PROGRESS IN NEUROSCIENCE PINS

Seminar Series of the
Brain & Mind Research Institute
Weill Cornell Medical College (WCMC)
&
The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 10/27/16, 4 PM, coffee at 3:45 PM
Weill Auditorium

"Expanding Mechanisms and Therapeutic Targets for Neurodegenerative Disease"

Aaron D. Gitler, Ph.D., Associate Professor of Genetics, Stanford University, School of Medicine

Abstract

My lab is using the baker's yeast, Saccharomyces cerevisiae, as a simple, yet powerful, model system to study the cell biology underpinning human neurodegenerative diseases, including ALS, Parkinson's disease, and Alzheimer's disease. Our long-term goal is to identify the critical genes and cellular pathways affected by misfolded human disease proteins. We have focused on the ALS disease proteins TDP-43 and FUS/TLS and have used yeast models to define novel disease mechanisms and have extended our findings into animal models and even recently into human patients. We recently 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. This underscores the power of such simple model systems to help reveal novel insight into human disease. These screens are also providing new and completely unexpected potential drug targets. Launching from these studies in yeast to test known ALS disease genes, we have also been using yeast as a discovery platform to predict novel ALS disease genes based on functional properties (for example, the presence of a prion-like domain) and to combine this approach with human genetics and next generation sequencing to further define the complex genetic landscape of ALS. We anticipate that our efforts will be broadly applicable to other human disease situations, many of which are deeply rooted in basic biology.

Recent Relevant Publications:

1. Elden, A.C., H.J. Kim, M.P. Hart, A.S. Chen-Plotkin, B.S. Johnson, X. Fang, M. Armakola, F. Geser, R. Greene, M. Lu, A. Padmanabhan, D. Clay, L. McCluskey, L. Elman, D. Juhr, P.J. Gruber, U. Rüb, G. Auburger, J.Q. Trojanowski, V. M.-Y. Lee, V.M. Van Deerlin, N.M. Bonini, AD. Gitler, Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS, Nature, 2010. 466(7310):1069-1075.
2. Jovičić, A., J. Mertens, S. Boeynaems, E. Bogaert, N. Chai, S.B. Yamada, J.W. Paul, III, S. Sun, J.R. Herdy, G. Bieri, N.J. Kramer, F.H. Gage, Ludo Van Den Bosch, W. Robberecht, A.D. Gitler, Modifiers of C9orf72 dipeptide repeat toxicity connect nucleocytoplasmic transport defects to FTD/ALS, Nat Neurosci, 2015. 18(9): 1226-1229.
3. Kramer, N.J., Y. Carlomagno, Y. Zhang, S. Almeida, C.N. Cook, T.F. Gendron, M. Prudencio, M. Van Blitterswijk, V. Belzil, J. Couthouis, J.W. Paul III, L.D. Goodman, L. Daughrity, J. Chew, A. Garrett, L. Pregent, K. Jansen-West, L.J. Tabassian, R. Rademakers, K. Boylan, N.R. Graff-Radford, K.A. Josephs, J.E. Parisi, D.S. Knopman, R.C. Petersen, B.F. Boeve, N. Deng, Y. Feng, T.H. Cheng, D.W. Dickson, S.N. Cohen, N.M. Bonini, C.D. Link, F.B. Gao, L. Petrucelli, A.D. Gitler, Spt4 selectively regulates the expression of C9orf72 sense and

Weill Cornell Medicine

MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·