Neurodevelopmental disorders: from basic science to novel therapeutic approaches

You are cordially invited to the lecture given by:

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Abstract:

Neurodevelopmental disorders encompass a wide range of childhood-onset medical conditions caused by different genetic mutations and interaction with environmental factors, affect ~2% of the population, and are a leading cause of intellectual disability and autism spectrum disorder. Evidence is accumulating that either loss or gain in dosage of proteins involved in cognitive and behavioural processes can be deleterious to the nervous system by causing a failure in the ability to maintain neuronal homeostasis. My studies are focused on the MECP2 duplication syndrome, one of the most common genomic rearrangements in males, characterized by autism, intellectual disability, motor dysfunction, anxiety, epilepsy, recurrent respiratory tract infections and early death. To determine whether the phenotypes of MECP2 duplication are reversible upon normalization of MeCP2 levels, I first generated and characterized a new mouse model that over-expresses a conditional allele of Mecp2 that could be deleted in the adult animal (Nature 2015). Upon normalization of MeCP2 in adult symptomatic mice, several phenotypes were rescued at the behavioral, physiological, and molecular levels. Next, I reduced MeCP2 using an antisense oligonucleotide (ASO) strategy, which has greater translational potential. I found that ASO treatment induced a broad phenotypic rescue in adult symptomatic MECP2 duplication mice, abolished abnormal EEG discharges and behavioral seizures, and corrected abnormal gene expression in the hippocampus. I am currently characterizing a novel ?humanized? mouse model of MECP2 duplication syndrome that will precisely mimic the human condition by having two copies of human MECP2 and no copies of the mouse gene. These mice will serve as the ideal model for preclinical tests as they represent the closest construct validity model for the human condition. In addition, I am generating and characterizing neurons induced from patients? derived pluripotent stem cells (iPSCs).

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