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This new early stage investigator R01 proposal explores how current guideline directed medical therapy (GDMT) has completely modified the chronic heart failure (HF)disease state, specifically with regards to cardiac myocyte signaling via the nitric oxide receptor, soluble guanylyl cyclase (sGC). Although GDMT is widely used, this modified chronic HF disease state is virtually ignored by preclinical studies. We discovered that sGC is dysregulated in the hypertrophied, dysfunctional heart and that β-blocker therapy, a cornerstone of GDMT, alters sGC signaling in the diseased heart in a way that establishes potentially novel, but latent, cardioprotective cascades. Both pressure- and volume-overload induce re-localization of sGC away from caveolae, invaginations of the plasmalemma that compartmentalize signal transduction. Within caveolae, sGC appears protected from oxidation and remains responsive to nitric oxide (NO). In the hypertrophied, failing heart, sGC that is outside of caveolae becomes oxidized and NO-responsiveness is blunted. Recently, we discovered that in the face of volume overload stress, β-blockade prevented myocardial sGC dissociation from caveolae, restored NO-responsiveness of sGC outside of caveolae, and induced functional coupling between β_3 adrenoceptor (β_3AR) and sGC within a non-lipid raft membrane microdomain. Intriguingly, this functional β_3AR/sGC coupling was specific to the non-lipid raft microdomain and was not found in either control nor untreated, hypertrophied hearts. The current proposal applies the PI's expertise in cardiac sGC signaling, molecular physiology, and clinical HF to the field of cyclic guanosine monophosphate (cGMP) membrane microdomain signaling. This area has great HF therapeutic potential given that membrane microdomains act as critical nodes for integrating adrenergic, calcium, and cyclic nucleotide signaling. This proposal will test our hypothesis that GDMT changes the NO responsiveness and functional coupling of sGC within distinct membrane microdomains of cardiac myocytes, thereby resulting in untapped cardioprotective potential that differs from that in non-failing or untreated failing hearts. Our preliminary studies suggest that the non-lipid raft microdomain may represent dyadic junctions. In Aim 1, we will determine the physiological function of plasmalemmal caveolae- vs. dyadic junction-associated sGC/cGMP signaling in cardiac myocytes. In Aim 2, we will define the effect of GDMT on myocardial caveolae- vs. dyadic junction associated sGC/cGMP signaling in the pressure overloaded heart. In Aim 3, we will elucidate how GDMT promotes sGC caveolae-localization and enhances NO-responsiveness. With our novel cardiac-specific sGC knockout, microdomain-targeted sGC constructs, and cardioselective AAV9-mediated transgene delivery, we will provide vital mechanistic evidence for the development of innovative, synergistic therapies for the millions of HF patients already optimized on GDMT.