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Research Symposium

DEVELOPMENT OF AN SRF INHIBITOR PEPTIDE FOR THE TREATMENT OF CARDIAC FIBROSIS

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Approximately 18.6 million deaths worldwide were attributed to cardiovascular disease (CVD) in 2019; in the US alone the estimated direct and indirect cost of CVD for 2016 to 2017 was $363 billion. Cardiac fibrosis, a condition leading to increased cardiac stiffness and decreased cardiac plasticity, is one of the main contributing factors of CVD. The hallmark of cardiac fibrosis is activation of cardiac fibroblasts to myofibroblasts and changes in the extracellular matrix resulting in increased tissue stiffness. Serum Response Factor (SRF) and its co-activator myocardin-related transcription factor A (MRTF-A) represent one key mechanism regulating myofibroblast activation, where increased MRTF-A/SRF signaling has been shown to activate cardiac fibroblasts to myofibroblasts. Despite the role of MRTFA/SRF over-activity in multiple disease pathways, no direct inhibitor of SRF has been identified. A small 21-mer peptide, the B1 box motif of MRTF-A, can bind to SRF and effectively inhibit MRTF-A/SRF complex formation in vitro. In this research, we aim to optimize the binding affinity of the 21-mer peptide to SRF and its ability to inhibit MRTFA/SRF complex formation through computational and biochemical techniques. Therefore, we utilized Amplified Luminescence Homogenous Proximity Assay (ALPHA) to develop a high throughput assay to screen different peptides for their ability to block formation of the MRTF-A/SRF complex. We determined that a 14-mer peptide has the same IC50 as the 21-mer peptide in our assay, 1.6μM vs.1.3μM, respectively. This suggests that a shorter, and perhaps more drug-like peptide may be effective in disrupting this protein: protein interaction. Additionally, we explored different mutations identified through previous research or computational analysis that indicated that a single tyrosine to phenylalanine mutation can increase the potency in our biochemical assay almost 2-fold, resulting in an IC50 of 0.5μM for the 21-mer peptide with the phenylalanine substitution. The current project direction focuses on co-crystallography of SRF and peptides to use for a basis of analysis to determine peptide modifications that can increase binding affinity to SRF and to provide a structural basis for other optimizations like cyclic peptides or addition of non-native amino acids.

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