

## **Pat Levitt, Ph.D.**

M.I.N.D. Institute Distinguished Lecturer Series – January 14, 2009

### ***Biographical Information***

Dr. Levitt studies the molecular and cellular mechanisms that control the development of the forebrain, and the causes of such developmental and neuropsychiatric disorders as autism, anxiety and schizophrenia. The brain begins to establish functional circuits before birth, but has its greatest growth period from birth until around three years of age. The brain then undergoes a substantial period of remodeling during childhood and adolescence. Levitt's laboratory is comprised of a group of highly collaborative researchers who investigate the genetic basis for the establishment of forebrain circuits that regulate mood, emotion, stress and complex higher functions. The laboratory also studies the impact of experience and environmental factors, such as social interactions or exposure to drugs of abuse, which may alter the formation and functioning of these systems. Mammalian model systems are used to experimentally probe these issues. Genes implicated in neurodevelopment are studied in human neuropsychiatric and developmental disorders. The goal of combining animal model and human genetic research is to identify mutations and polymorphisms that may alter the function of genes sufficiently to increase the risk for expressing a particular disorder.

### ***Presentation Abstracts***

#### ***Translational studies on the MET tyrosine kinase receptor system in the autisms (4 pm)***

Rapid progress is being made on a number of fronts with regard to understanding the etiologies that underlie the autisms. The autisms are among the most common of neurodevelopmental disorders, and are highly heterogeneous in disorder phenotype, longitudinal trajectory of symptoms and response to treatment. A brief overview of the current state of thinking regarding the genetic and environmental risk factors will be discussed. Work from Dr. Levitt's laboratory will be the focus of the remainder of the lecture. The convergence of human genetics in autism and basic developmental neurobiology studies suggests that MET receptor tyrosine kinase signaling is important for the proper assembly of forebrain circuits, particularly those involving cortical projection neurons in which MET is heavily expressed. Dysregulation of MET signaling leads to functional disruptions in both model systems and in humans. Multiple, convergent human genetic data implicate this signaling pathway as a major risk factor for autism. First, the Levitt lab discovered that a single nucleotide polymorphism in the 5' regulatory region of the human *MET* gene is associated with autism. Second, there has been replication of this result in 6 different family cohorts, identification of copy number variants (CNVs) and rare mutations in the *MET* gene, and association with autism of two other genes in the *MET* signaling pathway. Third, certain single gene, syndromic disorders with high prevalence of autism also involve this same cellular signaling pathway. Fourth, the *MET* promoter variant is functional, as it reduces gene transcription. Fifth, studies of human postmortem samples show that *MET* and other upstream molecules that regulate *MET* signaling are dysregulated in autism. A model of autism etiology will be presented in light of these basic and clinical research findings.

#### ***Where are we with the autisms: an update on genetics and neuroscience advances (6 pm)***

Rapid progress is being made on a number of fronts with regard to understanding the factors that increase the risk for developing the autisms. The autisms are among the most common of neurodevelopmental disorders. Autism risk also is highly heritable. Understanding the autisms, however, has been challenging because of the significant heterogeneity in the 1) severity of each of the core functions (social behavior, communication, and restricted interests), 2) progression of the symptoms, and 3) response to treatment. A brief overview of the current state of thinking regarding genetic risk will be discussed. Basic strategies used to perform genetic studies, and our own work on one particular set of risk genes, will be presented. In order to better understand disorder heterogeneity, recent analysis of genetic risk in different autism subgroups, based on single- and multi-incident families, and co-occurring medical conditions such as gastrointestinal disorders, will be discussed. New research also will be presented that makes the connection between genetic risk and environmental factors that may be key in autism expression. A single, causal model will not explain all autisms. Dr. Levitt will present a flexible model that converges on important neurobiological elements based on basic and clinical research findings from many laboratories.

