BIOMOD LABS · RESEARCH PEPTIDE CO.

RESEARCH COMPOUND MONOGRAPH · SERIES 1 · NO. 001

Tirzepatide

LY3298176 — a 39-residue synthetic peptide engineered at Eli Lilly as a dual agonist of the GIP and GLP-1 receptors, with a C20 fatty diacid side chain on Lys20 (γGlu-2×AEEA linker) — the first peptide of its dual-receptor class with characterised cellular pharmacology.

CAS REGISTRY	CATALOG REFERENCE	VIAL STRENGTH	CLASS
2023788-19-2	BM-LYO-001	20 mg / vial	Synthetic peptide · 39 a.a. + C20 diacid

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Tirzepatide is a 39-residue synthetic peptide engineered at Eli Lilly and Company by Tamer Coskun, Kyle Sloop and colleagues as the first characterised dual agonist of the glucose-dependent insulinotropic polypeptide receptor (GIPR) and the glucagon-like peptide-1 receptor (GLP-1R). The molecule is built on a GIP-derived backbone with selected sequence elements that introduce balanced GLP-1R agonism, two Aib substitutions (positions 2 and 13) for DPP-IV resistance, and a C20 eicosanedioic acid (fatty diacid) side chain attached to Lys20 through a γGlu-2×AEEA (aminoethoxy-ethoxyacetic acid) linker. The C20 diacid — two carbons longer than the C18 diacid used in semaglutide — confers reversible non-covalent association with serum albumin and the extended duration of action documented in animal pharmacology studies. Importantly, biased-signalling characterisation by Willard and colleagues showed that while tirzepatide closely resembles native GIP in how it activates the GIPR, it differs markedly from GLP-1 in its activation of the GLP-1R, producing less agonist-induced receptor desensitisation at GLP-1R than native GLP-1. ***This monograph summarises published cellular pharmacology and preclinical findings for laboratory research reference only.***

01 Compound Profile

COMMON DESIGNATION	Tirzepatide · LY3298176
BACKBONE	39-residue synthetic peptide based on GIP sequence with selected GLP-1 sequence elements; Aib at positions 2 and 13
SIDE-CHAIN MODIFICATION	Lys20 acylated with γGlu-2×AEEA spacer + C20 eicosanedioic acid (fatty diacid)
CAS REGISTRY	2023788-19-2
MOLECULAR FORMULA	$C_{225}H_{348}N_{48}O_{68}$
AVERAGE MOLECULAR MASS	4813.53 g · mol^{-1}
PRIMARY MOLECULAR TARGETS	Glucose-dependent insulinotropic polypeptide receptor (GIPR) · Glucagon-like peptide-1 receptor (GLP-1R) — both Class B GPCRs; dual full agonism[1]
BIASED SIGNALLING NOTE	Closely resembles native GIP at GIPR; markedly differs from native GLP-1 at GLP-1R — reduced agonist-induced GLP-1R desensitisation compared with native GLP-1 (Willard et al., 2020)[2]
PHYSICAL FORM	White lyophilised solid
SOLUBILITY (LAB RECONSTITUTION)	Soluble in sterile water for injection; the lipid side chain creates surfactant-like behaviour; reconstituted solutions held cold and aliquoted
STORAGE (RESEARCH HANDLING)	Lyophilised solid: −18 °C, desiccated, light-protected; reconstituted solution refrigerated 2–8 °C; long-term aliquots at −18 °C; siliconized or polypropylene surfaces preferred for dilute concentrations
ANALYTICAL SPECIFICATION	≥ 98 % purity by HPLC (BIOMOD Labs internal release specification)

02 Origin and Chemistry

Tirzepatide was developed at Eli Lilly and Company by Coskun, Sloop, and colleagues as part of a research programme exploring single-molecule dual incretin receptor agonism. The chemistry strategy was distinct from the semaglutide / liraglutide lineage: rather than starting from the GLP-1 backbone and engineering improved pharmacokinetics, the Lilly team started from the GIP backbone and introduced selected sequence elements that

conferred GLP-1R agonism while preserving native-GIP-like behaviour at GIPR. The Aib substitutions at positions 2 and 13 confer DPP-IV resistance (the GIP backbone, like GLP-1, is normally a DPP-IV substrate). The Lys20 side-chain conjugation with γGlu-2×AEEA + C20 diacid provides reversible non-covalent association with serum albumin, paralleling the chemistry strategy used in semaglutide but with a C20 (rather than C18) diacid.[1]

Subsequent structural biology work by Sun and colleagues (2022) using cryo-EM characterised the binding modes of tirzepatide at GIPR and GLP-1R, providing molecular-level understanding of the unusual asymmetric pharmacology — tirzepatide engaging GIPR in a manner closely paralleling native GIP, but engaging GLP-1R differently from native GLP-1.[3]

03 Molecular Targets and Cellular Signalling

Tirzepatide is a full agonist at both the glucose-dependent insulinotropic polypeptide receptor (GIPR) and the glucagon-like peptide-1 receptor (GLP-1R), the two Class B G-protein-coupled receptors that constitute the incretin receptor family. Both receptors are coupled principally to Gαs in cell-line transfection systems; receptor activation produces cAMP elevation, PKA activation, and downstream signalling cascades that drive the pancreatic β-cell, gastric emptying, and central appetite regulation observed in animal models. The defining cellular-pharmacology finding from Willard et al. (2020) is the asymmetric biased signalling at the two receptors: tirzepatide's binding kinetics and receptor occupancy patterns at GLP-1R produce less β-arrestin recruitment and less receptor internalisation than equivalent levels of GLP-1R activation by native GLP-1, while its GIPR pharmacology more closely resembles native GIP.[2]

The dual-agonist architecture engages cell types not optimally targeted by selective GLP-1R agonists. Pancreatic β-cells express both GIPR and GLP-1R; adipocytes express GIPR but minimal GLP-1R; certain hypothalamic populations co-express both receptors. The aggregate cellular pharmacology of tirzepatide therefore differs from that of selective GLP-1R agonists (semaglutide, liraglutide) by engaging the GIPR-mediated pathways in addition to the GLP-1R-mediated pathways.[4] PRECLINICAL · MOUSE

04 Preclinical Findings

SYSTEM	PREPARATION	REPORTED OBSERVATION	REF.
Receptor activation	HEK293 cells transfected with hGIPR or hGLP-1R	Full dual agonism; balanced pharmacology characterised in cAMP assays	1
Biased signalling	GLP-1R cell-line assays comparing tirzepatide vs. native GLP-1	Reduced β-arrestin recruitment and receptor internalisation at GLP-1R	2
Structural biology	Cryo-EM of tirzepatide–receptor complexes	Defined binding modes at both GIPR and GLP-1R	3
Gastric emptying	Diet-induced obese mice	Transient delay of gastric emptying similar to selective long-acting GLP-1RAs (Urva et al. 2020)	5
Insulin sensitivity	Obese mouse models	Weight-independent insulin sensitisation mediated by GIPR agonism (Samms 2021)	4

SYSTEM	PREPARATION	REPORTED OBSERVATION	REF.
Body weight	Animal obesity models	Reduction of body weight exceeding selective GLP-1RAs	1

05 Research Synthesis & Limitations

METHODOLOGICAL NOTES

Tirzepatide is the prototype dual-incretin-receptor agonist peptide and is well-characterised in published primary literature at receptor, signalling, structural-biology, and animal-pharmacology levels. For researchers working with the compound, the asymmetric biased-signalling pharmacology (close-to-native at GIPR, biased at GLP-1R) means that effects observed in cells or animals should not be assumed to scale linearly from selective GLP-1R agonist findings. The C20 fatty diacid is two carbons longer than semaglutide's C18 diacid, conferring higher albumin affinity but also a somewhat greater tendency toward formulation challenges at high concentrations.

06 Laboratory Handling, Reconstitution, and Storage

Lyophilised tirzepatide is supplied under research-use specifications and held at −18 °C, desiccated. Reconstitution in sterile water for injection is the standard practice; the lipid side chain creates surfactant-like behaviour and adsorption to glass and certain plastic surfaces at dilute concentrations — siliconized glass or polypropylene tubes are preferred for dilute work. Reconstituted solutions are held refrigerated 2–8 °C for short-term work; long-term aliquoted storage at −18 °C with strict minimisation of freeze–thaw. Working concentrations are determined by the investigator's experimental design.

07 References

1 Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, Cui X, Briere DA, Cabrera O, Roell WC, Kuchibhotla U, Moyers JS, Benson CT, Gimeno RE, D'Alessio DA, Haupt A. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. *Mol Metab.* 2018;18:3–14. pubmed.ncbi.nlm.nih.gov/30473097

2 Willard FS, Douros JD, Gabe MBN, Showalter AD, Wainscott DB, Suter TM, Capozzi ME, van der Velden WJC, Stutsman C, Cardona GR, Urva S, Emmerson PJ, Holst JJ, D'Alessio DA, Coghlan MP, Rosenkilde MM, Campbell JE, Sloop KW. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight.* 2020;5(17):e140532. PMID: 32730231. pubmed.ncbi.nlm.nih.gov/32730231

3 Sun B, Willard FS, Feng D, et al. Structural determinants of dual incretin receptor agonism by tirzepatide. *Proc Natl Acad Sci USA.* 2022;119(13):e2116506119. PMC9060465. pmc.ncbi.nlm.nih.gov/PMC9060465

4 Samms RJ, Christe ME, Collins KA, Pirie L, Conkright JJ, Wojnicki S, Konkol DL, Cosgrove R, et al. GIPR agonism mediates weight-independent insulin sensitization by tirzepatide in obese mice. *J Clin Invest.* 2021;131(12):e146353. pubmed.ncbi.nlm.nih.gov/33938453

5 Urva S, Coskun T, Loghin C, Cui X, Beebe E, O'Farrell L, Briere DA, Benson C, Nauck MA, Haupt A. The novel dual GIP and GLP-1 receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists. *Diabetes Obes Metab.* 2020;22(10):1886–1891. PMID: 32519795. pubmed.ncbi.nlm.nih.gov/32519795

6 Frias JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K, SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med.* 2021;385(6):503–515. pubmed.ncbi.nlm.nih.gov/34170647