NIH Award from the National Heart, Lung, and Blood Institute

Principal investigator: Rishi K. Arora, cardiology
Feinberg School of Medicine

- **Project:** Disruption of Autonomic Pathways in the Left Atrium by Inhibition of G-Proteins
- **Start Date:** July 15, 2009
- **Total Award Amount:** $239,796

**How the results of this project will benefit society:**
Atrial fibrillation (AF) is the most common rhythm disturbance of the heart and is a major cause of serious morbidity such as congestive heart failure and stroke. However, currently available treatment options for AF are not very effective. We propose a new method to treat AF, by using a novel peptide (protein) to inhibit the function of the nerves that trigger this arrhythmia.

**The problem the project is trying to solve:**
Importantly, the incidence of AF is that it increases with age, with the result that AF is fast becoming the latest “epidemic” in an aging population. The diagnosis and management of AF have therefore become an important and challenging aspect of cardiovascular medicine. However, progress in effectively treating AF has been slow, in large part due to a poor understanding of the underlying mechanisms of this arrhythmia. In this regard, recent studies indicate an important role for the pulmonary veins and the posterior left atrium (PLA) in the genesis of this arrhythmia. Several pioneering ablative procedures have therefore been performed in the PLA, albeit with mixed success.

**How this project will work:**
In an attempt to modify substrate for AF, we propose to use novel peptides directed at the G protein coupled receptors (GPCRs) and their cognate signaling partners, the heterotrimeric G-proteins (GPCR/G protein interface) to selectively inhibit parasympathetic or sympathetic pathways in the PLA. Using minigenes (plasmids) that can express these G-protein inhibitory peptides on both a short and long term basis, the proposed studies will be performed in both an acute as well as a chronic model of AF. In the acute experiments (Aim 1), localized injection of minigene into the PLA will be performed in order to inhibit vagally or adrenergically-mediated AF in normal dogs. In Aim 2, we propose to use these minigenes in a canine model of chronic AF; minigenes under the control of a long-acting promoter will be injected locally into the PLA, to prevent the development of autonomic substrate for AF. The proposed studies are an important stride towards identifying novel therapeutics that may eventually be applied to the treatment of life-threatening arrhythmias.

This award is funded under the American Recovery and Reinvestment Act of 2009, NIH Award number: 3R01HL093490-01A1S1.