Genetics & Genome Biology Program
&
Centre for Brain & Mental Health

Invited Speaker Series

Improving the identification of reproducible and reliable phenotypic endpoints through natural history studies of rodent models of monogenic neurodevelopmental disorders

Rodney C. Samaco, PhD

Assistant Professor
Department of Molecular and Human Genetics,
Baylor College of Medicine (BCM)

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Place: Event Room 1
Peter Gilgan Centre for Research and Learning
686 Bay St

SickKids RESEARCH INSTITUTE
Genetics & Genome Biology

Host:
Monica Justice, PhD

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Title:

Improving the identification of reproducible and reliable phenotypic endpoints through natural history studies of rodent models of monogenic neurodevelopmental disorders

Presenter: Rodney C. Samaco, PhD

Affiliation, Title and Contact Information:

Assistant Professor
Department of Molecular and Human Genetics, Baylor College of Medicine (BCM)

Investigator
Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital (TCH)

Associate Director
Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center (EKS-IDDRC), BCM

Director
Rodent Neurobehavioral Core Facilities
EKS-IDDRC and TCH

Phone: (832) 824-8788
Email: rodney.samaco@bcm.edu

Abstract:

Among the numerous challenges that exist in the current landscape of understanding and treating neurodevelopmental disorders (NDD) is the relative absence of well-defined, reproducible and reliable phenotypic endpoints. The data gap within this area is striking, as issues concerning this problem remain a recurring theme that significantly resonates across basic science and clinical arenas. In cases of monogenic NDD, the study of genetic rodent models remains instrumental in strategies aimed to uncover the nature and extent to which phenotypic endpoints may serve as either biomarkers or outcome measures for pre-clinical investigations. However, previously under-appreciated factors including basic methodological differences in experimental design have become increasingly acknowledged as confounds that have historically contributed to the barriers to effectively move the field forward. Yet, the generalizability of "lessons learned" from studies of CNS mouse models remains to be fully embraced, especially by many nascent yet rapidly expanding fields. To address the pressing need to identify actionable therapies and avoid these potential missteps, we have been engaged in implementing experimental approaches that incorporate our existing knowledge of methodologies used in natural history studies of people. The focus of the current presentation is to highlight specific examples from rodent models of *Cdkl5* (CDKL5 disorder), *Ube3a* (Angelman syndrome), *Shank3* (Phelan-McDermid syndrome; ASD), *Tsc2* (Tuberous Sclerosis), and *Grm5* (neuropsychiatric indications) that underscore the value of longitudinal and cross-sectional studies. Additional considerations such as definitive ages and sexes, comparisons of null and disease-causing allelic variants, and implementation of replication studies across two different local test facilities or across two different national institutions have led to the collection of rich, comprehensive data sets that will help establish the baseline information for future large-scale endeavors, including testing therapeutic modalities in rodent precision disease models. This overall experimental framework may improve the identification of consensus biomarkers and outcome measures across multiple models of genetic NDD, and in some cases, strengthen interpretations by examining evolutionarily conserved features across genetic mouse and rat models. Taken together, our studies suggest that there is indeed value in studying genetic deficiency in rodents with respect to specific mental and behavioral features of human conditions by investing in approaches that examine the natural history of a disease model. Moreover, these data collected using an experimental design that aims to safeguard against potential confounds further strengthen the importance of foundational work that will ensure the quality of *in vivo* tools for use in eventual pre-clinical studies.