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Title	**Investigating novel modulators of TDP-43 pathology using human iPSC-derived neuronal models**
Abstract (max 300w)	**Introduction:** i^{3}Neurons (Wang *et al.* 2017) are a tool to study human neuronal pathophysiology. They are derived from a normal control human induced pluripotent stem cell (hiPSC) line and genetically engineered to express a doxycycline-inducible neurogenin-2 transgene. Neurogenin-2 overexpression rapidly differentiates hiPSCs into homogenous glutamatergic neurons. We have utilised i^{3}Neurons to investigate MND pathophysiology. In 97% of MND cases, motor neurons develop cytoplasmic aggregations of, and post-translational modifications to, the essential protein TDP-43. Replicating TDP-43 pathology within neuronal models will support interrogation of pathomechanisms driving MND onset and progression. **Objective:** To model TDP-43 pathology within i^{3}Neurons. **Methods:** hiPSCs were supplemented with doxycycline over a 3-day differentiation process to produce post-mitotic i^{3}Neurons. Immunolabeling revealed i^{3}Neurons exhibited dense axonal networks and express neuronal markers, β-III-Tubulin and Tau. To induce TDP-43 pathology, 10-day old i^{3}Neurons were transduced with lentivirus for expression of human synapsin 1 (*hSYN1*) promoter-driven mutant TDP-43$^{dNLS/2KQ}$-GFP and imaged over a 17-day period. This TDP-43 mutant has a defective nuclear localisation signal and acetylation mimicking mutations to replicate cytoplasmic TDP-43 pathology in MND. **Results:** Approximately 80% of i^{3}Neurons were transduced with hSYN1-TDP-43$^{dNLS/2KQ}$-GFP 72h post-transduction. We observed GFP-positive puncta reminiscent of TDP-43 inclusions located within neuronal somas and neurites in a proportion of transduced i^{3}Neurons after 11 days. Cell Profiler image analysis showed that the majority of puncta were of uniform size and eccentricity. **Conclusion:**

	The ability for i3Neurons to recapitulate human neuronal physiology makes it a powerful *in vitro* model to investigate mechanisms driving TDP-43 pathology and therapeutic interventions for MND.

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