

# College of Science

## Neuroscience Faculty Candidate

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**Tuesday, March 01, 2016**  
**Kelly Hall 310**  
**3:00pm – 4:00pm**

### **“Astrocyte Dysfunction in Rett Syndrome”**



Rett Syndrome is an X-linked neurodevelopmental disorder, caused by mutations in methyl-CpG-binding protein 2 (MeCP2) in > 95% of cases. RTT is typified by normal development until 6-18 months of age, when motor and communicative skills regress and hand stereotypies, autonomic symptoms, and seizures begin to present. Restoration of MeCP2 function selectively to astrocytes reversed several phenotypes in a murine model of RTT, but the mechanism of this rescue is unknown. Astrocytes are the most numerous cells in the CNS and carry out many essential functions required for ‘normal’ brain functioning. One such task is the regulation of extracellular potassium, which when elevated alters neuronal functioning. This process is mediated by a ‘glial’ specific potassium channel Kir4.1. The importance of this channel in human brain is underscored by recent studies in human patients that link mutations in the Kir4.1 gene (KCNJ10) to developmental disorders characterized by early onset seizures, ataxia, epilepsy, severe cognitive impairments and autism; all hallmarks of Rett syndrome. Here we demonstrate by ChIP assay that Kir4.1 is a direct molecular target of MeCP2 in wild type mice. Astrocytes from MeCP2 deficient mice express significantly less Kir4.1 mRNA and protein in cortex and brainstem; two brain structures affected in girls with RTT. Importantly, the loss of protein is observed early in the disease progression in RTT mice, prior to the observable symptoms and associated with a >50% decrease in Kir4.1, increased baseline [K<sup>+</sup>]<sub>o</sub> and aberrant neuronal firing. These are the first data implicating a direct molecular target of MeCP2 in astrocytes and provide novel mechanistic insight explaining how astrocytic dysfunction may contribute to RTT.

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