CELLULAR & SYSTEMS NEUROSCIENCE SEMINAR SERIES

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Genetic screens in model organisms provide insight into neurodegenerative disease mechanisms

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My goal is to discover the cellular and molecular mechanisms by which protein aggregates contribute to neurodegeneration and to harness these mechanisms to devise novel therapeutic strategies. We use the bakers yeast, Saccharomyces cerevisiae, as a simple, yet powerful, model system to study the cell biology underpinning protein-misfolding diseases, which include Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). We are focusing on the ALS disease proteins TDP-43 and FUS/TLS and have generated yeast models to define mechanisms by which these proteins cause ALS. Because these proteins aggregate and are toxic in yeast, we have used these yeast models to perform high-throughput genomewide modifier screens to discover suppressors and enhancers of toxicity. Launching from the studies in yeast, we have extended our findings into animal models and even recently into human patients. For example, we discovered mutations in one of the human homologs of a hit from our yeast TDP-43 modifier screen in ALS patients. Mutations in this gene are relatively common (~5% of cases) making it one of the most common genetic risk factors for ALS discovered to date. These screens are also providing new and completely unexpected potential drug targets, underscoring the power of such simple model systems to help reveal novel insight into human disease.