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, 2/2/17, 4 PM, coffee at 3:45 PM
Weill Auditorium

"Repeat associated non-ATG (RAN) translation: new *starts* and *directions* in neurologic disease"

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Abstract

Microsatellite expansion mutations cause more than 30 different neurologic diseases. In 2011, we discovered that in the absence of an AUG initiation codon, expanded CAG and CUG repeats can express homopolymeric proteins from all three reading frames. We showed this repeat-associated non-ATG (RAN) translation is occurs in spinocerebellar ataxia type 8 (SCA8) and myotonic dystrophy type 1 (DM1). Since this initial discovery, we and others have demonstrated that RAN translation occurs in C9orf72 amyotrophic lateral sclerosis / frontotemporal dementia (ALS/FTD), Fragile X tremor ataxia syndrome (FXTAS) and Huntington's disease (HD). An emerging theme is that coding and non-coding expansion mutations are bidirectionally expressed, producing two mutant RNAs and up to six mutant proteins. These findings impact our fundamental understanding of gene expression and protein translation and should now be considered for a broad category of neurological disorders. Recent efforts to understand the mechanisms of RAN translation and insights into the roles that RNA gain-of-function and RAN mechanisms play in ALS/FTD, Huntington disease, ataxia and myotonic dystrophy will be discussed.

Recent Relevant Publications:

1. Xia G, Y. Gao, S. Jin, S.H. Subramony, N. Terada, **L.P.W. Ranum**, M.S. Swanson, T. Ashizawa. (2015) Genome modification leads to phenotype reversal in human myotonic dystrophy type 1 iPS-cell derived neural stem cells. Stem Cells 33:1829-38 PMID 25702800.
2. Bañez-Coronel, M., F. Ayhan, A.D. Tarabochia, T. Zu, B.A. Perez, S.K. Tusi, O. Pletnikova, D.R. Borchelt, C.A. Ross, R.L. Margolis, A.T.Yachnis, J.C. Troncoso, **L.P.W. Ranum** (2015) RAN translation in Huntington's Disease. *Neuron,* 88:667:677.
3. Yuanjing Liu, Amrutha Pattamatta, Tao Zu, Tammy Reid, David R. Borchelt, Anthony T. Yachnis, Laura P.W. Ranum (2016) C9orf72 BAC Mouse Model with Motor Deficits and Neurodegenerative Features of ALS/FTD. *Neuron*, 90:521–534.

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