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Drug discovery in a drosophila model of ALS based on TDP-43

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ALS is an adult onset, progressive neurological disorder characterized by selective degeneration and motor neuron death. Recently, several RNA binding proteins have been linked to motor neuron disease, including TDP-43 and FUS. These findings led to a paradigm shift in the current models for neuronal degeneration and suggest that a significant component of ALS may be due to dysregulation of RNA metabolism. Several mutations have been identified TDP-43, which has emerged as a common denominator for the majority of ALS cases known to date. To elucidate the mechanisms underlying neurodegeneration and to develop therapeutic strategies we have established a Drosophila model of ALS based on human TDP-43. Transgenic flies expressing different TDP-43 variants exhibit several features of ALS including neuronal loss, locomotor defects and reduced survival. Using this model, we have developed an in vivo screening strategy based on the adult lethality phenotype caused by wild-type or mutant TDP-43 (D169G, G298S, A315T and N345K) expression in motor neurons. To identify compounds that rescue the neurotoxicity of TDP-43 in vivo we screened the Prestwick collection of FDA approved drugs. This screen has several advantages including: 1) it is performed in vivo, 2) it is based on a robust phenotype (100% lethality), 3) can lead to rapid identification of known safe drugs that are already used in humans and 4) it can inform the future development of novel small molecules with enhanced neuroprotective capabilities. I will report on the findings from the primary screen that identified several drug categories with neuroprotective potential.

Biography

Dr. Zarnescu completed her Ph.D from Pennsylvania State University in 2000 and postdoctoral studies from Emory University School of Medicine in 2005. Since 2006 she has been an Assistant Professor of Molecular and Cell Biology, Neuroscience and Neurology at University of Arizona. She has published more than 15 research and review articles in the areas of Drosophila development, neurobiology and models of human disease.

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