Dr. John Morrow

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This proposal details a comprehensive 5-year training program for my career development in cardiovascular research. I have planned this mentored research program to provide the additional scientific training necessary for an independent career in academic research. I will gain in-depth experience in the areas of biochemistry, gene regulation, cellular electrophysiology, and in vivo physiology as applied to animal models of heart failure and arrhythmias. Dr. Steven Marx will by my primary mentor for scientific and career development. Dr. Marx is a leader in the field of cardiovascular ion channels. The project will be performed in collaboration with Dr. Ira Goldberg, an expert in lipids and myocardial metabolism. In addition, an advisory committee of established cardiovascular scientists (Drs. Andrew Marks, Robert Kass, and Fadi Akar) and an administrator (Dr. Jamie Rubin) will provide scientific and career advice.

The central hypothesis of this application is that increased cardiac myocyte lipid content leads to abnormal regulation of ion channels and gap junctions, promoting arrhythmia. Increased cardiac myocyte lipid stores are observed in obese and diabetic patients and this is proposed to contribute to the pathophysiology of heart failure, a syndrome termed lipotoxic cardiomyopathy. We have recently found that a mouse model of lipotoxic cardiomyopathy, a transgenic mouse with cardiac-specific overexpression of PPARγ, has prolonged QRS and QT intervals, and dies suddenly at 2-8 months of age from ventricular tachycardia (VT). PPARγ is a ligand-activated transcription factor that regulates lipid and glucose metabolism. These PPARγ cardiac overexpression mice gradually develop a dilated cardiomyopathy with impaired systolic function and have abnormal accumulation of intracellular lipids, but sudden death often occurs before HF develops. We have found that individual cardiac myocytes from these cells have prolonged action potential duration, probably from reduced potassium current. Further, connexin 43, the main component of the ventricular gap junction, is downregulated at the transcriptional level and the protein level, which is known to promote VT. This mouse is thus a unique model of an increasingly common form of human heart disease associated with diabetes and obesity, with a natural history that recapitulates a common cause of death in these patients.

My aims are:
1. To characterize the abnormal cellular electrophysiology leading to arrhythmias in lipotoxic cardiomyopathy
2. To characterize abnormal cardiac conduction in lipotoxic cardiomyopathy
3. To determine the molecular mechanisms of reduced connexin expression in lipotoxic cardiomyopathy.

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