Response by Aviva M Tolkovsky, Michel Goedert, Manuela Melone, Maria-Grazia Spillantini to the Journal Club "Dorsal Root Ganglion Neurons Carrying a P301S Tau Mutation: A Valid In Vitro Model for Screening Drugs against Tauopathies?" by Alberts et al.

We thank Alberts et al. for choosing to review our paper. The authors rightly point out that all *in vitro* models of complex neurodegenerative diseases have drawbacks. However, understanding their limits may also point to disease mechanisms.

The authors write: "These [in vitro] models may provide useful knowledge about tau pathology while limiting interference of other factors." Indeed, they will tell us what is cell autonomous. However, having a simple model allows one to rebuild complexity from the base up. For example, mimicking a more physiological environment by adding astrocytes or microglia, or soluble factors produced by them, may help understand bystander effects.

The authors write: "A drawback of the DRG model is that these sensory neurons are not usually implicated in tauopathies." While sensory loss is not a hallmark of tauopathies clinically, few investigations have been performed on the PNS. We cite two reports where pathological tau inclusions are described in DRG or cervical ganglia while a recent paper found hyperphosphorylated tau (AT8) in nerve biopsies from patients with chronic peripheral neuropathy (Vital et al., 2014). Collecting more samples of DRG and peripheral nerves (rarely collected at autopsy) in tauopathies and other neuropathies may shed more light on this issue.

The authors write: "Moreover … regulation of tau assembly and hyperphosphorylation are gene-dose-dependent. Extending the transgenic lines with a variety of P301S-htau insertions may therefore provide a way of studying this concentration effect at the level of DRGs." Indeed, tau pathology in heterozygous P301S tau mice develops with 5-7 months delay. Interestingly, these mice show an extended period before disease develops rather than diminished severity once it does develop (Allen et al., 2002; Delobel et al., 2008). This suggests that filaments are not in equilibrium with soluble tau. Whether pathology is more severe on a tau knockout background is currently under investigation.

The authors write: "Furthermore, since tau truncations are observed in tauopathies … it would be interesting to test whether tau is also fragmented in the DRG model." We did not detect any tau fragmentation in extracts from DRGs of P301S tau mice, even when tau was maximally hyperphosphorylated, conformationally abnormal (MC1+ve), and filamentous. This is in keeping with Delobel et al. (2008), who showed that a small proportion of tau was cleaved at the caspase site (D421) in homozygous P301S tau mouse CNS, concluding that cleavage was not required for the development of pathological tau or filament formation.

Finally, the authors write: "Despite the usefulness of the mouse DRG model…appropriate human-derived cell culture models might resemble human tau pathology more closely." Human pluripotent stem (iPS) cells derived from genetically identified individuals with tauopathies indeed hold great promise. We have already initiated such studies using human embryonic stem cells (Iovino et al., 2010). However, it remains to be seen if the pathogenic events responsible for the human diseases can all be reproduced in iPS cells, whereas transgenic mice overexpressing even one isoform of human mutant tau develop several aspects of human tauopathies, not least cognitive decline. Comparing iPS cells derived from individuals with a P301S mutation in *MAPT* with mice transgenic for human mutant P301S tau will establish the usefulness of iPS cells as a disease model.