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COMMENT

Rising Star 2026: pursuing novel strategies for precision incretin pharmacology

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Abbreviations

GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP-1R	Glucagon-like peptide-1 receptor



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The prevalence of obesity and its comorbidity type 2 diabetes has remained a persistent public health challenge that, in recent years, has led to a wave of revolutionary therapeutic developments that exhibit high efficacy, minimal safety risk and challenge the necessity for future drug iterations [1]. The early identification of the glucagon-like peptide-1 receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide receptor (GIPR) as potent targets for regulating satiety and glycaemia initiated a scientific gold rush to transform their cognate ligands, GLP-1 and GIP, into engineerable domains that maximise therapeutic effect. Significant progress has been made in identifying the fundamental biological mediators of pharmacological GLP-1R and GIPR responsiveness; however, the modified agonists themselves, including their peculiarities and the potential arising from distinct structure–function interactions within biological systems, have received comparatively less attention. There are persistent challenges of gastrointestinal adverse events, lean mass loss, efficacy ceilings and treatment adherence with current GLP-1R and GLP-1R/GIPR therapies. Given this, it is worth asking whether the strategic framework of single- and multi-receptor targeting can realise maximal benefit and adherence, or whether seeking Formula 1 performance from a family sedan is the analogous outcome of overlooking the exploitable potential within the pharmacodynamic and structure–function properties of engineered agonist–receptor interactions [1].

For the past few decades, glucose-lowering and anti-obesity pharmacological advances have largely followed a top-down strategy: engineer a rationally modified peptide, confirm retention of canonical signalling typically through cyclic AMP (cAMP)-responsive endpoints and evaluate efficacy in vivo. This framework has been instrumental to therapeutic development, providing a rapid but robust translational go/

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no-go pipeline. As foremost examples of this success, peptide acylation and sequence hybridisation, which facilitate prolonged efficacy and multi-receptor targeting, respectively, have underpinned current gold standard metabolic pharmacotherapies, including the GLP-1R agonists liraglutide and semaglutide and the GLP-1R/GIPR dual agonist tirzepatide. Yet, only recently have these peptides been reevaluated at mechanistic resolutions capable of characterising serendipitous pharmacology that may contribute to therapeutic efficacy or reveal further desirable properties for rational optimisation.

Even among canonical GLP-1R agonists decorated with alternative acylation strategies, important pharmacological mysteries remain. Despite similar receptor cAMP potencies, a daily dosing regimen of semaglutide achieves greater weight loss than liraglutide at a > tenfold lower daily dose (0.2 mg/day vs 3.0 mg/day)—a therapeutic superiority unlikely to be sufficiently explained by differences in half-life alone [2]. Our upcoming research investigates unique pharmacodynamic properties conferred by differential fatty acid acylation and identifies a fatty acid acylation-type influence on intracellular receptor-trafficking parameters, with potential implications for CNS accessibility and satiety.

Sequence hybridisation provides a parallel example. GLP-1R/GIPR dual agonists, including tirzepatide, were rationally designed to retain potent cAMP activation at both cognate receptors. Yet, despite sharing sequence similarity with both endogenous ligands while remaining structurally distinct from either, tirzepatide unexpectedly exhibits a unique pharmacodynamic bias at the GLP-1R, revealing pharmacology not readily predicted from either parent peptide [3]. We investigated the potential of this pharmacology by developing a semaglutide-based analogue that, although a GLP-1R monoagonist, recapitulated tirzepatide's pharmacodynamic bias at the GLP-1R. Moreover, through direct comparison with semaglutide, the canonical unbiased control, we identified biased GLP-1R activity as a rational strategy for significantly enhancing body-weight-lowering efficacy in mice [4]. With our ongoing research supported by this EASD/EFSD Rising Star award, we seek to uncover non-canonical molecular mechanisms underlying the efficacy of biased agonism at the GLP-1R and GIPR, including whether individual agonists preferentially engage distinct isoforms of downstream signalling effectors, a pharmacological property we term 'effector isoform bias'.

A newly developing branch of therapeutic approach involves supplementing GLP-1R and GIPR activation with the targeted delivery of small-molecule payloads. Conjugating intracellularly releasable small molecules, whether nuclear-acting or effector-modifying, to GLP-1R/GIPR-targeting peptides can restrict payload delivery to receptor-expressing cells, thereby limiting off-target tissue exposure while creating potential synergy between peptide-receptor signalling and intracellular payload activity. We explored the underpinnings of this process by characterising the pharmacodynamics of a GLP-1:oestrogen conjugate at the GLP-1R, alongside the mechanisms governing its intracellular delivery and liberation that drive enhanced metabolic action [5, 6]. We further expanded this toolbox in 2022, reporting on the novel conjugation of an insulin-sensitising PPARα/γ dual agonist to GLP-1, which enhanced glycaemic control over the unconjugated combination therapy via GLP-1R-expressing tissues [7]. In 2026, representing a nexus of multiple pharmacological strategies, we developed a novel GLP-1:GIP:pan-PPAR quintuple agonist (GLP-1:GIP:lanifibranor) that exhibited profound effects on body weight and glucoregulation via targeted polypharmacology [8]. This molecular development not only exemplifies the potential of the peptide:small-molecule combinatorial toolbox, but also reveals exploitable biological dichotomies, such as finding that targeted lanifibranor delivery into GLP-1R-expressing tissues primes the body-weight-lowering response to GLP-1R/GIPR dual agonism, whereas delivery into GIPR-expressing tissues preferentially potentiates glycaemic control [8]. Future strategies to land the 'perfect' molecule likely lie in the tripartite interplay among pharmacologically active targeting peptides, small molecules and tissue context, and may unlock a degree of therapeutic customisation unattainable through current strategical frameworks.

As my research goals expand, the EASD/EFSD Rising Star award provides a genuine launching pad towards research independence and the scientific freedom to pursue questions at the interface of fundamental receptor pharmacology and therapeutic translation. As we develop new strategies in precision incretin pharmacology for obesity and diabetes by integrating the concepts outlined above into novel therapeutic platforms, this award helps spotlight the progress and broader potential of this emerging field.

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Declarations

Author's relationships and activities The author declares that there are no relationships or activities that might bias, or be perceived to bias, their work.

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