A transcriptional regulator as a modulator of TDP-43 and G_4C_2 hexanucleotide repeat toxicity in amyotrophic lateral sclerosis disease models

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The TAR DNA binding protein of 43 kDa (TDP-43) was identified as the major disease protein in ubiquitinated cytoplasmic inclusions in neurons of patients with amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) with ubiquitinated inclusions (FTLD-TDP). Through a screen in *Drosophila* to define modifiers of TDP-43 toxicity, the Bonini laboratory has identified modulators that mitigate TDP-43-associated neurodegeneration. Among them, I focus on a modifier, which regulates transcriptional pausing and has not previously been implicated in neurodegenerative disease. In addition to the toxicity of TDP-43, my preliminary findings suggest that the toxicity of G_4C_2 hexanucleotide repeat expansion, which is another important disease factor of ALS and FTLD, is also suppressed by downregulation of the transcriptional regulator.