

## **TITLE: Molecular Mechanisms Underlying Congenital Heart Disease**

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### **RESEARCH PROJECT DESCRIPTION**

**Background:** *Congenital cardiac anomalies* are the most prevalent birth defects, affecting over 1% of live births. Despite remarkable progress in understanding cardiac development, the mechanisms underlying cardiac maldevelopment in embryos that result in malformations are largely unknown. Inherited mutations of the *Nkx2-5* gene cause a variety of cardiac malformations, and currently nearly 40 heterozygous mutations have been reported in humans. *Nkx2-5* mutation is accompanied by diverse forms of cardiac malformations in humans and can cause a range of symptoms, from near-normal to severe, leading to heart failure. We have recently developed a mouse *Nkx2-5* mutant model representing the most common genetic defect found in humans. Genetic mutations impacting cardiac maldevelopment have been identified, however there is wide variation in the phenotype severity for those affected. This variability suggests a prominent role of epigenetic (non-genetic) factors in the pathology of congenital heart defects. We will investigate both genetic and epigenetic factors on the developing heart.

**Methods:** We will characterize the mouse models of human congenital heart defects, taking into consideration both genetic and epigenetic effects.

**Role of medical student:** Medical students will participate in mouse genotyping using PCR, analyses of mRNA expression using quantitative RT-PCR, and analyses of cardiac anomalies by tissue sectioning.

**Funding:** NIH R21 grant.

### **References:**

- Ashraf H., Pradhan L, et al. A mouse model of human congenital heart disease: high incidence of diverse cardiac anomalies and ventricular noncompaction produced by heterozygous *Nkx2-5* homeodomain missense mutation. *Circulation: Cardiovasc Genet.* **2014**:423-433.
- Chowdhury R., Ashraf H., et al. A mouse model of human congenital heart disease: progressive atrioventricular block induced by a heterozygous *Nkx2-5* homeodomain missense mutation. *Circulation: Arrhythmia and Electrophysiology.* **2015**:1255-64.

Additional information is available at <http://physiology.med.ufl.edu/faculty/kasahara/>.