blinded, placebo-controlled crossover design enrolling schizophrenia patients who were highly symptomatic despite receiving therapeutic doses of an atypical antipsychotic. The results revealed that intranasal oxytocin (40 international units twice a day), administered as an adjunct to subjects' antipsychotic drugs for 3 weeks improved positive and negative symptoms significantly more than placebo (Feifel *et al*, 2010). In addition, oxytocin improved the performance on a verbal memory task (CVLT-II) (manuscript in preparation). Recently an independent group of investigators at University of North Carolina conducting an independent trial of adjunctive intranasal oxytocin in schizophrenia also reported positive therapeutic effects (Pedersen *et al*, 2010). These positive therapeutic findings are indirectly bolstered by growing evidence of endogenous oxytocin's role in the manifestation of schizophrenia symptoms. For example, a recent study found higher plasma oxytocin levels were associated with more pro-social behavior in schizophrenia patients and with less severe psychopathology in female patients (Rubin *et al*, 2010). The mechanisms underlying oxytocin's beneficial effects on schizophrenia symptoms are not known, but candidate processes are its known ability to regulate mesolimbic dopamine pathways and modify activation of the amygdala. Based upon the promising initial findings our group and others are now conducting larger clinical trials of intranasal oxytocin in schizophrenia and proof-of-concept studies in other disorders are also underway. However, many questions need to be addressed in order to develop optimized oxytocin-based treatments. For example, what is the optimal intranasal dose and dosing schedule for long-term therapeutic CNS effects? Also, is the intranasal route the optimum route of delivering oxytocin? Furthermore, development of proprietary oxytocin mimetics, preferably small molecule agonists, is needed to facilitate industry interest in this therapeutic target and accelerate translation of oxytocin's promise into widely available treatments. If these challenges can be met and the positive early results hold up in larger trials, it may signal the beginning of an exciting new era in the treatment of schizophrenia and perhaps other neuropsychiatric disorders, something desperately needed given the disappointing lack of progress in developing efficacious novel mechanism treatments in this field.

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DISCLOSURE

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Feifel D, Macdonald K, Nguyen A, Cobb P, Warlan H, Galangue B *et al* (2010). Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. *Biol Psychiatry* **68**: 678–680.

Feifel D, Reza T (1999). Oxytocin modulates psychotomimetic-induced deficits in sensorimotor gating. *Psychopharmacology (Berl)* **141**: 93–98.

Lee PR, Brady DL, Shapiro RA, Dorsa DM, Koenig JI (2005). Social interaction deficits caused by chronic phencyclidine administration are reversed by oxytocin. *Neuropsychopharmacology* **30**: 1883–1894.

Macdonald K, Macdonald TM (2010). The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harv Rev Psychiatry* **18**: 1–21.

Pedersen C, Rau S, Salimi K, Gibson C, Leserman J, David P (2010). Oxytocin treatment improves social cognition and reduces psychotic symptoms in schizophrenia. *Neuropsychopharmacology* **35**: S211.

Rubin LH, Carter CS, Drogos L, Pournajafi-Nazarloo H, Sweeney JA, Maki PM (2010). Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. *Schizophr Res* **124**: 13–21.

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Dysregulation of mTOR Signaling in Neuropsychiatric Disorders: Therapeutic Implications

Autism is a widespread disorder characterized by deficits in social interactions, impairments in communication, and repetitive and stereotypic behaviors. Identification of genetic markers has proved difficult, owing to the highly complex and variable nature of the disease. Although autism spectrum disorders (ASDs) arise as a consequence of mutations in genes with multiple molecular functions, they appear to converge on common biological pathways to give rise to autism-relevant behaviors (Abrahams and Geschwind, 2008). One such pathway is the PI3K-mammalian target of rapamycin (mTOR) signaling cascade. The mTOR pathway is a central regulator of cell growth, proliferation, survival, and cap-dependent protein translation. In brain, components of the mTOR pathway are present at synapses, where they regulate dendritic spine morphology, and are essential to synaptogenesis. Growing evidence indicates that dysregulation of mTOR is involved in human diseases, including cancer, diabetes, and autism. Mutations in tuberous sclerosis complex (*TSC*)1, *TSC2*, neurofibromatosis 1 (*NF1*), and *PTEN* lead to overactivated PI3K-mTOR pathway, autism-relevant behaviors, and tuberous sclerosis, neurofibromatosis, or macrocephaly.

Fragile X syndrome (FXS) is the most common heritable form of intellectual disabilities, and a leading genetic cause of autism. Recent findings that PI3K-mTOR signaling is overactivated at synapses of Fragile X mice (Sharma *et al*, 2010) and in humans with FXS provide the first evidence that genetic mutation not only of components within the mTOR signaling cascade, but also distant regulatory proteins, can lead to autism-related phenotypes. Overactivated mTOR signaling is linked to elevated cap-dependent translation and impaired synaptic plasticity in Fragile X mice (Sharma *et al*, 2010). mGluR1/5 links via Homer to PIKE (PI3 kinase enhancer) at synapses, where it engages PI3K–mTOR signaling in response to synaptic stimulation. PIKE, an upstream activator of mTOR and identified target of

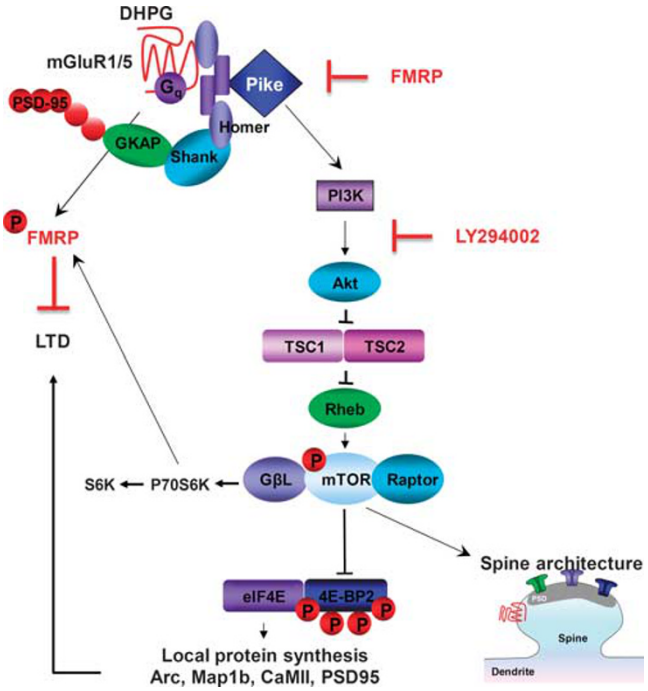

Figure 1. Scheme showing the link between deficits in FMRP and overactivated mTOR. Our findings support a model where, in WT mice, FMRP represses PIKE, an upstream activator of PI3K signaling and identified target of FMRP, and thereby inhibits mTOR signaling. Upon activation, group I mGluRs act *via* Gq and Homer to bind PIKE and engage PI3K signaling, which activates mTOR. mTOR drives cap-dependent translation and local synthesis of synaptic proteins such as Arc, Map1b, CaMII, and PSD-95, critical to mGluR-LTD. In addition, mTOR regulates LIMK and cofilin, which promote spine morphogenesis. In mice lacking FMRP, PIKE is derepressed, resulting in overactivation of mTOR, accumulation of synaptic proteins, and exaggerated, protein synthesis-independent LTD. The PI3K inhibitor LY294002 corrects p-mTOR and restores DHPG sensitivity. A prediction of the model is that dysregulation of mTOR signaling contributes to the cognitive and social interaction deficits observed in humans with Fragile X.

FMRP (Darnell *et al*, 2011) is elevated at the synapses of *Fmr1* KO mice (Gross *et al*, 2010; Sharma *et al*, 2010), providing a functional link between loss of FMRP and overactivated mTOR signaling (Figure 1). These findings identify dysregulation of mTOR signaling as a phenotypic feature common to FXS, TSC1 and 2, NF1, and PTEN-associated autism syndromes. Whereas other syndromic ASDs arise from mutations in components of the PI3K–mTOR pathway, FXS arises from silencing of the gene encoding FMRP, an RNA-binding protein that represses translation of a large array of RNAs including PIKE. This, in turn, results in elevation of PIKE and overactivation of PI3K–mTOR signaling. These observations raise the possibility that dysregulation of mTOR may be a unifying theme in a growing number of ASDs and ASD-associated syndromes.

On the basis of the clear link between overactivated mTOR signaling and autism, the mTOR pathway represents a promising therapeutic target for the treatment of ASDs. Treatment with the mTORC1 inhibitor rapamycin has shown promising results in PTEN knockout mice (Zhou *et al*, 2009) and TSC2 + /− mice (Ehninger *et al*, 2008). Thus, interventions that target mTOR signaling should be at the leading edge of future translational research in the autism field.

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The authors declare no conflict of interest.

Abrahams BS, Geschwind DH (2008). Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet* **9**: 341–355.

Darnell JC, Van Driesche SJ, Zhang C, Hung KY, Mele A, Fraser CE *et al* (2011). FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. *Cell* **146**: 247–261.

Ehninger D, Han S, Shilyansky C, Zhou Y, Li W, Kwiatkowski DJ *et al* (2008). Reversal of learning deficits in a Tsc2+/− mouse model of tuberous sclerosis. *Nat Med* **14**: 843–848.

Gross C, Nakamoto M, Yao X, Chan CB, Yim SY, Ye K *et al* (2010). Excess phosphoinositide 3-kinase subunit synthesis and activity as a novel therapeutic target in fragile X syndrome. *J Neurosci* **30**: 10624–10638.

Sharma A, Hoeffer CA, Takayasu Y, Miyawaki T, McBride SM, Klann E *et al* (2010). Dysregulation of mTOR signaling in fragile X syndrome. *J Neurosci* **30**: 694–702.

Zhou J, Blundell J, Ogawa S, Kwon CH, Zhang W, Sinton C *et al* (2009). Pharmacological inhibition of mTORC1 suppresses anatomical, cellular, and behavioral abnormalities in neural-specific Pten knock-out mice. *J Neurosci* **29**: 1773–1783.

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Habenular Signaling in Nicotine Reinforcement

Tobacco dependence is a complex genetic trait, with greater than 50% of the risk of developing dependence attributable to genetic factors (Li *et al*, 2003). Nicotine, the major psychoactive component in tobacco smoke responsible for dependence, functions in the brain through neuronal nicotinic acetylcholine receptors (nAChRs). A major breakthrough in understanding the genetics of tobacco dependence was the finding that allelic variation in the *CHRNA3-CHRNA5-CHRNB4* gene cluster, which encodes the $\alpha 3$, $\alpha 5$, and $\beta 4$ nAChR subunits, respectively, increases vulnerability to