Title: Dissecting Neurodevelopmental disorders

Brain circuits are first established by gene programs then dynamically sculpted and refined in response to the external environment during early postnatal development. Disruption of proper sensory input or key experiences results in abnormal excitatory/inhibitory circuits that will never be able to respond normally in the future. Growing evidence indicates that neurodevelopmental disorders like Autism Spectrum Disorders (ASD) may result from disruption of this fine balance early in life. ASD are complex genetic disorders characterized by impaired language, abnormal social interactions and repetitive behaviors. The diagnostic symptoms of ASD may in fact be reflective of lower-order processing defects as a result of abnormal circuit development and plasticity in primary sensory areas. Research into the mechanisms governing such processes is revealing many different molecular components that could be therapeutically targeted to restore normal brain function.

Our research focuses on the circuit dissection and development of new treatments for neurodevelopmental disorders such as Rett Syndrome (RTT). We discovered a clear visual cortical phenotype in mouse models of RTT and demonstrated its rescue by environmental and genetic manipulation (Durand et al, Neuron 2012). Interestingly, after an apparently normal onset of visual function, a progressive regression of visual acuity is observed directly correlating with the onset of RTT phenotype. Notably, a selective inhibitory circuit, Parvalbumin-positive cells (PV), is hyper-connected very early in development resulting in silencing of cortical circuits. Strikingly, PV hyper-connectivity and visual acuity defects can be rescued by directly acting on mechanisms that normally control plasticity in developing cortical circuits: namely, sensory experience per se (by dark rearing) or disrupting NMDA receptor (NR2A) subunit composition.

These results reveal a specific role for Mecp2 in the experience-dependent refinement of cortical circuits by regulating the excitation of pivotal inhibitory neurons. The identification of a particular receptor pathway within a specific cortical circuit now offers an accessible membrane target for drug intervention strategies that do not rely on the re-expression of Mecp2 itself. We recently performed a pre-clinical trial of a low dose of ketamine, an FDA-approved NMDA-R antagonist, in a murine model of RTT. Daily exposure to ketamine reverses deficits in cortical neuronal activity and connectivity along with significant improvements in general health and survival. These data support a potential drug intervention strategy for RTT in a clinical setting.

Overall, our findings strongly suggest that visual processing in RTT patients may be altered and can be used as a robust biomarker of both cortical status and its response to therapy. To this end, we have begun assessing the cortical function of the visual system in young girls with RTT using visual-evoked potentials (VEP) as we did in RTT mouse models. Remarkably, we found significant differences between typically developing children and RTT patients, supporting the introduction of standardized VEP analysis into clinical and research settings to probe the neurobiological mechanisms underlying functional impairment and to longitudinally monitor progression of the disorder and response to treatment.