



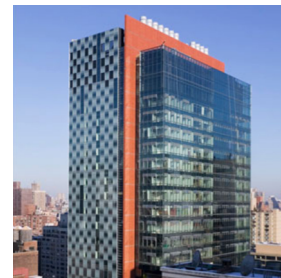
PROGRESS IN NEUROSCIENCE PINS

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, 10/20/16, 4 PM, coffee at 3:45 PM

A-950



“Gene Therapy for Understanding and Treating Brain Diseases”

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Abstract



Gene transfer technology has revolutionized neuroscience, and is poised to change the way we approach human neurological and psychiatric disease. Since we first described the use of adeno-associated virus (AAV) as a safe and effective gene delivery vehicle for the living brain in *Nature Genetics* in 1994, this technology has become ubiquitous in nearly every neurobiology lab in the world, and has facilitated applications of shRNA, optogenetics and other forms of genetic manipulation of neurons. For the past 25 years, we have focused upon using AAV to better understand models of Parkinson's disease (PD) and psychiatric disorders. We first applied gene therapy to the adult human brain in a phase I study in patients with PD, using AAV2 to transfer the gene for glutamic acid decarboxylase to the subthalamic nucleus. This led to a second phase II trial, which remains the only randomized, double-blind study of gene therapy in the human brain to achieve positive results, with improvements observed in both clinical scores and functional imaging. Since most approved and experimental therapies for PD focus upon typical motor symptoms, we are currently exploring in the lab methods to address other debilitating symptoms, such as dyskinesia, vocal dysfunction and depression. Finally, we are examining the use of a new technology recently approved for use in the human brain, focused ultrasound, as a potential means for focal blood-brain barrier disruption to facilitate non-invasive gene delivery to specific brain targets.

Recent Relevant Publications:

1. LeWitt PA, Rezai AR, Leehey MA, Ojemann SG, Flaherty AW, Eskandar EN, Kostyk SK, Thomas K, Sarkar A, Siddiqui MS, Tatter SB, Schwalb JM, Poston KL, Henderson JM, Kurlan RM, Richard IH, Van Meter L, Sapan C, Durr M, Kaplitt MG, Feigin A (2011) A randomized multicenter double-blind clinical trial of AAV-GAD gene therapy for advanced Parkinson's disease. *Lancet Neurol*, 10(4):309-319
2. Alexander B, Warner-Schmidt J, Eriksson T, Tamminga C, Ghose S, Arango-Lievano M, Vernov M, Stavarche M, Musatov S, Flajolet M, Svenningsson P, Greengard P, Kaplitt MG. (2010) Reversal of Depressed Behaviors by p11 Gene Therapy in the Nucleus Accumbens. *Science Trans Med*, 2:54ra76.
3. Marongiu R, Arango-Lievano M, Francardo V, Morgenstern P, Zhang X, Cenci MA, Svenningsson P, Greengard P, Kaplitt MG. (2016) Gene therapy blockade of dorsal striatal p11 improves motor function and dyskinesia in parkinsonian mice. *Proc Natl Acad Sci U S A*, 113:1423-1428



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