A C-type Natriuretic Peptide for Treatment of Heart Failure

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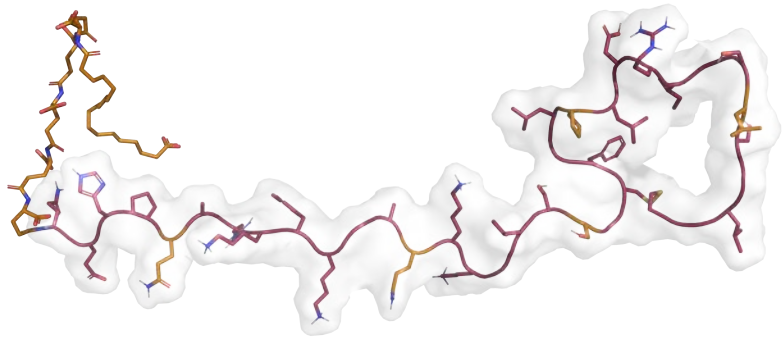
Heart failure with preserved ejection fraction (HFpEF) represents a significant unmet medical need given the high disease burden and paucity of approved therapies. C-type natriuretic peptide (CNP) has therapeutic potential in HFpEF due to its broad range of beneficial effects on cardiovascular structure and function. This study focused on the design and development of a CNP analog (**65)**, for once-weekly subcutaneous administration aimed at the treatment of HFpEF. Utilizing solid-phase peptide synthesis, we synthesized over 1,300 CNP analogs, exploring substitutions and modifications to improve potency, stability, and pharmacokinetics. Our findings guided the design of **65** incorporating five strategic substitutions and an engineered fatty acid protractor to enhance chemical stability, improve pharmacokinetics, and lower the isoelectric point (pI). Low pI was found to be essential for minimizing injection site reactions and improving subcutaneous bioavailability.



65 demonstrated a promising pharmacokinetic profile for once weekly treatment and an improved bioavailability compared to high pI CNP analogs. Furthermore, **65** was engineered for solubility at pH 6.5 to enable stability in liquid formulation and dosing through a pre-filled pen. *In vivo* assessments supported the therapeutic potential in HFpEF of fatty acid-derivatized low pI CNP analogues. **65** is currently under clinical investigation in Phase 1.

[1] A. L. B. Kodal, J. Ewald, et al., *J. Med. Chem.*, **2025**, *68*, 26365-26382.