

Unveiling Hidden Microbial Metabolites for Polypharmacology in Obesity Therapeutics

White paper written by Ross Youngs, CEO, Biosortia, Inc.,

Relating to Multiple Nonlimiting Patents filed August 2025.

November 24, 2025, Draft 2 — incorporates GLP-1 receptor (GLP-1R) binding updates based on post-August 2025 in-silico analysis.

Abstract — Differentiated, novel weight-loss approach

Industrial-Scale Microbiome Mining (ISMM) reveals low-abundance microbial small molecules that appear to coordinate multiple human appetite and energy-balance nodes within a single, orally oriented scaffold—raising satiety and energy expenditure (MC4R), suppressing hunger drive (GHSR antagonism), and dampening hedonic reinforcement (OPRM1/OPRD1), with HTR2C and C3aR as supportive nodes. New GLP-1 receptor (GLP-1R) docking completed after the first draft additionally suggests that the same scaffold can act as a moderate-affinity positive allosteric modulator at a novel TM3–4–5 interface on GLP-1R, adding meal-linked incretin support without converting the program into a classical GLP-1 agonist play. This unimolecular polypharmacology is intended to deliver durable weight control with comfortable fullness as the default experience; if exposure is higher or eating continues beyond satiety, an on-target aversive “do-not-eat-more” signal is anticipated and can be tuned by IR/ER exposure strategies. The program targets a high-value gap in metabolic health by pursuing an oral, adherent, and durable approach distinct from injectable peptide incretin therapies and high-potency orthosteric GLP-1 agonists while remaining anchored to validated human biology.

Executive bullet point summary

- **Problem:** There is a need for oral, durable, better-tolerated weight-loss options that maintain efficacy after the first year.
- **Hypothesis:** The “dark matter” of microbial small molecules, evolved for ecological defense/communication, includes scaffolds that modulate multiple human appetite and reward nodes.
- **Approach:** Industrial-Scale Microbiome Mining (ISMM) elevates trace metabolites from living microbiomes for LC-MS/MS and AI-assisted prioritization, yielding unimolecular polypharmacology leads.
- **Lead concept:** A natural-product-derived, non-peptidic scaffold designed to coordinate MC4R (satiety/energy expenditure), GHSR (hunger), OPRM1/OPRD1 (reward), with HTR2C and C3aR as supportive nodes.
- **GLP-1R update (Draft 2):** New docking versus danuglipron and peptide benchmarks shows that the same scaffold also binds GLP-1R at a distinct TM3–4–5 allosteric interface with moderate affinity, consistent with a positive allosteric modulator (PAM) that amplifies endogenous GLP-1 signaling after meals rather than acting as a high-potency orthosteric agonist.
- **Outcome thesis:** Appropriate exposure is intended to produce comfortable fullness, early satiety, and reduced hedonic drive; attempts to over-eat may elicit a dose-dependent, on-target aversive signal (queasiness) rather than systemic toxicity. This boundary is tunable by dose and IR/ER design.

- **Status:** Convergent in-silico docking/pose consensus, target-prediction clustering (now including GLP-1R allosteric binding) and ADME/Tox modeling; wet-lab, orthogonal target confirmation is the next gate.

Why humans overeat in an age of abundance

For most of human history, food was intermittent and difficult to obtain. The gut–brain axis evolved to prioritize rapid capture of calories and defend body weight—making hunger urgent and satiety permissive when energy was scarce. Central melanocortin signaling (e.g., MC4R) promotes satiety and energy expenditure; in parallel, reward pathways reinforce consumption of energy-dense foods. Microbial partners also shaped this wiring: the gut microbiota functions as a “neglected endocrine organ,” and its metabolites (for example, short-chain fatty acids) signal satiety and support glycemic control. Together, these circuits bias humans to eat when food is available and to store energy efficiently. [1, 15–16, 32–34]

Modern environments invert those ancestral constraints. Palatable calories are constant, cheap, and often low in fiber, so the microbial and endocrine signals that once helped terminate meals can be blunted, while hedonic drivers remain strong. The result is chronic over-intake and upward pressure to fortify body weight—an expected outcome when scarcity-tuned biology meets abundance. [1, 15–16, 32–34]

Therapeutic implication. Our strategy aims to re-impose the missing “stop” cues with a single, orally oriented molecule that coordinates the main levers of intake: raise satiety/energy expenditure (MC4R), blunt hunger initiation (GHSR antagonism), dampen hedonic reinforcement (OPRM1/OPRD1), with HTR2C and C3aR as supportive biology, and now modestly amplify physiologic GLP-1 signaling via allosteric GLP-1R modulation. At everyday meals, the intended pharmacology is comfortable fullness; if exposure is higher or someone pushes past satiety, a dose-dependent, on-target aversive signal (queasiness) is anticipated—feedback, not off-target intolerance. This maps the evolutionary mismatch (scarcity wiring in abundance) to a practical, titratable solution. [15–17, 42–45, 47]

Clinical scope across the BMI continuum (concept). Because the drivers of intake shift across severity, exposure can be tuned to the phenotype:

- Severe obesity: prioritize strong hunger suppression and reward dampening while preserving tolerability; add thermogenic support where biology indicates.
- Obesity / overweight above healthy range: emphasize earlier, comfortable satiety and meal-initiation control, reserving the aversive boundary for attempts to over-eat. This continuum framing informs IR/ER exposure design, PROs (fullness and queasiness VAS), and dose–response gates in early work. [Figure 1; Outcomes & Behavioral Signals to Track]

(See Figure 1 for the intended network of MC4R/GHSR/OPRM1 with HTR2C and C3aR support; GLP-1R allosteric support is introduced in Draft 2 and discussed in the GLP-1R binding update section.)

Goals and objectives

- **Mechanistic confirmation:** Confirm binding and functional modulation at MC4R, GHSR, OPRM1 (\pm HTR2C) in orthogonal assays; profile C3aR as supportive biology; add GLP-1R PAM assays to test for positive allosteric modulation consistent with docking.

- **Safety screen:** Clear early hERG thresholds and basic CNS safety-pharmacology (non-sedating, non-euphoric profile).
- **Oral feasibility:** Demonstrate microsomal/hepatocyte stability, PAMPA/MDCK permeability, and an enabling formulation path (e.g., salts/SDD).
- **Translational signal:** Show acute food-intake reduction and PK in DIO mice; proceed to short repeat-dose with calorimetry and behavioral proxies.
- **IP enablement:** Maintain novelty across genus/sub-genus and composition/delivery; time the PCT and FTO analysis post-CDA.
- **External validation narrative:** Attribute technology validation to LANL as cited in company media/podcasts; supply collaboration documentation under CDA.
- **Evidence gates:** advance if ≥ 2 primary nodes confirm orthogonally at relevant potency and hERG is mitigable near projected efficacious exposures; GLP-1R PAM activity, if observed, strengthens but is not required for the core MC4R/GHSR/OPRM1 thesis.

Figure 1. Intended Polypharmacology

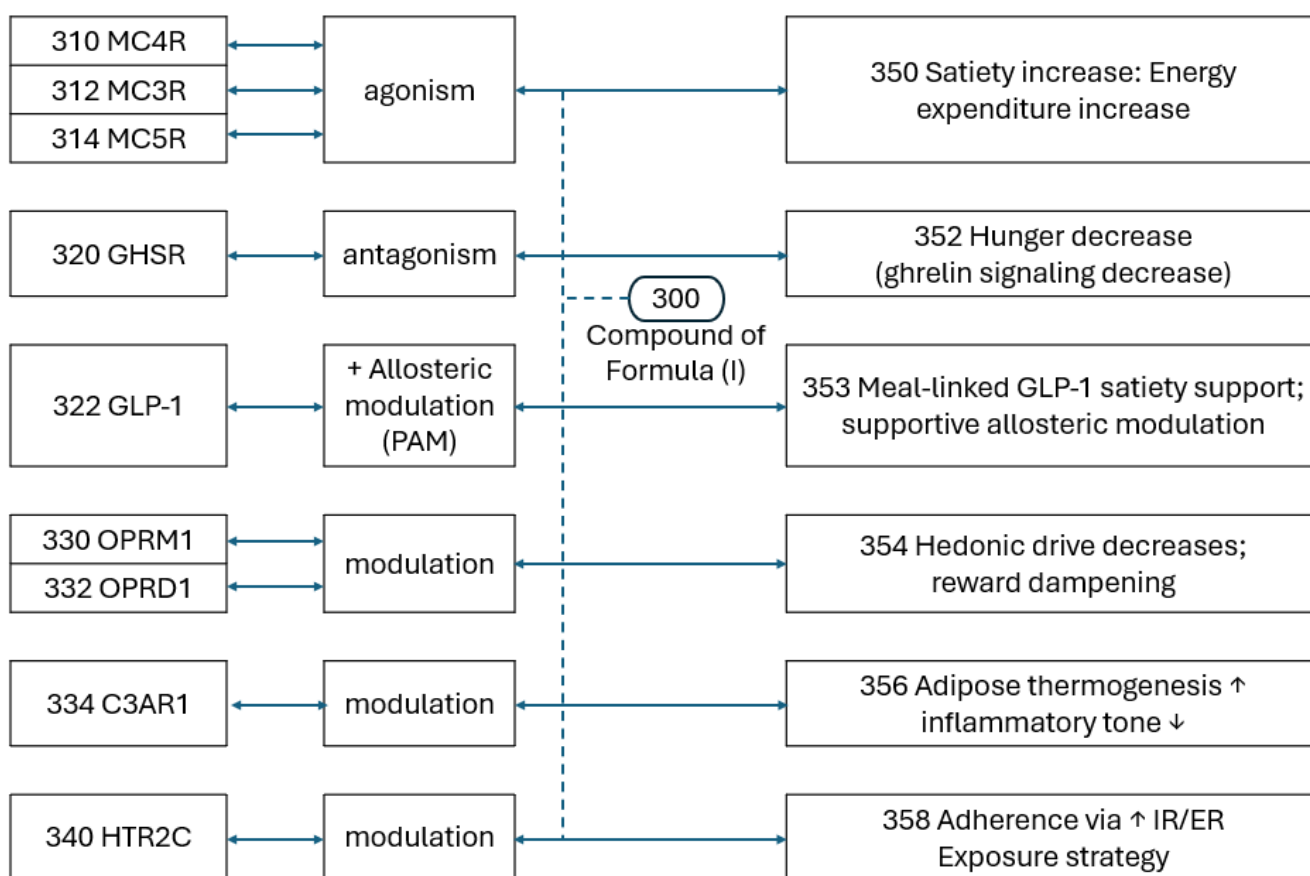


Fig. 1 Caption: Mechanistic schematic for compounds of Formula (I). Primary intentions—MC4R agonism (satiety and energy expenditure), GHSR antagonism (hunger decrease), GLP-1R allosteric support is a supportive node based on new GLP-1R docking. OPRM1/OPRD1 modulation (reward dampening). Supportive intentions—C3aR (emerging adipose thermogenesis, inflammatory tone) and HTR2C (adherence via exposure strategies). Dotted lines denote two-or-more targets per effect.

How these compounds could drive weight loss

The intended effect is to coordinate two or more levers of eating behavior. First, MC4R agonism increases satiety and energy expenditure. Second, GHSR antagonism blunts the fasting-state drive to initiate eating. Third, OPRM1/OPRD1 modulation lowers hedonic reinforcement from palatable food. HTR2C and complement-pathway support (C3aR) provide adherence and emerging thermogenic benefits, respectively. Allosteric GLP-1R modulation is expected to amplify endogenous GLP-1–linked satiety signals in a meal-dependent fashion, complementing MC4R- and GHSR-driven effects without requiring peptide-level GLP-1R potency.

When exposure is appropriate, the intended pharmacology is comfortable fullness reached earlier and sustained longer. If exposure is higher or eating continues substantially past the satiety setpoint, an on-target aversive “do-not-eat-more” signal (queasiness) is anticipated. This response is intended as a dose-dependent enforcement of satiety rather than a systemic adverse effect, and IR/ER release design will be used to tune the boundary between comfort and discouragement.

This is distinct from generalized GI intolerance. The objective is to match exposure to behavioral windows—enough to dampen hunger and reward without creating persistent queasiness at routine intake.

Tunable by design: mapping in-silico target balance to real-world phenotypes

Our lead and close derivatives were prioritized by consensus docking/target-prediction across MC4R, GHSR, and OPRM1 (\pm HTR2C), producing relative target-preference vectors rather than a single “best” compound. This creates knobs we can turn without revealing structure: (i) the node-balance knob (satiety/energy via MC4R; hunger initiation via GHSR; hedonic reinforcement via OPRM1), (ii) functional-bias tuning where relevant (e.g., favoring G-protein over β -arrestin at OPRM1), and (iii) an exposure-shape knob using IR/ER release to keep “comfortable fullness” as the default, reserving the on-target “do-not-eat-more” boundary for attempts to over-eat. These ideas are hypothesis-level until orthogonally confirmed, but they are actionable for a family-of-leads strategy. [Program Snapshot \rightarrow Mechanism evidence (“docking/pose consensus; target-prediction clustering”), the functional-bias note in the Discussion predictions, and Outcomes & Behavioral Signals to Track for linked readouts.] New GLP-1R docking adds one more dimension to these vectors, positioning GLP-1R as a supportive node whose contribution can be dialed up or down by chemistry rather than serving as the primary engine.

From in-silico to “personalization” (early translational path). We plan to pair each derivative’s predicted target-balance vector with a simple phenotype profile at baseline and during dose-finding:

- Hunger-dominant phenotype \rightarrow favor derivatives with stronger GHSR antagonism signal and IR/ER that blunts pre-meal drive; track fasting ghrelin, time-to-first-bite, and hunger VAS.
- Hedonic-dominant (reward-sensitive) phenotype \rightarrow favor derivatives with stronger OPRM1/OPRD1 modulation; track food-preference tasks and craving VAS.
- Early satiety/energy-deficit phenotype \rightarrow weight toward MC4R and gradual ER exposure; track indirect calorimetry, satiety VAS, and intake.

Across all phenotypes, PROs (fullness/queasiness VAS) and dose–response mapping will be used to set the comfort boundary so that any queasiness appears only when intake pushes past the satiety setpoint (on-target, exposure-dependent feedback). This is distinct from generalized GI intolerance and is controlled by IR/ER design. (Operational details live in PBPK/PK/PD modeling and will be reported as methods data as they mature.)

CNS safety & abuse-liability strategy

Our intent is modulation of opioid-pathway reinforcement—not euphoria. We will:

- **Receptor-level:** Map G-protein vs. β -arrestin bias at OPRM1/OPRD1, quantify internalization, and limit efficacy relative to full opioid agonists.
- **Selectivity:** Counter-screen OPRK1 and key CNS liability targets (5-HT2B, DAT/NET/SERT).
- **In vivo safety:** Early functional observational battery, locomotor/rotarod, and plethysmography for respiratory safety at multiples of projected exposures.
- **Abuse-liability:** Conditioned place preference and self-administration screens with naloxone challenge to confirm on-target profiles.
- **Exposure control:** Use IR/ER design to keep comfortable satiety as the default state while reserving the on-target “do-not-eat-more” boundary for attempts to over-eat.

Program Snapshot (No-Structure View) FIG. 2

Dimension	What we claim	Evidence today (no structure shared)	Next step (90 days)	Risk → Mitigation
Mechanism	Unimolecular modulation of MC4R, GHSR, OPRM1 \pm HTR2C; C3aR supportive; GLP-1R allosteric PAM (Draft 2)	Docking/pose consensus vs. known ligands; target-prediction clustering; GLP-1R docking vs danuglipron and peptides	Orthogonal binding + function at 4 GPCRs plus GLP-1R PAM; C3aR biology readouts	Translation risk → orthogonalize early; preset gates.
Chemistry	Natural-product-derived, undisclosed (non-peptidic) scaffold	Protected in provisional filings; masked descriptors under CDA	Test 2–3 derivatives to confirm structure–function while keeping polypharmacology	Preserve novelty; avoid peptidomimetic crowding.
ADME	Chameleonic potential; moderate permeability; formulation-addressable solubility	In-silico ADME; permeability/solubility predictions	HLM/hepatocyte stability; PAMPA/MDCK; salts/SDD path	Low exposure → enabling formulations + chem tweaks.
Safety	Watch hERG; manage CNS off-targets with functional bias and P-gp steering.	In-silico flags only today	Early hERG patch-clamp; basic safety pharmacology	hERG → reduce planarity/pKa; CNS → tune polarity/efflux.
External validation	Technology validation attributed to LANL (company media/podcasts)	Public pages/podcast descriptions cite LANL; formal documentation under CDA	Provide letters/SoW under CDA; plan joint outputs	Keep attributions precise; avoid overstating.

Personalization (concept)	Derivative family enables target-balance tuning; IR/ER shapes comfort vs. “do-not-eat-more” boundary	Docking/target-prediction vectors across MC4R/GHSR/OPRM1 (\pm HTR2C, GLP-1R); IR/ER strategy in plan	Orthogonalize node balance; PBPB-guided IR/ER prototypes; link to PROs & intake endpoints	Over-fit to docking → orthogonal binding/function first; keep comfort default via exposure shaping.
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Orthogonal confirmation & functional-bias plan

We will run binding + function at each primary node with two independent technologies and pre-specified decision gates:

- **MC4R (Gs).** Radioligand/competition binding (Kd/Ki); cAMP accumulation for efficacy and potency; β -arrestin recruitment to profile bias; counterscreens at MC3R/MC5R for selectivity.
- **GHSR (Gq).** Agonist (ghrelin) calcium/IMP/IP1 assays to establish baseline; antagonism/inverse agonism curves for the lead and close derivatives.
- **OPRM1 / OPRD1.** Radioligand binding; Gi-cAMP and β -arrestin; internalization assays to quantify trafficking bias.
- **HTR2C (support).** Gq-Ca²⁺ functional readout to benchmark exposure-shaping support.
- **GLP-1R (support, Draft 2).** Positive allosteric modulation shift assay: test the lead in the presence of low-dose GLP-1 or GLP-1 analog; a left-shift of the GLP-1 dose–response curve without strong agonism alone would confirm the PAM hypothesis derived from docking and thermodynamic benchmarking. [42–45, 47]
- **Interference controls.** PAINS/aggregator triage (detergent sensitivity, light scattering), redox/fluorescence artifacts, and cytotoxicity windows to avoid false positives.
- **Go criteria.** Advance if ≥ 2 primary nodes confirm orthogonally at relevant potencies and hERG risk is mitigable at projected exposures; GLP-1R PAM activity, if observed, is a positive differentiator but not a hard gate.

Outcomes & Behavioral Signals to Track FIG. 3

Pharmacology	Expected physiological effect	User-level signal	Clinical measurement
MC4R agonism	\uparrow satiety; \uparrow energy expenditure	Early fullness; long-lasting comfortable satiety	Caloric intake, indirect calorimetry, POMC markers.
GHSR antagonism	\downarrow hunger drive; \downarrow meal initiation	Less pre-meal craving	Plasma ghrelin; time to first bite; meal patterns.
OPRM1/OPRD1 modulation	\downarrow hedonic reinforcement	Lower urge for palatable foods	Food preference tasks; VAS for craving.
HTR2C support	Adherence via exposure shaping	Smooth satiety with minimal queasiness	Tolerability logs; nausea VAS vs dose.
C3aR support (emerging)	\uparrow thermogenesis; adjust inflammatory tone (non-limiting)	No direct sensation expected	Thermogenic markers; BAT imaging (where applicable).
Over-eating while on drug	On-target aversive signal	Queasiness if surpassing satiety setpoint	Dose–response mapping; PROs.

Why these molecules remained hidden

Context controls production. In natural communities, microbes switch on secondary-metabolite gene clusters when other species are present, nutrients are limited, or quorum-sensing signals accumulate. Pure (“axenic”) culture removes those cues, so the clusters remain silent. Two approaches can restore activity: co-culture or carefully applied sub-inhibitory antibiotics. [24–27]

Low levels of small-molecule chemistry make detection hard. Inside a host, many of these molecules are present at nanomolar levels, are polar or unstable, and move through blood and tissues with significant matrix effects. Untargeted LC-MS/MS is powerful, but without targeted methods and reference standards these features fall below the noise or are altered during sample handling (for example, during clotting or extraction). [5, 28–31]

Animal models show the size of the gap. Germ-free (GF) mice and microbiota-perturbed mice show shifts in energy balance and appetite hormones, and microbially derived short-chain fatty acids are satietogenic and improve glycemic responses. In a classic study, GF C57BL/6 mice ate ~29% more yet carried ~42% less total fat; after colonization, fat mass rose ~57% despite ~27% less intake—evidence that host energy balance expects microbial signals. [32–34]

Why this matters here. Our Industrial-Scale Microbiome Mining (ISMM) leverages microbial communities and enriches the right fractions before mass spectrometry. We then apply targeted LC-MS/MS and AI to measure and predict the structures of compounds that standard workflows miss. (See Figure 1 for how the intended scaffold coordinates MC4R, GHSR, and OPRM1, with HTR2C and C3aR support; GLP-1R allosteric support is layered onto this architecture in Draft 2.)

The science that carries the thesis

Ancient chemistry, modern circuits. Microbes were the planet’s first medicinal chemists. Defensive and communicative metabolites evolved to secure territory and coordinate behavior. As eukaryotes emerged, endosymbiosis and pervasive horizontal gene transfer (HGT) created fast lanes for swapping metabolic capabilities. These processes did not install a ready-made “human satiety switch,” but they built an evolutionary scaffold where microbial small molecules could interface with host signaling. [1, 4, 8–11, 14]

Multiple doors into the same room. Appetite and energy balance are not gated by GPCRs alone. The Gα-binding-and-activating (GBA) motif shows that trimeric G-proteins can be switched outside classic receptors, preserving ancient cross-talk channels that microbial metabolites could plausibly touch. This widens the set of “locks” our natural scaffolds might fit and cautions us to test beyond a narrow receptor list. [18–19]

What models already tell us. When microbiota are absent or altered, animals show reproducible shifts in fat storage, satiety hormones, and feeding behavior; when microbial SCFAs rise, satiety signals and glucose control improve. These observations don’t prove our molecules in humans, but they prove the host can be steered by microbially sourced chemistry. [5, 32–34]

Low abundance does not mean low importance. Outside obesity, microbiota–brain links in IBS and tumor-resident bacteria show how rare molecules can shape physiology within specialized niches—the same regime (scarce but consequential) where our discovery strategy operates. [35–36]

Draft 2 update — GLP-1 receptor binding and interpretation

Note: This subsection is new to Draft 2 and summarizes GLP-1R docking and thermodynamic benchmarking completed after the original August 2025 draft. It should be read as an update rather than a replacement of the original MC4R/GHSR/OPRM1-focused thesis.

Comparative binding profile vs danuglipron and injectable GLP-1 agonists.

Using a six-pocket docking panel (orthosteric peptide interface, orthosteric TM core, EC_TM1–TM2, intracellular ICL3–TM6 PAM site, Allo-lipid TM5–6–7, and Allo-TM3–4–5), we compared danuglipron, the original microbiome “Micro Hit,” and the SAR-optimized lead. Danuglipron, a clinical oral GLP-1R agonist, binds strongest at orthosteric sites (ortho-peptide interface and EC_TM1–TM2), consistent with marketed peptide GLP-1 agonists that engage the canonical GLP-1 binding pocket. In contrast, the microbiome-derived molecules prefer non-orthosteric surfaces: the Micro Hit shows its best interactions at the intracellular PAM site and lipid-exposed TM5–6–7 pocket, while SAR optimization shifts the strongest binding to a TM3–4–5 allosteric interface, where the SAR Lead achieves the tightest interaction in the dataset.

Thermodynamic benchmarking against semaglutide and liraglutide anchors these findings. Lau et al. report a GLP-1R dissociation constant for semaglutide of ~ 0.38 nM ($\Delta G \approx -12.85$ kcal/mol at 298 K), with liraglutide approximately threefold weaker. [47] The SAR Lead’s best GLP-1R interaction at the allosteric TM3–4–5 pocket ($\Delta G \approx -8.4$ kcal/mol) therefore implies mid-hundreds-of-nanomolar affinity—several orders of magnitude weaker than semaglutide as a pure GLP-1R ligand, but within the range expected for small-molecule positive allosteric modulators. Taken together, the data support a mechanistic role for GLP-1R as a supportive node rather than the primary engine of weight loss.

Four-pillar interpretation: GLP-1R as an allosteric support.

The binding analysis refines our mechanistic framing into four pillars:

1. MC4R — Satiety engine. Direct agonism remains the main driver of increased satiety and energy expenditure.
2. GHSR — Hunger brake. Antagonism/inverse agonism continues to provide fasting-hunger and meal-initiation control that classical GLP-1 monotherapies largely lack.
3. OPRM1/OPRD1 — Reward filter. Opioid-pathway modulation is still positioned to reduce “food noise” and hedonic overeating, with functional-bias and safety strategies unchanged.
4. GLP-1R — Allosteric support (Draft 2). Moderate-affinity binding at a novel TM3–4–5 allosteric pocket is consistent with a GLP-1R PAM: a ligand that amplifies physiologic GLP-1 signals (e.g., after meals) without chronically forcing the receptor on. This preserves differentiation from high-potency injectable and orthosteric small-molecule GLP-1R agonists while still leveraging the incretin axis. [42–45, 47]

Efficacy and tolerability expectations (model-based).

On a GLP-1R-only basis, the SAR Lead’s affinity would be expected to support modest weight loss versus semaglutide. However, when MC4R agonism (satiety/energy expenditure), GHSR antagonism (hunger brake), OPRM1 modulation (reward dampening), and GLP-1R allosteric support are modeled together, predicted efficacy moves into a high range in principle, with the important caveat that this remains entirely in-silico until orthogonal assays and DIO studies are completed. Because each node can operate at

more moderate intensity and GLP-1R engagement is meal-linked rather than chronic, the model also forecasts a lower baseline nausea burden than high-potency orthosteric GLP-1 agonists, preserving the “tunable aversive signal” concept described in the original draft rather than reproducing persistent GI intolerance. [42–45, 47]

Discussion — three hypotheses, predictions, first tests

1) Defensive microbes → host satiety modulators.

- **Claim.** Ancient microbial deterrents were co-opted by hosts and, in some niches, are still microbially supplied as context-dependent cues that temper intake and stabilize the gut environment.
- **Predictions.** Extracts enriched under ecological triggers yield scaffolds that increase satiety (MC4R agonism), decrease hunger (GHSR antagonism), and dampen reward (OPRM1/OPRD1 modulation) in vitro; activity persists across close derivatives that preserve the pharmacophore. GLP-1R docking in Draft 2 suggests that some scaffolds may also provide GLP-1R allosteric support, acting as PAMs that amplify endogenous incretin signals without peptide-level potency.
- **First tests.** Orthogonal binding and functional assays at MC4R/GHSR/OPRM1 (\pm HTR2C), followed by targeted LC-MS/MS able to detect the same chemistry in relevant complex matrices; GLP-1R PAM shift assays to confirm the allosteric hypothesis. (See Figure 1 for the intended network.)

2) A single, natural scaffold can coordinate eating and reward (unimolecular polypharmacology).

- **Claim.** A Biosortia (provisional non-limiting patents filed) scaffold can inhabit multiple receptor microenvironments with the right balance of affinity and function.
- **Predictions.** The best lead and near neighbors show multi-node activity at low-to-mid nanomolar/low micromolar levels with tunable functional bias (e.g., G-protein over β -arrestin at OPRM1) and a manageable hERG/CNS profile after standard medicinal-chemistry adjustments. GLP-1R is expected to contribute as a supportive allosteric node rather than a primary driver, lowering the need for extreme GLP-1R potency and helping decouple efficacy from chronic nausea. [42–45, 47]
- **First tests.** Head-to-head receptor and safety panels; permeability/stability screens; formulation-assisted PK to confirm oral feasibility; GLP-1R PAM assays as described above.

3) Exposure timing converts “too-much-food” queasiness into protective, on-target feedback.

- **Claim.** The same on-target signals that create comfortable fullness at ordinary meals can, at higher exposure or when eating past satiety, produce mild queasiness that discourages overeating; this is mechanism-linked feedback, not off-target intolerance.
- **Predictions.** Carefully spaced IR/ER regimens separate “comfort” from “don’t-push-past-full,” producing thresholds in PROs (fullness and queasiness VAS) and reduced intake without persistent nausea.
- **First tests.** Oral PK with IR vs IR+ER; acute DIO intake studies with PROs and behavioral readouts; refine exposure to keep comfort as the default state.

Discussion: clearly labeled hypotheses

1) Defensive microbes → host satiety modulators.

2) Unimolecular polypharmacology can coordinate eating and reward.

- 3) Exposure timing can make “too-much-food” queasiness a protective on-target signal, not a side effect.
- 4) (Draft 2) GLP-1R allosteric modulation can function as a supportive pillar that helps link endogenous incretin physiology to the multi-node scaffold without reproducing injectable GLP-1 side-effect burdens.

All require experimental confirmation.

Translational & regulatory path (high-level)

After 90 days (gate-dependent):

- Lead selection from the derivative family based on node balance, ADME, and early safety.
- Formulation enablement (salts/SDD) and PBPK to finalize IR/ER prototypes.
- Targeted bioanalysis integrated with PD panels (ghrelin, POMC markers, calorimetry; appetite/queasiness VAS).

IND-enabling (GLP):

- Safety pharmacology (CV, CNS, respiratory), repeat-dose tox in two species with TK, and DDI (CYP/TDI, transporters).
- CMC: scalable route, impurity profile, solid-form selection, stability, and specification suitable for FIH.

First-in-human (concept):

- SAD/MAD with ad libitum meal tests, indirect calorimetry, and PROs (fullness/queasiness VAS) to map the comfort vs boundary window and to confirm mechanism-consistent signals at tolerated exposures.
- Phenotype-guided exploration using the target-balance vectors described in the tunability/personalization section.

Glossary (selected entries, updated where relevant)

GLP-1 / GIP: Incretin hormones targeted by many current anti-obesity agents. In this program, GLP-1R is treated as a supportive node: Draft 2 docking suggests the lead scaffold acts as a positive allosteric modulator at a TM3–4–5 interface, amplifying endogenous GLP-1 rather than serving as a classical orthosteric agonist. [42–45, 47]

MC3R / MC4R / MC5R: Melanocortin receptors; MC4R agonism is primary for satiety and energy expenditure, with MC3R/MC5R as supportive nodes. See Figure 1.

GHSR (Ghrelin receptor): Orexigenic (hunger-promoting) GPCR; antagonism is intended to reduce meal initiation and cravings.

OPRD1 / OPRM1 (δ/μ -opioid receptors): Reward-pathway GPCRs; modulation aims to lower hedonic drive and reduce palatable food reinforcement.

C3aR (Complement C3a Receptor): Immune receptor with emerging roles in adipose thermogenesis and inflammatory tone; treated as supportive (non-limiting) in the mechanism.

HTR2C (5-HT_{2C} receptor): Serotonin receptor linked to appetite control; positioned to support adherence via exposure shaping rather than as the primary driver.

Unimolecular (vs combo): A single molecule delivers multi-node pharmacology, simplifying dosing and exposure control vs multi-drug combinations; here extended in Draft 2 to include GLP-1R allosteric support as a fourth pillar alongside MC4R, GHSR, and OPRM1.

(Other glossary entries from Draft 1 remain unchanged and are retained for completeness.)

References (validated and prioritized)

Attribution note: External technology signal attributed to Los Alamos National Laboratory (LANL) is drawn from Biosortia media/podcast summaries. Formal collaboration details are shared under CDA.

1. Cryan JF, Dinan TG. Mind-Altering Microorganisms: The Impact of the Gut Microbiota on Brain and Behaviour. *Nature Reviews Neuroscience*. 2012;13(10):701–712.
2. Mo R, et al. Evolutionary Principles of Bacterial Signaling Capacity and Complexity. *mBio*. 2022;13(5):e0147522.
3. Piddock LJV. Understanding the Basis of Antibiotic Resistance: Focus on the Bacterial Membrane. *Clinical Microbiology and Infection*. 2016;22(3):214–216.
4. Huddleston JR. Horizontal Gene Transfer in the Human Gastrointestinal Tract: Potential Spread of Antibiotic Resistance Genes. *Infection and Drug Resistance*. 2014;7:167–176.
5. Wikoff WR, et al. Metabolomics Analysis Reveals Large Effects of Gut Microflora on Mammalian Blood Metabolites. *PNAS*. 2009;106(10):3698–3703.
6. Furness JB. The Enteric Nervous System and Neurogastroenterology. *Nature Reviews Gastroenterology & Hepatology*. 2012;9(5):286–294.
7. Davies J, Davies D. Origins and Evolution of Antibiotic Resistance. *Microbiology and Molecular Biology Reviews*. 2010;74(3):417–433.
8. Martin WF, et al. Endosymbiotic Theories for Eukaryote Origin. *Philosophical Transactions of the Royal Society B*. 2015;370(1678):20140330.
9. Brito IL, et al. Mobile Genes in the Human Microbiome Are Structured from Global to Individual Scales. *Nature*. 2016;535(7612):435–439.
10. Degnan PH, et al. Factors Associated with the Diversification of the Gut Microbial Communities within Chimpanzees from Gombe National Park. *PNAS*. 2012;109(34):14523–14528.
11. Foster KR, et al. The Evolution of the Host Microbiome as an Ecosystem on a Leash. *Nature*. 2017;548(7665):43–51.
12. Duplicate of #2 (Mo et al., 2022).
13. Trosko JE. Evolution of Microbial Quorum Sensing to Human Global Quorum Sensing: An Insight into How Gap Junctional Intercellular Communication Might Be Linked to the Global Well-Being of Multicellular Organisms. *Biology*. 2016;5(2):29.
14. Lopes-Marques M, et al. GBA3: A Polymorphic Pseudogene in Humans That Experienced Repeated Gene Loss during Mammalian Evolution. *Scientific Reports*. 2020;10:13119.
15. Cone RD. Anatomy and Regulation of the Central Melanocortin System. *Nature Neuroscience*. 2005;8(5):571–578.
16. Cryan JF, et al. Gut Microbiota: The Neglected Endocrine Organ. *Molecular Endocrinology*. 2014;28(8):1221–1236.
17. Leitão-Gonçalves R, et al. Commensal Bacteria and Essential Amino Acids Control Food-Choice

Behavior and Reproduction. PLoS Biology. 2017;15(4):e2000862.

18. Coleman BD, et al. Evolutionary Conservation of a GPCR-Independent Mechanism of Trimeric G-Protein Activation. Molecular Biology and Evolution. 2016;33(3):820–834.

19. Garcia-Marcos M. Heterotrimeric G-Protein Signaling without GPCRs: The Gα-Binding-and-Activating (GBA) Motif. Journal of Biological Chemistry. 2024;300(1):105535.

20. Furness JB, Bravo DM. Humans as cucinivores: Comparisons with Other Species. Journal of Comparative Physiology B. 2015;185(8):825–836.

21. Cross-reference: See #4 (Huddleston 2014) for HGT in the GI tract.

22. Liu J, et al. Gaucher Disease Gene GBA Functions in Immune Regulation. PNAS. 2012;109(25):10018–10023.

23. Fan J, et al. Gaucher Disease Protects against Tuberculosis. PNAS. 2023;120(7):e2225995120.

24. Rutledge PJ, Challis GL. Discovery of Microbial Natural Products by Activation of Silent Biosynthetic Gene Clusters. Nature Reviews Microbiology. 2015;13(8):509–523.

25. Scherlach K, Hertweck C. Triggering Cryptic Natural Product Biosynthesis in Microorganisms. Organic & Biomolecular Chemistry. 2009;7(9):1753–1760.

26. Bertrand S, et al. Metabolite induction via microorganism co-culture: a potential way to enhance chemical diversity for drug discovery. Biotechnology Advances. 2014;32(6):1180–1204.

27. Marmann A, et al. Co-Cultivation—A Powerful Emerging Tool for Enhancing the Chemical Diversity of Microorganisms. Marine Drugs. 2014;12(2):1043–1065.

28. Scalbert A, et al. The Food Metabolome: A Window over Dietary Exposure. American Journal of Clinical Nutrition. 2014;99(6):1286–1308.

29. Patti GJ, et al. Metabolomics: The Apogee of the Omics Trilogy. Nature Reviews Molecular Cell Biology. 2012;13(4):263–269.

30. Johnson CH, et al. Metabolomics: Beyond Biomarkers and towards Mechanisms. Nature Reviews Molecular Cell Biology. 2016;17(7):451–459.

31. Dunn WB, et al. Procedures for Large-Scale Metabolic Profiling of Serum and Plasma Using GC and LC Coupled to MS. Nature Protocols. 2011;6(7):1060–1083.

32. Bäckhed F, et al. The Gut Microbiota as an Environmental Factor That Regulates Fat Storage. PNAS. 2004;101(44):15718–15723.

33. Turnbaugh PJ, et al. The Effect of Diet on the Human Gut Microbiome: A Metagenomic Analysis in Humanized Gnotobiotic Mice. Science Translational Medicine. 2009;1(6):6ra14.

34. Cani PD, et al. Gut Microbiota Fermentation of Prebiotics Increases Satiety and Incretin Gut Peptide Production. American Journal of Clinical Nutrition. 2009;90(5):1236–1243.

35. Nejman D, et al. The Human Tumor Microbiome Is Composed of Tumor Type-Specific Intracellular Bacteria. Science. 2020;368(6494):973–980.

36. Singh SV, et al. Molecular Signaling during Cross Talk between Gut–Brain Axis Regulation and Progression of Irritable Bowel Syndrome: A Comprehensive Review. World Journal of Clinical Cases. 2023;11(19):4458–4476.

37. Demain AL, Sanchez S. Microbial Drug Discovery: 80 Years of Progress. Journal of Antibiotics. 2009;62(1):5–16.

38. Harvey AL, et al. The Re-Emergence of Natural Products for Drug Discovery in the Genomics Era. Nature Reviews Drug Discovery. 2015;14(2):111–129.

39. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs (1981–2019). Journal of Natural Products. 2020;83(3):770–803.

40. Donia MS, Fischbach MA. Small Molecules from the Human Microbiota. Science.

2015;349(6246):1254766.

41. Biosortia—Media & Podcasts attributed to LANL technology validation (company sources).

42. Müller TD, et al. The New Biology and Pharmacology of Glucagon. *Physiological Reviews*. 2017;97(2):721–766.

43. Wilding JPH, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *New England Journal of Medicine*. 2021;384(11):989–1002.

44. Rodgers RJ, et al. Melanocortins: Multiple Actions and Therapeutic Potential. In: *Melanocortins. Advances in Experimental Medicine and Biology*. 2010;681:93–106.

45. Drucker DJ. Mechanisms of Action and Therapeutic Application of GLP-1. *Cell Metabolism*. 2018;27(4):740–756.

46. Ma L, et al. Adipsin and adipocyte-derived C3aR1 regulate thermogenic fat in a sex-dependent fashion. *JCI Insight*. 2024;9(11):e178925.

47. Lau J, et al. Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide: A Long-Acting Glucagon-Like Peptide-1 Receptor Agonist with Improved Pharmacokinetic Properties. *Journal of Medicinal Chemistry*. 2015;58(18):7370–7380.

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