

**TITLE: Molecular mechanisms for prevention and rescue of heart failure**

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**RESEARCH PROJECT DESCRIPTION**

**Background:** The dynamics of cardiac contraction and relaxation are fundamentally related to actin-myosin interactions. A range of factors regulate this process and contribute to the adaptation of cardiac function to physiological or pathological stressors, in turn suggesting potential therapeutic strategies for heart failure. Phosphorylation of myosin light chain 2 (MLC2), bound to myosin at the head-rod junction, has been shown to facilitate actomyosin interactions leading to enhanced cardiac contraction. In humans with heart failure, the level of phosphorylation of MLC2 has been shown to decrease. In 2008, we identified cardiac myosin light chain kinase (cMLCK) encoded by the *Mylk3* gene. Our recent study suggests that cMLCK is a critical factor in preventing pressure-overloaded heart failure. Pressure-overload by aortic banding led to severe heart failure in cMLCK deficient (*Mylk3*<sup>-/-</sup>) mice but did not affect cardiac contractility in mice overexpressing cMLCK.

**Methods:** We will characterize the beneficial effects of cMLCK overexpression and investigate their mechanism(s) of action. We will utilize genetically engineered mice with cMLCK overexpression as well as viral gene therapy (adeno-associated virus).

**Role of medical student:** Medical students will participate in mouse genotyping using PCR, as well as analyses of mouse cardiac function using MRI, echocardiogram, left-ventricular pressure measurement with left-ventricular catheterization and electrocardiogram. Funding for the project is provided by the AHA Grant-in-Aid.

1. Chan J.Y., Takeda M, Briggs L.E., Graham M.L., Lu J.T., Horikoshi N., Weinberg E.O., Aoki H., Sato N., Chien K.R., and **Kasahara H.**: Identification of cardiac-specific myosin light chain kinase. ***Circ.Res.* 2008;102:571-580. PMID: 18202317**
2. Warren S.A., Briggs L.E., Zeng H., Chuang J., Chang E.I., Terada R., Li M., Swanson M.S., Lecker S.H., Willis M.S., Spinale F.G., Maupin-Furlow J., McMullen J.R., Moss, R.L., **Kasahara H.**: Myosin light chain phosphorylation is critical for adaptation to cardiac stress. ***Circulation* 2012: 126:2575-2588. PMID: 23095280**

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