

# Building a Better Phospholamban: Using Structure and Dynamics-Based Design to Engineer Therapeutic Mutants for Treating Heart Failure

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## **Abstract**

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Heart disease is the leading cause of death in the United States. Heart failure, one of the chronic conditions of heart disease, is marked by a loss of strength in muscle contractility. Impairment in calcium signaling in cardiac muscle cells has a direct impact on the development of heart failure. Interactions between an enzyme, the sarcoplasmic reticulum  $\text{Ca}^{2+}$  ATPase (SERCA), and its regulatory inhibitor, the membrane protein phospholamban (PLN), play an important role in the regulation of cardiac muscle relaxation and contraction. PLN is a membrane protein that inhibits SERCA, an enzyme that facilitates transport of calcium ions into the sarcoplasmic reticulum to allow relaxation to occur. Several naturally occurring mutations in PLN lead to inherited heart diseases. In order to augment SERCA activity and increase cardiac relaxation, we are designing PLN mutants which will be able to selectively increase SERCA activity by down-regulating PLN inhibition. The ultimate goal is to identify the most promising PLN mutants, deliver them into animal models using gene therapy, and test whether they improve cardiac relaxation. Based on the known structure of PLN, we have designed, cloned, and isolated new generation of PLN mutants for study and explored the interactions between PLN mutants and protein phosphatase 1 (PP1), one of the main enzymes that dephosphorylates PLN and controls PLN inhibition activity. We have successfully completed preparation of PLN mutant samples for activity assays. These interactions will eventually be correlated to changes in SERCA activity to determine if the therapeutic mutants can deliver expected results.

Keywords: Phospholamban, Therapeutic, Dynamics, Inhibition, Dephosphorylation, contractility, cloning, Regulation, SERCA2A