**Supplementary Discussion**

In the αSyn toxicity model, the human α-Synuclein protein containing the disease-associated A53T missense mutation (Outeiro and Lindquist, 2003) was integrated into the genome and controlled by the galactose-inducible promoter. Previous studies reported a dynamic, regulated equilibrium between the membrane-bound and the cytosolic form of αSyn, with a toxic effect on growth when multiple copies of the human protein are expressed in the yeast model (Flower 2007, Outeiro 2003). The HTT construct expresses exon 1 of the HTT protein with an expanded polyglutamine (polyQ) repeat of 72 glutamines fused to GFP (Krobitsch and Lindquist, 1999). When overexpressed in yeast cells, the construct was shown to generate toxic aggregates (Krobitsch and Lindquist, 1999, Deunnwald et al., 2006). In the Aβ42 model the beta-amyloid peptide, generated from the proteolytic cleavage of the amyloid precursor protein, was fused to the endoplasmic reticulum (ER) targeting signal and integrated in multiple copies in the yeast genome. The ER retention signal allowed the introduction of the polypeptide into the yeast secretory pathway, recapitulating the mammalian trafficking of both Aβ42 and its amyloidogenic precursor protein (Treusch et al., 2011). As for the aforementioned constructs, the overexpression of Aβ42 was shown to decrease cell growth and a number of suppressors or enhancers were detected when screening for Aβ42 toxicity modulators (Treusch et al., 2011). The TDP43 proteinopathy model contains multiple integrated copies of the human 43-KDa TAR-DNA-binding protein (TDP-43) fused to GFP. This aggregation-prone protein was shown to accumulate in the nucleus shortly after the induction of expression, and to further translocate to the cytosol with the consequent formation of multiple inclusions associated with a toxic gain-of-function phenotype (Johnson et al., 2008). Lastly, the FUS overexpressing strain contains one integrated copy of the human FUS/TLS nucleic acid binding protein. FUS was shown to co-localize with p-body and stress granule components and to form cytoplasmic aggregates. The cellular toxicity of FUS, associated to its mislocalization and cytoplasmic accumulation, could be either due to a loss of function in the nucleus or a gain of toxic function in the cytoplasm (Ju et al., 2011; Sun et al., 2011).