We have spent the last two decades investigating novel molecular targets for correcting ventricular dysfunction in heart failure. We have identified the G protein-coupled receptor (GPCR) kinase-2 (GRK2) as such a target. We have shown that inhibiting the activity of this kinase or genetic deleting this kinase in the heart can prevent and reverse heart failure in mouse models. Moreover, a gene therapy approach with a peptide inhibitor of GRK2 (βARKct) has been used in several small and large animal models to rescue heart failure. This includes a recent study in a pre-clinical pig model of heart failure and βARKct gene delivery reversed ventricular dysfunction and caused reverse remodeling. A clinical trial is being planned and these studies will be presented. In addition to a gene therapy approach for GRK2 inhibition we are pursuing small molecule pharmacological inhibition and recent studies have shown the FDA approved anti-depressant drug paroxetine is a specific GRK2 target outside its actions to prevent serotonin re-uptake. We have recently published results that will be presented showing that paroxetine can reverse heart failure in an animal model and this therapeutic effect is independent to its CNS effects. This paves the way for paroxetine derivatives and other small molecules to target GRK2 for future heart failure therapy.