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, 11/9/17, 4 PM, coffee at 3:45 PM

Weill Auditorium

"Challenges and opportunities translating fragile X pathophysiology in mice to treatments in humans"

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Abstract

The myriad neurological and psychiatric symptoms associated with fragile X syndrome (FX)— including intellectual disability and autism, hyperactivity, hypersensitivity to sensory stimuli, and epilepsy—belie a simple etiology: the transcriptional silencing of the *FMR1* gene. The encoded protein, FMRP, binds mRNA and regulates translation. At excitatory synapses in the forebrain, neural activity drives mRNA translation through metabotropic glutamate receptor 5 (mGluR5), and in 2002 we discovered that some protein synthesis-dependent consequences of mGluR5 activation are exaggerated in the mouse model of FXS (the *Fmr1* KO). This insight culminated in the "mGluR theory" of fragile X, positing that diverse neurological and psychiatric symptoms of the disease could arise by exaggerated protein synthesis downstream of mGluR5. Tests of the theory over the past 15 years in animal models (mice, rats, flies, fish) have resoundingly and unequivocally validated this theory, raising the possibility of developing a disease modifying therapy for FXS based on inhibition of mGluR5 and the signaling pathways that couple it to FMRP-regulated protein synthesis. However, a number of large randomized controlled trials using mGluR5 negative allosteric modulators (NAMs) have failed. Before we accept these findings as yet another example of a failure of a mouse model to predict therapeutic efficacy in humans, it is important to consider the limitations of the first-generation NAMs and clinical trial designs. There are encouraging human and animal data suggesting that different approaches, also based on normalization of protein synthesis, may be successful.

Recent Relevant Publications:

1. Bhakar, A.L. et al. The pathophysiology of fragile X (and what it teaches us about synapses). Annu. Rev. Neurosci. 35, 417–443 (2012).
2. Stoppel, L.J. et al. β-arrestin2 couples metabotropic glutamate receptor 5 to neuronal protein synthesis and is a potenQal target to treat fragile X. Cell Rep. 18(12), 2807-2814 (2017).
3. Berry-Kravis, E. et al. Arbaclofen in fragile X syndrome: results of phase 3 trials. J Neurodev. Disord. 9(3), Online (2017).

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