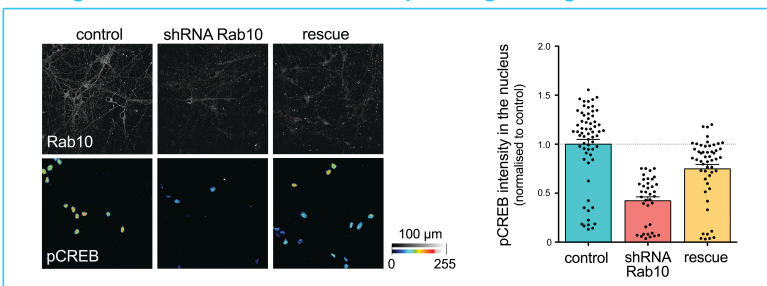
Retrograde accumulation of endogenous TrkB



Inactive Rab10 increases TrkB in early endosomes



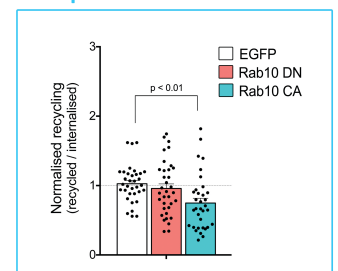
Retrograde activation of neurotrophic signalling



Knocking-down Rab10 by using shRNA impairs **retrograde transport and signalling of TrkB** in hippocampal neurons.

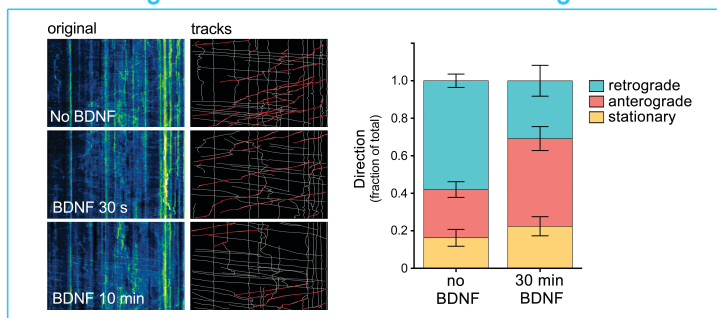
In axons, the expression of a dominant negative (DN) mutant of Rab10 **increases co-localisation of internalised TrkB** with the early endosome marker **Rab5**, with no effect on recycling.

Recycling of TrkB does not require Rab10 activation



3. Mobilising and activating Rab10 on the axon.

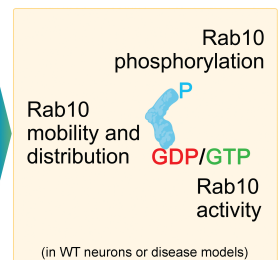
BDNF changes the direction bias of Rab10 organelles



The strategy

Tools to manipulate

- **Mutants** (dominant negative, constitutively active, phosphomimetic, phosphodeficient)
- **Drugs** (antidiabetic drugs, LRRK2 inhibitors)
- **Optogenetics** (light-inducible dimerisation between Rab10 and DENND4, MICAL-L2 and LRRK2)



Tools to measure

- **Rab10** (phospho-specific and total antibodies, GST-MICAL-L2, Rab10-EGFP)
- **Neurotrophic signalling** (antibodies, FRET probes, kinase translocator reporters)
- **Morphology and function** (Sholl's analysis, Synaptophysin-pHluorin)