

**P035** A mutation in dynein rescues axonal transport defects and extends the lifespan of ALS mice  
Dairin Kieran<sup>1#</sup> Stephanie Bohnert<sup>2</sup>, Majid Hafezparast<sup>3</sup>,  
Joanne Martin<sup>4</sup>, Elizabeth Fisher<sup>1</sup>, Giampetro Schiavo<sup>2</sup> and  
Linda Greensmith<sup>1</sup>

1. Institute of Neurology, Queen Square, London. 2 Cancer Research UK, 3. University of Sussex, 4. Queen Mary University, London. # Current Address: Royal College of Surgeons in Ireland.

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative condition characterized by motoneuron degeneration and muscle paralysis. Although the precise pathogenesis of ALS remains unclear, mutations in Cu/Zn superoxide dismutase (SOD1) account for approximately 20-25% of familial ALS cases. Transgenic mice over-expressing human mutant SOD1 develop an ALS-like phenotype of progressive motoneuron degeneration and paralysis. Evidence suggests that defects in axonal transport play an important role in neurodegeneration. In *Loa* mice, mutations in the motor protein dynein are associated with axonal transport defects and motoneuron degeneration. Here we show that retrograde axonal transport defects are already present in motoneurons of SOD1<sup>G93A</sup> mice during embryonic development. Surprisingly, crossing SOD1<sup>G93A</sup> mice with *Loa*/+ mice delays disease progression and significantly increases lifespan in *Loa*/SOD1<sup>G93A</sup> mice. Moreover, there is a complete recovery in axonal transport deficits in motoneurons of these mice, which may be responsible for the amelioration of disease. Thus, we propose that impaired axonal transport is a prime cause of neuronal death in neurodegenerative disorders such as ALS.