NIH Award from the National Institute of Neurological Disorders and Stroke

Principal investigator: Dalton James Surmeier, physiology, Feinberg School of Medicine

- **Project:** Rhythmicity and Synchrony in the Basal Ganglia
- **Start Date:** September 30, 2009
- **Total Award Amount:** $430,730

How the results of this project will benefit society:
Parkinson’s disease (PD) is the second most common neurodegenerative disease in the U.S., extracting an enormous human and economic toll. PD has no cure and nothing is known to slow the progression of the disease. Moreover, the therapeutic strategies for treating PD are limited. The proposed studies are focused on why dopamine neurons die in PD and what happens to the brain circuitry they control. Our near-term goal is to develop therapeutic strategies that will slow the loss of dopamine neurons and to re-engineer the networks these neurons control so that they perform correctly, even in the absence of dopamine.

The problem the project is trying to solve:
This research project takes on two major lines of study with strong translational potential. The first line of study focuses on the mechanisms underlying the pathological rhythmic bursting activity patterns in the basal ganglia network formed by the external segment of the globus pallidus (GPe) and the subthalamic nucleus (STN). This activity is thought to be responsible for the motor symptoms of PD. Our group has identified molecular adaptations in the GPe-STN network in PD models that could be responsible for this pathophysiology. The proposed studies will pursue this discovery and attempt to translate it into a gene therapy appropriate for late stage PD patients. The second line of study builds upon recent insights gained into the factors underlying vulnerability of dopaminergic neurons in the substantia nigra pars compacta (SNc) that are lost in PD. These studies suggest that the reliance upon voltage calcium channels to drive autonomous pacemaking renders SNc neurons vulnerable to mitochondrial insults. These studies also suggest this reliance can be reversed with a drug that is approved for human use. The proposed studies examine the cellular and molecular basis for this linkage and pursue questions that should be answered prior to a clinical neuroprotection trial.

How the project will work:
The Udall Center brings together five principal investigators (PIs) with complementary expertise from three research institutions. Three theme-based projects are proposed, each with three or more PIs contributing to the plan of attack. Projects 1 and 2 pursue the first line of study, one focusing on the adaptations in GPe neurons, the other focusing on adaptations in STN neurons in rodent and monkey models of PD. Project 3 pursues the second line of study, focusing on mechanisms controlling the vulnerability of SNc dopaminergic neurons in rodent models. In addition to three research projects, the Center has an Administrative Core to coordinate activities of the projects and a Molecular Core to serve the genetic profiling and gene therapy aims of the projects.

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