Role of C9ORF72 in proteostasis

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A genetic defect in the *C9ORF72* gene – an expansion of the GGGGCC hexanucleotide repeat in intron 1 – is the most common cause of inherited familial ALS. This defect is also the strongest genetic risk factor for the more common, non-inherited, sporadic form of ALS. The *C9ORF72* gene encodes an uncharacterised protein that is highly conserved in vertebrates, indicating that its function is likely to be important. We do not know how this genetic defect in *C9ORF72* causes disease. One possibility is that it causes less C9ORF72 protein to be produced. If this were the case there would not be enough C9ORF72 protein to perform its function in the cell and this may be the cause of disease. To be able to investigate if this is so we first need to find out what the function of C9ORF72 protein is. The purpose of this study is to find out what C9ORF72 does in the cell. We have some evidence that the C9ORF72 protein is involved in the removal of old or malfunctioning cellular proteins. We will investigate this in a number of ways using methods established in our laboratory such as immunoprecipitation experiments, proximity ligation assays, and microscopy. We will also look for other proteins that bind to C9ORF72 because this could provide us with clues to its function as well. Together these investigations will increase our understanding of C9ORF72 function and its role in ALS.

What is proteostasis?

The protein homeostasis or proteostasis network (PN) is a complex regulatory network that balances protein biosynthesis, folding, translocation, assembly/disassembly, and clearance (degradation). PN is a modular, yet integrated system that is sensitive to signaling pathways that direct development and aging and respond to folding stress. Cell survival is inseparably tied to protein quality control, and mismanagement of protein folding and function triggered by genetic, epigenetic and environmental causes poses a major challenge to human health.

The research will be done in the **Sheffield Institute for Translational Neuroscience (SITraN)** at the University of Sheffield. SITraN is a new Institute opened in November 2010 with the express purpose of fighting against motor neuron disease and other common neurodegenerative disorders of the motor system. Its key vision is to develop the necessary critical mass and facilities to exploit the potential of modern neuroscience, the 'post-genome' era, and exciting developments in biomedical therapeutics with specific focus on this devastating group of illnesses. The establishment of SITraN in Sheffield offers the opportunity for a coordinated approach to the development and clinical trialling of new therapies based on rational targets of proven preclinical effectiveness.

Kurt De Vos is lecturer in Translational Neuroscience at SITraN. His major research achievements in the field of human neurodegenerative disease are the characterisation of mitochondrial axonal transport defects in models of amyotrophic lateral sclerosis (ALS) (De Vos et al., 2007; Morotz et al., 2012) and hereditary spastic paraplegia (Kasher et al., 2009), the study of how mutations in the FUS gene that cause familial ALS influence FUS biology (Vance et al., 2009), and the investigation of how phosphorylation of the molecular motor subunit kinesin light chain 1 modulates the axonal trafficking of calsyntenin, a protein that is involved in the trafficking and processing of amyloid precursor protein in Alzheimer's disease (Vagnoni et al., 2011). Recently he has identified ER-mitochondria contacts as a novel player in the pathology of ALS (De Vos et al., 2012).