Tamoxifen increases survival, improves motor function and reduces levels of BIN1 and DNM2 in a mouse model of X-linked centronuclear (myotubular) myopathy

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X-Linked centronuclear myopathy (XLCNM) is a rare and severe congenital myopathy characterised by generalised muscle weakness and abnormal nuclei positioning. Most affected boys die in their first year of life and survivors fail to achieve independent ambulation. It is caused by mutations in the
Mtm1 gene encoding myotubularin, a ubiquitously expressed phosphoinositide phosphatase. No cure exists and very few pharmacological avenues are being explored. Here, we treated Mtm1-null mice with tamoxifen (TAM), a drug that modulates estrogen actions and that we have shown earlier to be
efficacious in dystrophic (mdx5Cv) mice, a model of Duchenne muscular dystrophy (DMD).

We report that TAM is also effective in Mtm1-null mice, a model of XLCNM. Wild type and Mtm1-null mice were given normal chow or a TAM-supplemented chow starting at weaning. Non-treated Mtm1-null mice died at around 40 days. By contrast, about half of the Mtm1-null mice treated with clinically relevant doses of TAM survived beyond 365 days of age. Clinical scoring showed that the motor function of the affected mice was markedly improved. In vivo force recordings performed at D40 and D80 revealed that the force of treated Mtm1-null was significantly improved after only 3 weeks
of treatment. Histological and electron microscopy analyses show partial rescue of muscle structure and triads, consistent with improved calcium homeostasis in FDB fibres. Quantitative PCR and western blots demonstrate reduction of BIN1 and DNM2, which act downstream of MTM1.

In conclusion, we found that tamoxifen extends the lifespan of Mtm1-null mice up to 10-fold and rescues their motor skills. Collectively, these findings suggest that estrogen signalling is a key pathway that modifies disease severity in unrelated myopathies as diverse as DMD and XLCNM. Tamoxifen is
safe and readily available. We believe that it deserves clinical evaluation for XLCNM.