PROGRESS IN NEUROSCIENCE
PINs

Seminar Series of the
Brain & Mind Research Institute
Weill Cornell Medical College (WCMC)
&
The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 1/9/14, 3:45 PM
Weill Auditorium

Presentation 1: Novel Mechanisms Regulating the Dopaminergic Phenotype through Tyrosine Hydroxylase Gene Transcription

Meng Wang, M.D./Ph.D., Post-doctoral Fellow
Cave Laboratory, WCMC

Abstract: Mechanisms regulating *Tyrosine hydroxylase* (*Th*) transcription are critical for the specification and maintenance of the dopaminergic neuronal phenotype. Recent studies in our laboratory have established a novel molecular regulatory mechanism for *Th* transcription that is conserved in most vertebrates. These studies show that heterogeneous nuclear ribonucleoprotein (hnRNP) K is a novel transactivator of *Th* transcription that binds to previously unreported and evolutionarily conserved G:C-rich regions in the *Th* proximal promoter. hnRNP K preferentially binds C-rich single DNA strands within these conserved regions, whereas binding to double stranded sequences requires the presence of CREB on an adjacent cis-regulatory element. These studies also found that the single DNA strands within the conserved G:C-rich regions adopt either G-quadruplex or i-motif secondary structures. Stabilizing these structures by small molecules represses *Th* promoter activity and suggests that these secondary structures are novel targets for pharmacological modulation of the dopaminergic phenotype.

References:

Brooks, T.A., Kendrick, S. & Hurley, L. Making sense of G-quadruplex and i-motif functions in oncogene promoters. *The FEBS journal* **277**, 3459-3469 (2010).

Balasubramanian, S., Hurley, L.H. & Neidle, S. Targeting G-quadruplexes in gene promoters: a novel anticancer strategy? *Nature reviews. Drug discovery* **10**, 261-275 (2011).

Presentation 2: Engrailed Genes are Required in the Cerebellar Nuclei for Purkinje Cell Survival and Cerebellar Growth

Ryan Willett, Ph.D., Research Fellow
Developmental Biology Program, Joyner Laboratory, MSKCC

Abstract: The cerebellum (Cb) is a posterior brain structure located above the hindbrain that is involved in motor coordination, balance and cognition. During the first two postnatal weeks the cerebellum undergoes a rapid expansion from a smooth anlage into a morphologically complex structure with specialized subregions. This growth is principally driven by two factors: 1) the expansion of the external granule layer (EGL) by granule cell precursor (GCP) proliferation and 2) growth of the inner granule layer (IGL) by differentiation of the GCPs into granule cells (GCs). Conditional knockout of *En1* and *En2* (En1/2) in rhombic lip derived cells (RLD-En1/2) and in cerebellar nuclei alone (CN-En1/2) produce a diminutive Cb and smaller CN. Here we demonstrate that CN defects in CN-En1/2 mutants cause a cell maturation delay in their presynaptic Purkinje cells (PCs), reduced SHH expression by these PCs, and reduced growth of the cerebellar vermis.

References:

Malagelada, C., López-Toledano, M., Willett, R., et al. RTP801/REDD1 regulates the timing of cortical neurogenesis and neuron migration. *J Neurosci,* 311 (9) 186-96. (2011).

Willett, R. & Green, L. Gata2 is required for migration and differentiation of retinorecipient neurons in the superior colliculus. *J Neurosci.* 31 (12) 4444-55. (2011).

Weill Cornell Medical College

MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·