PentraCOR: Bioengineering a Novel Synthetic Fusion Protein Therapeutic for Targeted Regulation of CORIN Gene Signaling in Hypermobile Ehlers-Danlos Syndrome

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Hypermobile Ehlers Danlos Syndrome (hEDS) is a connective tissue and joint disorder that millions of people are affected with. Patients affected suffer from chronic pain and increased risk of injury and other diseases. 20% of the population is also predicted to be affected by this condition in the future, making targeted therapeutics essential. Recent discoveries in the biological pathway associated has enabled researchers to attempt to develop targeted therapeutics. This study leverages and develops rationale behind the inhibition of the natriuretic peptide receptor 1 (NPR1) pathway as a potential therapeutic approach. An ANP antagonistic peptide, derived from the native atrial natriuretic peptide sequence, was identified and engineered to inhibit NPR1 activation. Due to its small size and predicted short half-life, a fusion strategy was implemented to improve biological stability and systemic viability. The antagonist was fused to a pentraxin scaffold using dual G4S linkers to enable multivalent presentation and increase circulatory bioavailability while maintaining potency. Identification of structural compatibility between the fusion construct and NPR1 was conducted in-silico utilizing computational metrics. Docking simulations demonstrated favorable binding orientation of the antagonist interaction interface. Experimental validation required recombinant expression of the ANP antagonist–pentraxin fusion protein. Plasmid constructs were amplified in E. coli and transfected into CHO cells. SDS-PAGE confirmed protein expression at approximately 25 kDa, though purification via phosphoethanolamine chromatography is currently being optimized. After said adjustments, functional receptor inhibition assays will occur to validate therapeutic potential.

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