

**Jeffrey Abrams** (Mentor: Dr. Steven Marx)

### **Project Summary**

Atrial fibrillation is the most frequently sustained arrhythmia observed in clinical practice, estimated to affect about six percent of Americans who are 65 years of age and older. Atrial fibrillation doubles the risk of death, and accounts for 15-20% percent of all strokes. The relatively low efficacy of pharmaceuticals and radiofrequency ablation/surgery, and high rates of recurrence have plagued the field for decades. In-depth laboratory studies of atrial fibrillation have been hindered by the lack of a bona fide mouse model that accurately recapitulates the typical spontaneous initiation and sustained episodes of atrial fibrillation observed in humans. Although systemic and cardiac disorders are predisposing contributors to atrial fibrillation, there is also likely an important component of genetic susceptibility, shown by recent genome-wide association studies and identification of relatively rare mutants in  $K^+$  channels,  $Na^+$  channels and ryanodine receptors, highlighting the role of ion channel dysfunction in the pathogenesis of atrial fibrillation. Our novel method of studying informative  $Na^+$  channel mutants in cardiomyocytes has enabled the development of a transgenic mouse with a phenotype of mild-moderate atrial enlargement, mild left ventricular dysfunction, and frequent and sustained episodes of spontaneous paroxysmal atrial fibrillation and ventricular arrhythmias as early as 5-6 weeks of age. These mice phenocopied gain-of-function human *SCN5A* mutations, which have been implicated in dilated cardiomyopathy and hypertrophy, and arrhythmias such as long QT syndrome, torsade de pointes and atrial fibrillation. The sustained and spontaneous nature of the atrial arrhythmias, a relatively unusual phenotype in mice, has enabled us to explore mechanisms of initiation and maintenance of atrial fibrillation using *in vivo* (telemetry), *ex vivo* (optical voltage mapping of Langendorff-perfused hearts), and *in vitro* (cellular electrophysiology) techniques. Two Specific Aims are proposed, designed to characterize the cellular electrophysiological mechanisms of atrial fibrillation caused by mutant *SCN5A* expression. The proposed experiments are designed to further develop and characterize this unique murine model of atrial fibrillation, with the ultimate goal of identifying and testing novel therapies.