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TEMASEK LIFESCIENCES LABORATORY

28 November 2019 (Thursday), 4pm
The Auditorium (Level 1)

Hosted by: Dr YU Fengwei

Genetic screens provide insights into Parkinson's disease and other neurodegenerative disease mechanisms

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Aaron Gitler is professor of genetics at Stanford University. He received is undergraduate degree at Penn State University and Ph.D. in cell and molecular biology at the University of Pennsylvania. He did postdoctoral research with Dr. Susan Lindquist at the Whitehead Institute for Biomedical Research at MIT. He then started as assistant professor at the University of Pennsylvania in 2007 and moved to Stanford in 2012.

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 baker's 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 (PD), and amyotrophic lateral sclerosis (ALS). We are focusing on the Parkinson's disease protein alpha-synuclein and the ALS disease protein TDP-43 and have generated yeast models to define mechanisms by which these proteins cause PD 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. In our PD studies, we have defined how PD genes and risk factors converge on alpha-synuclein aggregation and prion-like spreading, and validated these findings in mouse neurons, human iPS-derived neurons and in mouse models.

Recent Publications:

1. Yamada, S.B., T.F. Gendron, T. Niccoli, N.R. Genuth, R. Grosely, Y. Shi, I. Glaria, N.J. Kramer, L. Nakayama, S. Fang, T.J.I. Dinger, A. Thoeng, G. Rocha, M. Barna, J.D. Puglisi, L. Partridge, J.K. Ichida, A.M. Isaacs, L. Petrucelli, **A.D. Gitler**, RPS25 is required for efficient RAN translation of C9orf72 and other neurodegenerative disease-associated nucleotide repeats, Nat Neurosci, 2019. 22(9):1383–1388.

2. Bieri, G., M. Brahic, L. Bousset, J. Couthouis, N.J. Kramer, R. Ma, L. Nakayama, M. Monbureau, E. Defensor, B. Schüle, M. Shamloo, R. Melki, **A.D. Gitler**, LRRK2 modifies α-syn pathology and spread in mouse models and human neurons, Acta Neuropathol, 2019. 137(6): 961-980.

3.Becker, L.A., B. Huang, G. Bieri, R. Ma, D.A. Knowles, P. Jafar-Nejad, J. Messing, H.J. Kim, A. Soriano, G. Auburger, S.M. Pulst, J.P. Taylor, F. Rigo, and **A.D. Gitler**, Therapeutic reduction of ataxin 2 extends lifespan and reduces pathology in TDP-43 mice, Nature, 2017. 544(7650): 367-761.