Novel Cyclic Peptides Targeting the IL-1β/IL-1R Interaction: A Promising Therapeutic Approach for Atherosclerotic Cardiovascular Disease

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Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine that plays a critical role in the formation of atherosclerotic plaques. Patients with high-risk atherosclerotic cardiovascular disease who exhibit elevated arterial inflammation are currently limited in therapeutic options aimed at mitigating the inflammatory processes that lead to major adverse cardiovascular events (MACE).

In this presentation, we will describe a series of novel cyclic peptides identified and optimized through an mRNA display screen designed to inhibit the IL-1β/IL-1 receptor (IL-1R) protein-protein interaction. Initial screening identified peptides with moderate binding affinity but suboptimal cell potency. Through strategic optimization of key residues, informed by co-crystallization data and peptide affinity maturation techniques, we successfully enhanced cell potency while minimizing the risk of mast cell degranulation through the replacement of multiple arginine residues.

Our findings underscore the potential of these optimized cyclic peptides as therapeutic agents in addressing atherosclerotic inflammation and offer effective tools for future research into IL-1β antagonism.