## **BioChemistry Seminar**

The Agony and the Efficacy: New Frontiers in Incretin Drug Discovery

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GLP-1 receptor agonists have emerged as extraordinary tools in the battle against the global obesity epidemic. Detailed investigation of the pharmacology of this therapeutic class as well as related metabolic pathways has unveiled new opportunities for further optimization and personalization to better serve patients with obesity. Several such opportunities will be discussed. In particular, combinatorial pharmacology, by which multiple reinforcing mechanisms are incorporated into single treatments, has been harnessed to drive improvements in efficacy beyond what can be achieved with a single mechanism alone. These complementary pathways to potentiate GLP-1 activity include glucagon receptor agonism and, paradoxically, either agonism or antagonism of the GIP receptor. In additional, downstream signaling pathways activated by the GLP-1 receptor can be differentiated to fine-tune the pharmacological activity of next-generation GLP-1 analogs.



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