

Optogenetic Modulation of TDP-43 Proteinopathy

June 26

Tuesday, 12:30 pm

Weekly Colloquium

Billings Building
Rosedale Conference Room



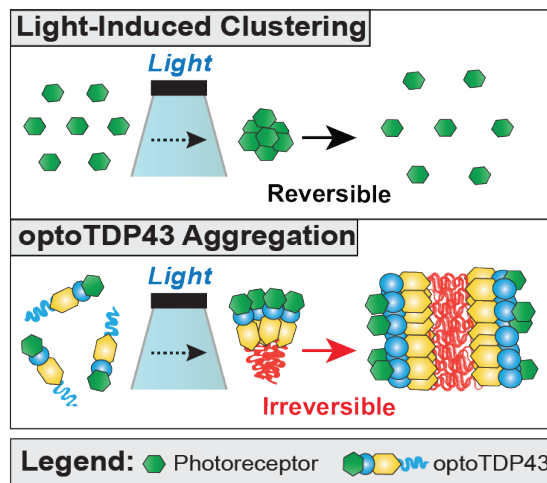
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Abstract

Pathological hallmarks of age-related neurodegenerative diseases are intracellular protein inclusions. TDP-43 is a predominantly nuclear DNA/RNA binding protein but is found mislocalized to the cytoplasm and aggregated in a variety of neurodegenerative diseases. TDP-43 proteinopathy is a neuropathological feature of amyotrophic lateral sclerosis, a fatal disease characterized by the degeneration of the motor neurons of the brain and spinal cord, and a predominant pathology in frontotemporal dementia, the most common cause of dementia in individual under the age of 65. Modeling TDP-43 and other neurodegenerative proteinopathies is challenging and relies on nonphysiological overexpression of wild-type or mutant variant of the proteins. This approach lacks any control over the aggregation process. Furthermore, these models do not often mimic key features of the diseases in patients. To overcome this problem, we developed a photokinetic technique that allows for the induction of neurodegenerative protein oligomerization under spatial and temporal control. Employing this light-based/optogenetic approach, we identified the intracellular requirements for the development of TDP-43 proteinopathy and identified mechanisms to disrupt the formation of these pathological inclusions.



(This work is not relevant to talk as it is a new area of interest for which a manuscript has been submitted)

Zhang,* C.J. Donnelly,* A.R. Haeusler, J. C. Grima, J.B. Machamer, E.L. Daley, S. Vidensky, M.A. Thomas, K.M. Cunningham, P. Steinwald, M.J. Matunis, J. Wang, R. Sattler, T.E. Lloyd, J.D. Rothstein. (2015). The C9ORF72 repeat expansion disrupts nucleocytoplasmic transport. *Nature* 525 (7567): 56-61. (*authors share equal contribution)

A.R. Haeusler, C.J. Donnelly, G. Periz, R. Sattler, E. A. Simko, P.G. Shaw, M. S. Kim, A. Pandry, J.D. Rothstein, J. Wang. (2013). Structural polymorphisms of C9ORF72 hexanucleotide repeats cause ALS/FTD defects through abortive transcription and nucleolar stress. *Nature* 507 (7491): 195-200.

C.J. Donnelly, P.W. Zhang, J.T. Pham, A.R. Haeusler, N.A. Mistry, S. Vidensky, E.L. Daley, E.M. Poth, B.N. Hoover, D.M. Fines, N. Maragakis, P.J. Tienari, L. Petrucelli, B.J. Traynor, J. Wang, F. Rigo, C.F. Bennett, S. Blackshaw, R. Sattler, J.D. Rothstein (2013) RNA toxicity from the ALS/FTD C9ORF72 expansion is mitigated by antisense intervention. *Neuron* 80 (2): 415-428.



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