Lesson learnt from a new C9orf72 mouse model of ALS

*Survival and Motor Phenotypes in FVB C9-500 ALS/FTD BAC Transgenic Mice Reproduced by Multiple Labs.*

Liu et al. 2016. [http://dx.doi.org/10.1016/j.neuron.2016.04.005](http://dx.doi.org/10.1016/j.neuron.2016.04.005)
Mordes et al. 2020. [https://doi.org/10.1016/j.neuron.2020.08.009](https://doi.org/10.1016/j.neuron.2020.08.009)

There are currently only two therapies available for the treatment of ALS, Riluzole and Edaravone. Part of the reason for the lack of efficacious treatments is due to the complex nature of the disease, with many factors hypothesised to impact its progression. Included amongst these factors are dysfunctional mitochondria, the part of the cell responsible for energy generation, and a dysfunctional endoplasmic reticulum, the part of the cell responsible for the synthesis of proteins. Researchers now believe that a novel treatment that targets these areas could provide a viable therapy for ALS.

The study, published in the New England Journal of Medicine, investigates the effect on ALS patients of oral consumption of Sodium Phenylbutyrate-Taurursodiol (SP-T), a treatment which combines sodium phenylbutyrate (a.k.a. Buphenyl, Ammonaps or triButyrate) and taurursodiol (a.k.a. Tauroursodeoxycholic acid), and has shown promise in experimental models of ALS. This combination of treatments has two effects;

1. Sodium phenylbutyrate increases levels of heat shock proteins, which are proteins produced in response to stressful conditions that alleviate the effect of a dysfunctional endoplasmic reticulum, stabilising newly synthesised protein by ensuring they are folded correctly, a key stage of protein production in the cell.

2. When mitochondria are distressed they release signals that trigger cell death, known as apoptosis, taurursodiol prevents these signal from being released, preventing the initiation of apoptosis.

The trial was a randomised, double-blind trial, meaning that of the 177 participants (all having developed ALS within the preceding 18-months), 137 were randomly assigned a prescription of SB-T and the remaining 48 given a placebo, with neither the patient or healthcare provider knowing which medication was being taken. The primary outcome being investigated was changes in ALSFRS-R score over the course of the 24-week trial, a measure of the functional ability of the patient, which usually declines over time. Other secondary outcomes such as muscle strength were also observed.

Results showed that whilst there were no significant changes in secondary outcomes in patients taking SP-T, there was a significantly slower decline in ALSFRS-R score. A longer-term trial, screening more patients and measuring survival as a primary outcome will be required before more concrete conclusions can be drawn on this novel treatment for ALS, but this data still represents a huge finding for ALS patients and may mean SP-T will be commercially available as therapy in the coming years.