A. Abstract. Protein misfolding is intimately associated with a number of devastating human neurodegenerative diseases, including Alzheimer's, Huntington's, Parkinson's, and ALS. Interestingly, though disparate in their pathophysiology, many of these disorders share a common theme manifest in the accumulation of insoluble protein aggregates in the brain. Recently, the major disease protein found in pathological inclusions in amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's Disease) was identified as TDP-43. We have generated a yeast model to explore mechanisms governing TDP-43 subcellular localization and aggregation. Remarkably, this simple model recapitulates several salient features of human TDP-43 proteinopathies and we have uncovered a direct connection between TDP-43 aggregation and cellular toxicity. Thus, we have established a new model for discovering and testing potential therapeutic strategies aimed at combating TDP-43 proteinopathies. **The goal of our proposal is to harness this new yeast model to perform a high-throughput chemical screen to identify compounds that prevent TDP-43 aggregation and cellular toxicity.** Hits from our screen, if validated in other systems, will be used to develop novel therapeutic strategies aimed at treating ALS.