Structural and Dynamic Insights into How Retatrutide Achieves Triple Agonism

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Abstract:

Obesity is one of the greatest health challenges our time, affecting approximately 1 in 8 adults worldwide [1]. It is a major driver of comorbidities, including type 2 diabetes, cardiovascular and kidney issues, fatty liver disease. Among available therapeutics, glucagon-like peptide 1 receptor agonists (GLP-1RAs) have emerged as leading options due to their superior weight loss efficacy, metabolic benefits, and safety. The next generation of GLP-1RAs extends beyond GLP-1R agonism. For example, retatrutide, a tri-agonist of GLP-1R, the glucose dependent insulinotropic polypeptide receptor (GIPR) and the glucagon receptor (GCGR) has demonstrated unprecedented weight loss in clinical trials [2].

Here, we present three cryo-EM structures of retatrutide bound to GLP-1R, GIPR, and GCGR in complex with Gs, providing atomic-level insights int its binding mode. Using 3D variability analysis (3DVA), we further characterize conformational heterogeneity within cryo-EM datasets, and compare these findings with structures bound to native peptides (GLP-1, GIP, GCG) as well as semaglutide, the current gold-standard GLP-1RA.

Finally, we complement the cryo-EM structures with hydrogen-deuterium exchange mass spectrometry (HDX-MS), enabling quantitative assessment of protein flexibility and stability. Through this integrative approach, we identify key differences in receptor dynamics across peptide-bound complexes, providing a more comprehensive understanding of how retatrutide achieves its tri-agonist action.

1. World Health Organization, *Obesity and overweight*. 2022.
2. Jastreboff, A.M., et al., *Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial.* N Engl J Med, 2023. **389**(6): p. 514-526.