ELSEVIER

Check for updates

Feature

Accelerating the orphan GPCR pipeline: GPR149 as a case study in dual-domain target validation

Michael A.S. Guth *

High failure rates in drug development for central nervous system (CNS) and metabolic diseases frequently stem from a lack of knowledge about their selected drug targets. With unknown ligand chemistry, orphan G-protein-coupled receptors (GPCRs) represent high-risk, but high-potential, high-reward opportunities for pharmaceutical development. Here, I describe a framework for de-risking such targets using GPR149 as a prototype. The Four-Pillar Framework, combining high-throughput screening, cryo-electron microscopy (EM), artificial intelligence (AI)-driven chemistry, and parallel circuit validation, unexpectedly revealed the dual metabolic (weight loss) and CNS applications of GPR149. In the process, a seemingly intractable orphan receptor has become a development asset with blockbuster potential. This methodology offers a reproducible template for exploring the 'dark GPCRome', particularly for disorders in which metabolic dysfunction and CNS comorbidities co-present in real-world patient populations.

Keywords: orphan GPCR; GPR149; deorphanization; target validation; dual-domain therapeutics; drug discovery pipeline; cryo-EM; AI-driven chemistry; circuit-level pharmacology; incremental risk mitigation

Introduction: prioritizing and de-risking the dark GPCRome

The 'dark GPCRome' represents one of the most significant untapped frontiers in modern drug discovery. Although GPCRs remain the most successful class of drug targets, accounting for ~35% of all US Food and Drug Administration (FDA)-approved therapeutics and nearly 60% of current prescriptions, most of this success is concentrated within a well-trodden subset of this superfamily.[(p1),(p2)] Most approved agents target the Class A (rhodopsin-like) subfamily, characterized by the seven-transmembrane helix architecture and highly conserved signaling motifs, such as DRY, CWxP, and NPxxY.[(p3)] However, a modern drug discovery lens necessitates moving beyond these established targets to de-risk 'dark' receptors that deviate from these canonical sequences, where structural and functional gaps have historically stalled development.

GPR149 epitomizes this non-canonical challenge. Although phylogenetically classified within the rhodopsin-like subfamily, GPR149 lacks the crucial charged residues of the hallmark Asp-Arg-Tyr (DRY) motif, featuring instead a divergent ERY triplet.[(p4)] This specific substitution at the 3.50 position (Ballesteros–Weinstein numbering) is not merely a sequence variation; it likely dictates high constitutive activity and unconventional G-protein coupling of the receptor.

Despite being cloned nearly a quarter-century ago (initially as PGR10), GPR149 remains a classic orphan, trapped in the

https://doi.org/10.1016/j.drudis.2026.104678

'valley of death' between academic phenotypic discovery and commercial R&D advancement.[p5]

The productivity paradox: Eroom's Law

This stagnation is not merely a function of difficult biology. It reflects a well-documented phenomenon known as 'Eroom's Law' ('Moore's Law' spelled backward). First articulated during the early 2010s, Eroom's Law describes the observation that the number of new drugs approved per billion dollars spent on pharmaceutical R&D has halved approximately every 9 years since 1950. This trend persists despite, or perhaps because of, technological advances in screening, computing, and molecular biology. The drivers include what has been termed the 'better than the Beatles' problem (new drugs must compete against an ever-improving catalog of effective generics), increasing regulatory caution, diminishing returns from brute-force screening approaches, and the tendency to simply allocate more resources to failing strategies rather than rethinking the underlying logic of discovery.[p1],[p2],[p3]

Orphan GPCRs sit at the epicenter of this challenge. They offer high-reward opportunities not simply because they are unexplored, but because their anatomical expression patterns, strategically enriched in hypothalamic feeding circuits, mesolimbic reward pathways, and glial populations governing myelination, position them as master regulators of physiology with direct therapeutic relevance. GPR149 exemplifies this logic: its localization to the arcuate hypothalamus and nucleus accumbens, coupled with validated roles in energy homeostasis and oligodendrocyte progenitor cell (OPC) differentiation, transforms an orphan receptor from a biological mystery into a strategic asset. Yet, this promise carries correspondingly high risk because of non-canonical signaling motifs, unknown ligand chemistry, and uncertain clinical translatability. Therefore, a paradigm shift is required: one that treats deorphanization not as a sequential hunt for a ligand but as an integrated, parallelized de-risking campaign.

A paradigm shift in target validation

Historically, deorphanization has been a step-by-step process hampered by long timelines and high failure rates. Final deorphanization occurred, in part, due to luck. Today, a paradigm shift is possible through the combination of disruptive technologies: multiplexed functional assays, AI-driven *de novo* design, and cryo-electron microscopy (cryo-EM). By enabling near-atomic-resolution imaging of fragile GPCR complexes in their native states without the need for crystallization, cryo-EM, coupled with generative AI, allows researchers to visualize dynamic biological mechanisms in action. Together, these tools offer the potential to methodically de-risk the entire biology of a target simultaneously, rather than simply hunting for a ligand.

GPR149: a prototype for dual-domain success

GPR149 is an ideal model because of its precise anatomical localization in circuits governing reward and energy homeostasis, specifically the nucleus accumbens in rodents (and potentially in humans) and the arcuate hypothalamus in humans.[p5],[p6] Phenotypic findings in Gpr149-null animals, which exhibit improved insulin sensitivity and altered energy homeostasis, provide the initial metabolic impetus.[p8] However, the clinical relevance of GPR149 is anchored by high-resolution human transcriptomic data, which confirm its expression in hypothalamic energy-management nodes, providing the species-specific justification required for an industrial de-risking campaign.[p5]

Beyond metabolism, GPR149 is a validated regulator of OPC function, suggesting a parallel role in CNS remyelination.[p9] In pathological states, GPR149 signaling contributes to the inhibitory environment that prevents OPCs from maturing into functional, myelin-producing oligodendrocytes, a hallmark of chronic demyelinating diseases such as multiple sclerosis (MS). This positions GPR149 not merely as a metabolic regulator but as a true 'neuro-metabolic-glial platform', a single target addressing both the synaptic 'firing' of reward circuitry and the structural 'wiring' of white matter integrity.

The integrated Four-Pillar Framework

I contend that GPR149 should be viewed as a test case for a novel, parallelized development logic rather than a standalone biological conundrum. To direct pharmaceutical strategy, I propose a testable mechanistic paradigm based on constitutive activity and $G_{i/o}$ coupling. More significantly, I introduce an Integrated Four-Pillar Framework designed to condense years of sequential study into a targeted, milestone-driven campaign. This method systematically transforms basic biological questions into de-risked development assets, positioning GPR149 as a first-in-class, dual-domain target and providing a reproducible blueprint for the dark GPCRome.

Creating the target product profile: a mechanistic framework for GPR149

Constructing the functional blueprint

A target product profile (TPP) reduces risk in drug development by serving as a strategic blueprint that aligns clinical, regulatory, and commercial goals from the outset. By specifying desired safety, efficacy, and product features, and distinguishing minimal from preferred characteristics, a TPP enables early, data-driven 'go/no-go' decisions that prevent costly late-stage failures. As a 'living document', the TPP evolves with emerging scientific insights. For an orphan receptor such as GPR149, constructing this profile begins not with a ligand but with a testable mechanistic hypothesis derived from bioinformatics and comparative pharmacology. This framework transforms a molecular mystery into specific, addressable questions that guide assay selection, generative chemistry strategy, and early *in vivo* validation.

For GPR149, converging lines of evidence suggest a compelling, actionable model: a constitutively active $G_{i/o}$-coupled receptor. I hypothesize that GPR149 exerts inhibitory tone in key neuronal and glial circuits through canonical signaling, inhibiting adenylyl cyclase, lowering cAMP, and modulating transmitter release. Although this model remains a working hypothesis, it provides the necessary framework for a focused discovery effort. The phenotypic signposts for this 'always-on' inhibitory tone are found in recent metabolic and behavioral studies. Whereas data published by Wyler *et al.* provide the metabolic coordinates,[p6] recent work by Agirman *et al.* provides the functional roadmap.[p7] By identifying a specific cluster of GPR149-expressing neurons in the hypothalamus that 'gate'

stress-induced emotional eating, their findings suggest that GPR149 signals the conversion of gut-derived metabolic stress into maladaptive feeding behaviors.

The pharmacological 'North Star': biased inverse agonism

This biological 'gate' directly dictates the medicinal chemistry approach. Whereas knockout models show a prevention of maladaptive eating, it is inferred that the wild-type receptor provides the persistent, baseline inhibitory tone that drives the pathology. Consequently, the search for tool compounds must prioritize G-protein biased inverse agonists designed to suppress this basal signaling while decoupling it from pathways that promote receptor internalization: (i) G-protein-biased inverse agonism: unlike classical antagonists that merely block ligand-mediated activation, inverse agonists are required to suppress the constitutive $G_{i/o}$ tone of GPR149 below baseline, effectively 'quieting' the receptor to recapitulate the beneficial knockout phenotype; (ii) mitigating β-arrestin-mediated internalization: by designing biased compounds that circumvent β-arrestin recruitment, GPR149 receptors remain membrane localized. This preserves surface expression and prevents the receptor sequestration typically triggered by sustained GPCR modulation; and (iii) ensuring therapeutic durability: maintaining receptor availability is vital for long-term efficacy. This biased approach preserves GPR149 sensitivity and prevents the diminishing returns that frequently necessitate dose escalation in chronic metabolic treatments.

This selection logic defines the pharmacological 'North Star' for the GPR149 program. Rather than seeking a generic binder, the campaign targets a precision tool that actively retunes receptor tone while preserving long-term responsiveness. As elaborated in Pillar III (Generative Chemistry), this bias-engineered profile transforms GPR149 modulation from acute symptom management into durable disease modification. By ensuring the cell does not 'hide' the receptor, it is possible to create a more predictable and valuable clinical asset, a distinction with direct positive implications for health economics valuation and payer reimbursement.

Structural divergence: why GPR149 defies canonical classification

To move beyond speculative modeling, I anchored this structural analysis in two distinct, expert-curated repositories. High-fidelity sequence records from UniProt (Accession Q86SP6), the global gold standard for protein annotation, and GPCRdb, the academically led resource at the University of Copenhagen specializing in structural alignments, confirm a striking architectural departure. Human GPR149 does not conserve the canonical Class A 'motifs' typically found at the TM3-ICL2 and TM7-helix 8 boundaries. These recurring structural themes, such as DRY (Asp-Arg-Tyr) and NPxxY (Asn-Pro-x-x-Tyr), are functional signatures; when altered, they signal a non-canonical architecture that mandates empirical characterization over sequence-based inference. Although GPR149 is taxonomically a Class A receptor, it lacks the standard 'molecular switches' that define the activation logic for the rest of the family.

In most Class A GPCRs, the DRY motif at the base of the third transmembrane (TM3) helix serves as the primary 'on/off' switch. The Arginine (R) residue usually forms an 'ionic lock' that stabilizes the inactive state until ligand binding causes a conformational change. GPR149 replaces this with an ERY triplet (residues 130–132). Whereas Glutamic acid (E) and Aspartic acid (D) are chemically similar (both are negatively charged), this specific substitution often correlates with constitutive activity. Practically, the GPR149 receptor can be 'leaky' or 'always on', maintaining a baseline tonic signal even in the absence of a ligand.

The departure at the seventh transmembrane helix (TM7) is even more substantial. The canonical NPxxY motif usually serves as an activation pivot that allows the receptor to change shape and signal to the interior of the cell. GPR149 utilizes a DPxxF variant (residues 301–305) instead. Replacing Asparagine (N) with Aspartate (D) and Tyrosine (Y) with Phenylalanine (F) removes a crucial hydroxyl group (–OH), fundamentally altering the internal hydration layer of the receptor and its *G*-protein coupling interface.

Structural and functional implications: not broken, but specialized

These non-canonical features establish GPR149 as a member of a unique Class A subset. I treat these motifs not as deficits, but as functional specializations. Similar acidic-Arg-Tyr variants are established activation microswitches in other functional GPCRs, including several orphan receptors. GPR149 is not 'broken' but is specialized. These variants represent a functional specialization rather than a loss of function or structural defect.

By grounding my structural hypothesis in curated records from UniProt and GPCRdb (databases maintained through expert annotation rather than unverified pipelines), I move beyond speculative modeling. This structural ambiguity necessitates the integrated Four-Pillar Framework, a methodology designed to override inferred coupling with path-agnostic assays and high-resolution structural characterization. This intelligence-driven discovery logic replaces single-pathway assumptions with the parallelized validation required to transition GPR149 from a 'dark' orphan to a viable clinical asset.

From hypothesis to execution: the inverse agonist paradigm

The search for tool compounds requires a molecular engineering strategy that prioritizes G-protein-biased inverse agonists. These must be specifically designed to suppress basal signaling while decoupling it from the β-arrestin pathways that promote receptor internalization. This paradigm is validated through a two-stage protocol: (i) *in vitro*: quantifying constitutive activity and inverse agonist efficacy in recombinant systems; and (ii) *in vivo*: testing whether inverse agonists, or chemogenetic tools (*Gi*-DREADDs) used as pharmacological surrogates, recapitulate the 'lean' and 'anti-binge' phenotypes in relevant metabolic models.

This parallel-track validation (i.e., biology running concurrently with chemistry) is the cornerstone of the de-risking strategy. Together, these predictions create the testable TPP summarized in Figure 1, which aligns the strategic expression of GPR149 with the key knowledge gaps that guide the de-risking process.

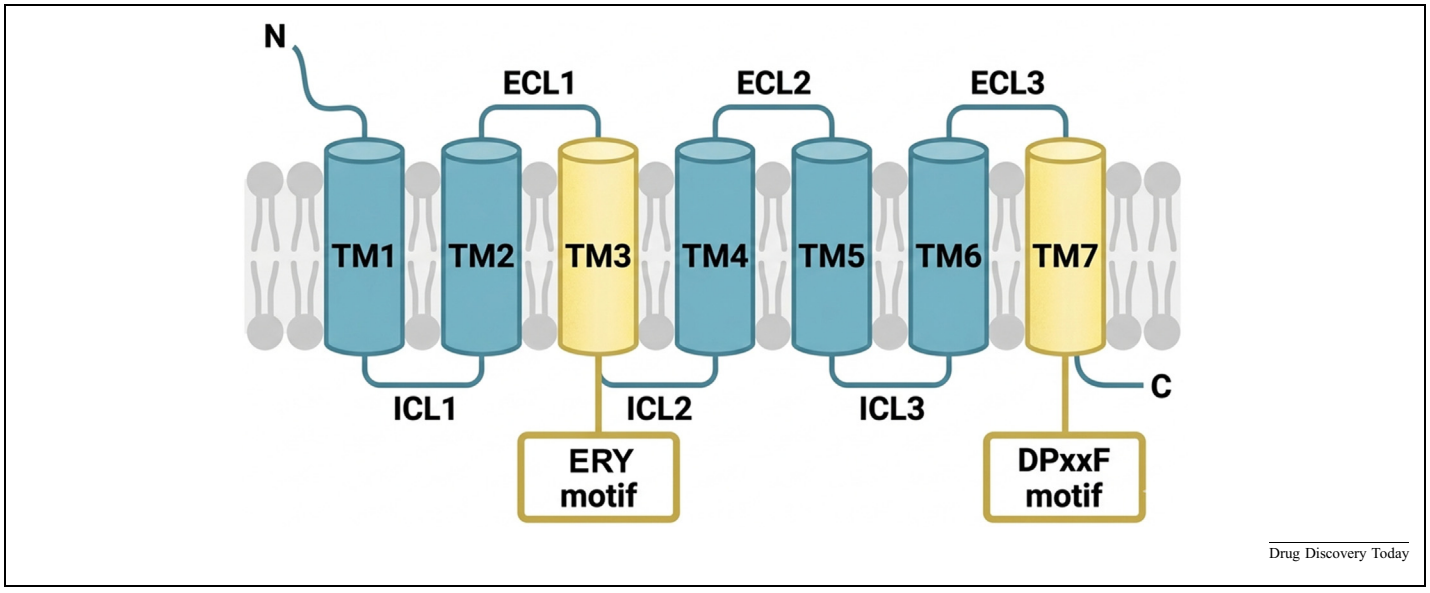

FIGURE 1

GPR149 structural architecture. Topological representation and conserved microswitch motifs of the orphan G-protein-coupled receptor (GPCR) GPR149. The diagram follows a strict alternating zigzag path. **(a)** ERY Motif (TM3): replaces the canonical DRY sequence; a crucial determinant of signaling bias. **(b)** DPxxF motif (TM7): replaces the NPxxY sequence. These structural signatures suggest that GPR149 prioritizes non-canonical pathways (e.g., β-arrestin) over traditional cAMP-mediated messengers. Experimental validation of these predicted signaling preferences remains a priority for future studies.

Ligand class agnosticism: a strategic imperative for screening

Conflicting structural clues (a large N-terminal region suggestive of peptide binding, yet phylogenetic links to lipid-sensing receptors) preclude any a priori assumption about the ligand class of GPR149. Therefore, the initial functional screen must be agnostic, interrogating diverse libraries that include peptides, lipids, metabolites, and synthetic small molecules. Even a low-potency surrogate ligand from any class would provide a crucial tool: a starting point or scaffold for medicinal chemistry optimization toward a high-affinity probe suitable for structural studies, and a first test of whether GPR149 signals through the hypothesized pathways. This agnostic strategy, outlined in Figure 2, directly tests the proposed hypotheses, including whether GPR149 exhibits baseline signaling tone. Constitutive activity is measured as differences in cAMP or β-arrestin recruitment between receptor-expressing and control cells under basal conditions, with no ligand added. If GPR149-expressing cells show different signaling compared with controls in the absence of any stimulus, that difference represents constitutive activity. The gold standard to test for constitutive activity is the inverse agonist test; (i) detect baseline difference: show that GPR149-expressing cells have lower cAMP compared with controls (for $G_{i/o}$) or higher baseline β-arrestin recruitment; (ii) reverse with inverse agonist: show that a known inverse agonist (once discovered) reduces this baseline signal back toward control levels. This two-step pattern confirms that the baseline difference is receptor-mediated rather than an artifact of overexpression.

The Integrated Four-Pillar Framework: From deorphanization to value

Converging technologies now support a parallel, Integrated Four-Pillar Framework that can move an orphan, such as GPR149, from mechanism unknown to mechanism mapped within a compressed timeline. The goal is not only to identify a ligand, but also to map signaling architecture, structural blueprint, and circuit-level function in an ordered way. This framework compresses years of sequential work into a milestone-driven campaign with explicit go/no-go gates.

Pillar I: high-throughput functional screening: functional bias and agnostic discovery

Agnostic functional screening aims to identify compounds that modulate GPR149 without any assumptions about its signaling preferences. To gain a comprehensive understanding of the pharmacological profile of GPR149, I recommend a dual-track assay approach. In modern GPCR drug discovery, an 'unbiased' screen usually refers to a primary, agnostic search for any activity. However, the high-value differentiation for a target such as GPR149 lies in functional bias, specifically selecting for $G_{i/o}$ over β-arrestin to maximize therapeutic effect while minimizing side effects: (i) cAMP inhibition: based on predicted $G_{i/o}$ coupling (notwithstanding the absence of a canonical DRY motif) functional cAMP inhibition assays serve as the primary method to detect both ligand-mediated and basal (constitutive) activity. This functional focus allows for the identification of inverse agonists capable of modulating high constitutive tone of a receptor; and (ii) *PRESTO-Tango:* this pathway-agnostic β-arrestin recruitment assay[p10] is utilized as a crucial filter. By identifying ligands with biased signaling profiles, researchers can more easily select candidates that favor $G_{i/o}$-mediated circuit recalibration while minimizing β-arrestin-mediated internalization, a key strategy for avoiding the tachyphylaxis and 'rebound' weight gain seen in systemic incretin therapies.

The lack of reported G-protein coupling for GPR149 in the current literature does not necessarily indicate a lack of function, but rather the limitations of standard

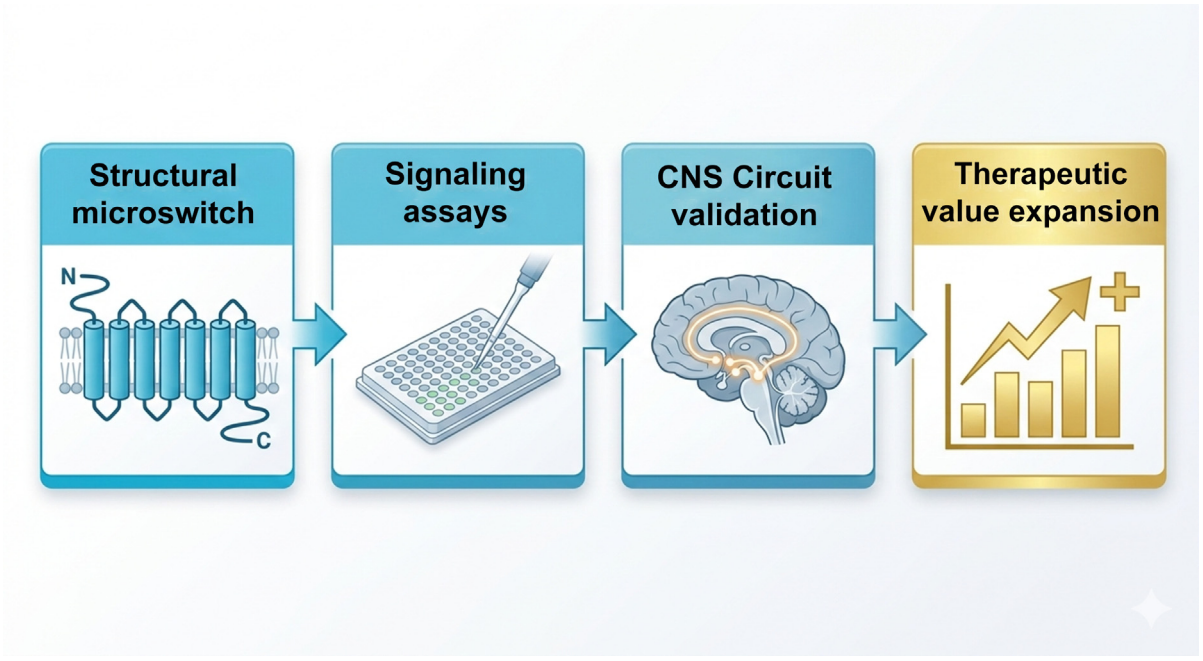

FIGURE 2

Integrated therapeutic expansion framework. Strategic framework for GPR149 deorphanization and evidence-led value expansion. Structural microswitch: defines signaling bias to inform assay selection, preventing false negative conclusions from canonical readouts. Signaling assays: application of path-agnostic readouts (e.g., BRET or PRESTO-Tango). Central nervous system (CNS) circuit validation: mapping of GPR149 neurons within metabolic and motivational circuits [hypothalamus to ventral tegmental area (VTA)]. Therapeutic value expansion: represents the accrual of real-world evidence to support indication expansion beyond obesity into addictive disorders and neuroplasticity.

screening modalities. The inherent difficulties in characterizing orphan GPCRs (unknown ligands, constitutive activity, and the need for specialized approaches) underscore the 'dark' nature of this orphan.[p11] This 'negative evidence' suggests that GPR149 utilizes non-canonical signaling or has high constitutive activity that masks traditional readouts, necessitating the path-agnostic Integrated Four-Pillar Framework proposed here.

This experimental uncertainty is addressed in Figure 3, which uses a mandatory troubleshooting loop to switch from canonical cAMP to non-canonical (β-arrestin/ERK1/2) readouts.

Library diversity is essential. Screens must examine peptides, lipids, and metabolites alongside synthetic small molecules. Even a low-potency 'hit' offers a vital chemical scaffold for stabilizing the receptor in structural studies.

Pillar II: structural biology: structural intelligence for rational design

Cryo-EM has revolutionized GPCR structural analysis, frequently surpassing X-ray crystallography by resolving active-state complexes in near-physiological conditions without the requirement for stable crystals.[p12] For GPR149, resolving the apo-state or a nanobody-stabilized structure is the definitive requirement for structure-based drug design: (i) Apo-state resolution: Capturing the 'unbound' configuration is crucial to confirming whether the non-canonical ERY motif of GPR149 induces a naturally 'open' (constitutively active) state.[p13] This structural evidence would validate the requirement for an inverse agonist to 'close' the receptor and release the inhibitory brake on satiety neurons, data that cannot be reliably inferred from sequence alone; (ii) nanobody-stabilized mapping: because GPCRs sample multiple conformational states on sub-millisecond timescales, they remain challenging targets for high-resolution mapping.[p13] Utilizing nanobodies as molecular staples locks GPR149 into specific active or inactive orientations,[p14] providing the 3D map required for precise lead optimization.[p15],[p16]

The structural deorphanization of GPR149 is no longer a purely theoretical exercise; recent cryo-EM successes with related 'dark' orphans demonstrate the technical feasibility of this approach.[p11],[p17] By anchoring rational design in empirical structural data, Pillar II identifies allosteric pockets often invisible to homology modeling and mitigates the 'hallucination' risks inherent in predicting the behavior of non-canonical motifs, such as ERY and DPxxF.

Whereas cryo-EM captures static snapshots, molecular dynamics (MD) simulations are required to reveal the conformational landscapes and activation mechanisms that unfold over time.[p18] For GPR149, MD simulations explore how divergent motifs influence the transition between inactive and active states, identifying transient binding pockets and guiding mutagenesis for structural validation.[p19] These simulations further inform bias engineering by modeling interactions that stabilize conformations favoring $G_{i/o}$-coupling over β-arrestin recruitment.[p20],[p21] Consequently, a physical 3D structure represents the ultimate de-risking milestone, transitioning the program from informed guessing to true structure-based drug design.

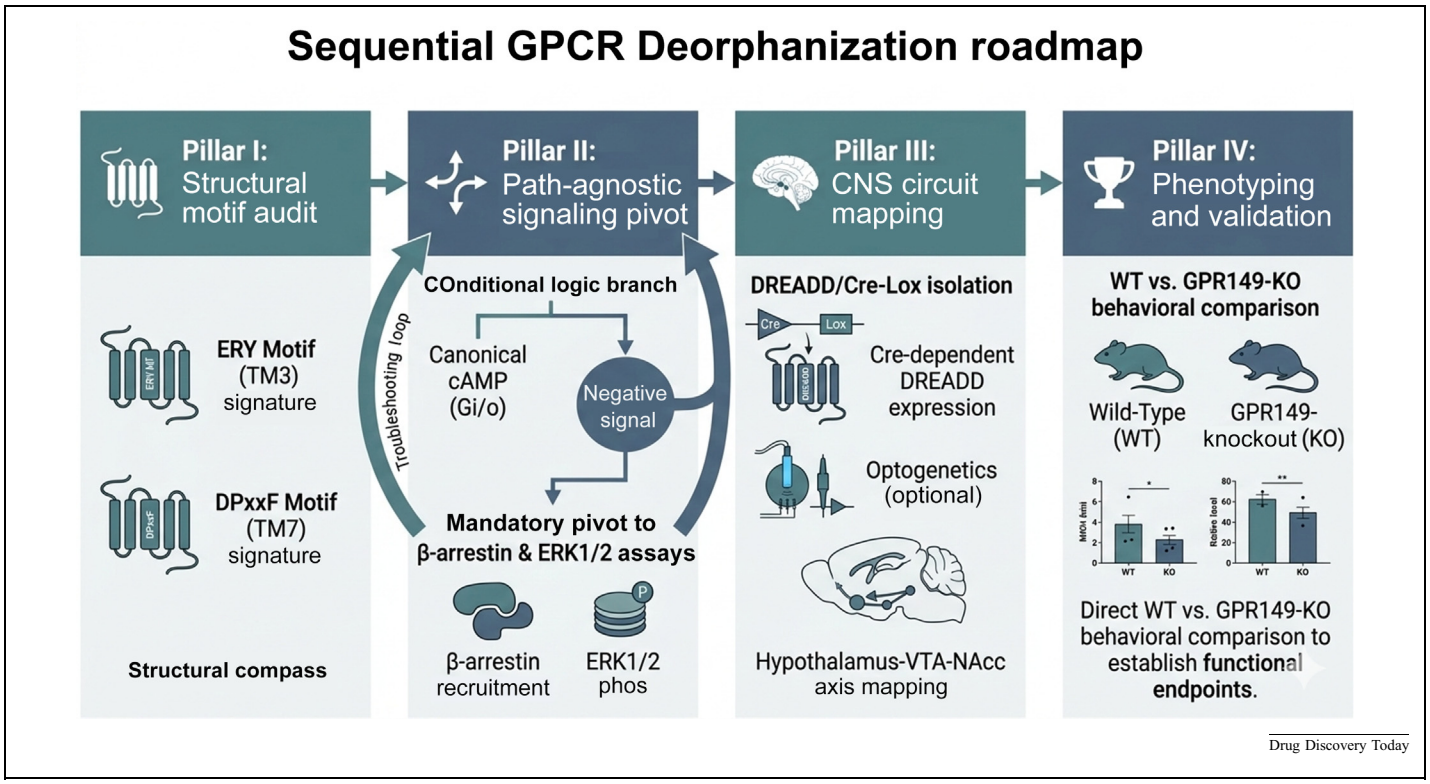

FIGURE 3

The integrated deorphanization roadmap and troubleshooting framework. Operational flowchart for GPR149 deorphanization and functional validation. This iterative protocol addresses technical bottlenecks in dark G-protein-coupled receptor (GPCR) research by prioritizing structural-informed assay selection over canonical assumptions. Structural motif audit: the discovery process initiates with the identification of non-canonical motifs (ERY/DPxxF), which serve as a biological 'compass' for downstream signaling experiments. The signaling pivot and troubleshooting loop: to mitigate the high risk of false negatives in traditional cAMP-centric screens, the framework incorporates a mandatory feedback loop. If canonical assays fail to detect a signal or exhibit low dynamic range because of high constitutive activity, the protocol triggers a shift to path-agnostic (β-arrestin) readouts, ensuring no tractable target is prematurely abandoned. *In vivo* circuit mapping: validated signaling data are translated into neural circuit models using Cre-Lox and DREADD systems to isolate GPR149-expressing neurons within the hypothalamus–ventral tegmental area (VTA)–nucleus accumbens (NAcc) axis. Phenotyping conclusion: the roadmap concludes with comparative behavioral phenotyping of wild-type (WT) versus GPR149-knockout (KO) mouse models. This direct comparison provides definitive proof-of-concept for the 'dual-domain' role of the receptor in both metabolic homeostasis and motivational salience.

Pillar III: AI-enabled generative chemistry: property-optimized design

With a high-resolution structural model, AI-powered generative chemistry shifts the focus from screening extant libraries to the *de novo* design of property-optimized scaffolds. This approach leverages machine learning to explore chemical space at an unmatched scale, utilizing improved molecular string representations to ensure the reliability and structural integrity of generated leads.[p22] By navigating this expanded chemical universe, generative modeling identifies novel chemotypes that might be overlooked by traditional medicinal chemistry intuition.[p23]

This 'search for beautiful molecules' balances structural novelty with synthetic accessibility and favorable absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles.[p23] The goal of Pillar III is not merely the identification of active ligands, but a property-optimized generative design that emphasizes $G_{i/o}$ bias. By integrating modules that predict metabolic stability and toxicity alongside expert medicinal chemistry feedback, the campaign iterates toward candidates with clinical relevance from the outset. These property-optimized leads are then prioritized for circuit-level validation and chemogenetic phenotyping, as detailed in Pillar IV.

Pillar IV: circuit-level validation: concurrent engineering and parallel-track de-risking

The ultimate test of any GPR149 mechanism occurs *in vivo*. A circuit-level validation program should run in parallel with molecular discovery, embodying a principle of concurrent engineering: biological proof-of-concept advances alongside chemistry, rather than waiting for a lead molecule to emerge.

This parallel-track approach addresses a fundamental inefficiency in traditional drug discovery. In conventional linear development, 'starting the biology' refers to the point where a lead compound exists and can be tested in animal models. This creates a sequential dependency: no molecule means no biological proof-of-concept, and biological failure late in the program means sunk chemistry costs.

With the dual-path framework, drug developers can validate the therapeutic impact of modulating GPR149 before a high-affinity ligand exists. Chemogenetic tools (*Gi*-DREADDs) can mimic receptor inhibition in GPR149-expressing neurons in the hypothalamus and nucleus accumbens (NAcc), providing crucial proof-of-concept for metabolic and behavioral efficacy in parallel with early chemistry

efforts.[p24] Specifically, this approach allows determination of whether silencing GPR149-expressing hypothalamic circuits via *Gi*-DREADDs can effectively block the stress-induced emotional eating behaviors recently mapped by Agirman *et al.*[p7]

This parallel-track methodology ensures that functional consequences and safety are understood at the systems level early, reducing late-stage attrition risk. The four pillars operate as an iterative loop: when cAMP-centric readouts are negative or ambiguous, the design explicitly pivots to β-arrestin and complementary assays rather than abandoning the target. This operational troubleshooting loop is summarized in Figure 3. By design, the framework delivers decisive biological intelligence and portfolio value whether a clinical candidate emerges, a concept known in business strategy as 'option value': even if the primary metabolic indication falters, the structural and circuit-level insights retain value for neurorepair or other indications.

GPR149 as a dual-domain target: the metabolic–CNS axis and the neuroplasticity framework

The ventral tegmental area (VTA)–NAcc circuit is the primary engine in the human brain for reward, motivation, and addiction. In this mesolimbic pathway, dopamine neurons in the VTA project to the NAcc to reinforce behaviors, process pleasure, and drive reward-seeking. However, in chronic obesity and drug and alcohol addiction, this circuit becomes hijacked. Dysregulation in VTA–NAcc signaling drives the maladaptive 'food/drug/alcohol addiction' phenotypes that make weight loss and sobriety notoriously difficult to maintain.

GPR149 serves as a molecular governor within this hijacked circuitry. Transcriptomic data place GPR149 precisely within these VTA, NAcc, and hypothalamic nodes that regulate energy balance.[p5],[p6] This anatomical positioning suggests that the receptor is strategically located at the functional bridge between metabolic state and motivated behavior, an intersection I define as the metabolic–CNS axis.

Within this framework, negative neuroplasticity is the therapeutic goal: correcting the maladaptive neural consolidations that perpetuate chronic obesity and addiction. By inducing negative neuroplasticity, a GPR149-targeted treatment aims to 'unlearn' these pathways, restore healthy homeostatic setpoints, and recalibrate satiety and sobriety signaling. Simultaneously, the role of GPR149 in the glial compartment, specifically, its support of OPC differentiation and remyelination, stabilizes the structural plasticity required for long-term recovery.

This integration of neuronal and glial function can be captured in a simple, powerful metaphor: 'firing' and 'wiring' (Table 1). This dual-domain approach aligns with broader industry trends, where multi-target strategies now represent the fastest-growing segment of the drug development pipeline.[p25]

Most metabolic drugs address only the 'firing', that is, the acute signaling of satiety and reward. By including the 'wiring' (glial-mediated repair of neural infrastructure) GPR149 modulation offers a mechanism for true disease modification. Expanding the therapeutic area from metabolic disease to a broader addiction/recovery and neuro-repair framework effectively triples the valuation of the assets and transforms GPR149 from a prospective 'weight loss drug' into a neuro-restorative platform.

In Health Economics & Outcomes Research (HEOR) terms, this distinction justifies a premium price point. A drug that does more than alleviate symptoms, that is, that repairs the underlying neural infrastructure damaged by chronic metabolic or substance-use stress, commands a different valuation compared with symptomatic treatments. Treating GPR149 a priori as a metabolic-CNS-glial target focuses the discovery program on true disease modification, embedding clinical differentiation and risk mitigation from the outset.

The glial mechanism: a validated differentiator and secondary therapeutic axis

The therapeutic potential of GPR149 extends beyond neuronal circuits. In murine models, its knockout accelerates OPC differentiation and remyelination through the MAPK/ERK pathway, a well-defined glial mechanism that positions the receptor as a brake on myelin repair.[p9]

Remyelination, the process by which OPCs generate new oligodendrocytes to reform myelin sheaths around damaged axons, is a natural repair mechanism that often fails in demyelinating diseases, such as MS. By releasing the inhibitory brake of GPR149, a therapeutic candidate could enhance this endogenous repair process, addressing the structural pathology underlying white matter damage.[p9]

White matter abnormalities are well documented not only in MS, but also across psychiatric disorders including schizophrenia, bipolar disorder, and major depression, where impaired connectivity contributes to symptom severity. Therefore, a mechanism that promotes remyelination holds relevance far beyond classic demyelinating diseases.

This dual-domain logic is no longer speculative. The proposed TPP is anchored in a dual therapeutic axis, supported by recent evidence characterizing GPR149 as a regulator of both energy homeostasis (demonstrated in a murine model)[p6] and CNS myelination,[p9] establishing a novel research frontier for multi-morbid metabolic and neurodegenerative conditions.

Although GPR149 shows promise in accelerating OPC differentiation, we must remain cognizant of the clinical setbacks faced by other glial-targeted orphans. Specifically, the GPR17 axis, previously considered a premier target for remyelination, was recently associated with a lack of sufficient therapeutic potential for standalone clinical development.[p26] This underscores the importance of the parallelized validation in the Four-Pillar Framework. GPR149 differentiates itself from the GPR17 precedent by occupying a 'Dual-Domain' niche. Unlike GPR17, which is primarily a glial-focused target, GPR149 modulates both the structural 'wiring' (myelination) and the acute 'firing' (reward-seeking behavior) of the CNS. This multifaceted profile suggests that GPR149 might succeed where single-domain targets have failed, provided that the discovery program utilizes the integrated validation proposed herein.

The convergence is striking: the same receptor that gates stress-induced eating in hypothalamic circuits[p7] also regulates the structural integrity of white matter.[p9] If a single compound can engage both pathways, the therapeutic reach could extend from obesity and addiction to MS and psychiatric diseases with white matter pathology, a profile that differentiates GPR149 from current incretin-based thera-

TABLE 1

GPR149 'firing' and 'wiring': a dual-domain functional framework.

Domain	Metaphor	Function	Role of GPR149
Neuronal	'Firing'	Synaptic signaling, reward processing, satiety	$G_{i/o}$-mediated inhibitory tone in VTA–NAcc and hypothalamic circuits
Glial	'Wiring'	Structural integrity, myelination, long-term repair	Brake on OPC differentiation and remyelination

pies (tirzepatide and semaglutide) and positions it for blockbuster potential.

Differentiation from GLP-1 agonists: the 'wiring' advantage

This distinction warrants explicit emphasis. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), the current standard of care for obesity, modulate synaptic 'firing': the acute signaling of satiety and reward. They recalibrate appetite signals but do not address the structural 'wiring' damage inflicted by chronic metabolic stress. The glial mechanism GPR149 offers a true disease-modifying advantage: repairing the neural infrastructure while recalibrating the signals. This positions GPR149 not as a 'me-too' incretin competitor but as a 'Blue Ocean' therapeutic platform addressing both the functional and structural dimensions of metabolic disease.

A significant documented limitation of current GLP-1 and GIP receptor agonists is the high rate of weight regain immediately following the discontinuation of therapy.[p27] This phenomenon suggests that although incretins provide profound acute chemical modulation, they do not induce the durable structural repair of hypothalamic circuits necessary for long-term maintenance. GPR149 offers a differentiated approach; by targeting the glial infrastructure ('wiring') in addition to acute reward signaling ('firing'), GPR149 modulators could offer more durable efficacy.

Thus, the framework of GPR149 as a receptor with inherent signaling tone, $G_{i/o}$-coupling, and a validated glial component creates a highly strategic TPP. This clarity dictates a cAMP-centric screening strategy, prioritizes inverse agonists, necessitates agnostic library screening, and establishes a two-domain efficacy profile, the essential foundation for de-risking GPR149 and executing an integrated campaign.

The incretin paradigm: a blueprint for GPR149 value expansion

The development of GLP-1RAs provides a concrete reference for the 'metabolic–CNS' logic. Originally developed for type 2 diabetes mellitus, these agents have redefined the TPP for metabolic disease by moving beyond simple glycemic control to include the modulation of weight loss, reward processing, and affective state.[p28],[p29] This evolution illustrates a crucial principle: receptors that bridge somatic and motivational physiology can deliver benefits far beyond their initial indications.

Lasting efficacy in the GLP-1 class is increasingly attributed to drug-induced negative neuroplasticity, that is, the structural weakening of maladaptive reward circuits, rather than acute metabolic fluctuations alone.[p30] This functional roadmap is directly applicable to GPR149. Despite the mechanistic divergence between Class B (GLP-1R) and non-canonical Class A receptors, GPR149 engagement offers a unique 'wiring' advantage: it could promote restorative neuroplasticity while counteracting the positive neuroplasticity (i.e., the 'locked-in' reinforcement) associated with comfort foods and addictive stimuli that drive chronic obesity.[p31]

For GPR149, this suggests a dual-domain therapeutic opportunity: a 'metabolic-neuro' profile where suppression of baseline $G_{i/o}$ tone not only recalibrates the homeostatic set-point, but also stabilizes the affective fluctuations, such as metabolic anxiety and compulsive 'food and drug noise', which frequently trigger relapse in chronic obesity or intoxication.

Mechanistic validation: the imidazole propionate axis and glial divergence

The framework of GPR149 as a metabolic–CNS bridge is supported by evidence that the microbial–hypothalamic axis drives maladaptive eating. The gut-derived metabolite imidazole propionate (ImP) acts on hypothalamic circuits to spur stress-induced eating,[p7] a hallmark of positive neuroplasticity. The unique spatial enrichment of GPR149 in the arcuate and ventromedial hypothalamus (VMH), coupled with its predicted $G_{i/o}$-mediated inhibitory signaling, positions it as the leading candidate for the ImP receptor. Identifying this molecular node via the Integrated Four-Pillar Framework transforms a biological mystery into a de-risked pharmaceutical asset.

Although the ImP–GPR149 axis addresses circuit-level behavior, GPR149 offers a distinct glial divergence not found in the incretin class. Beyond neuronal signaling, GPR149 is confirmed in OPCs, where it natively inhibits differentiation and remyelination.[p9] Therefore, a GPR149-targeted inverse agonist would provide a dual-action therapeutic effect: (i) neuronal ('firing'): recalibrating the VTA–NAcc reward circuitry and restoring homeostatic set-points; and (ii) structural ('wiring'): promoting remyelination to stabilize long-term recovery and provide neuroprotection.

This mechanistic duality expands the TPP into a Blue Ocean strategy (uncontested market space), differentiating the asset from the crowded GLP-1RA market and strengthening reimbursement prospects for multi-morbid populations.

Strategic implications: pipeline design, HEOR, and reimbursement logic

As a dual-domain target, GPR149 offers advantages over monotherapy targets and an improved path for payer reimbursement. The economic burden of illness in obesity, metabolic syndrome, and their CNS comorbidities, including addiction, depression, and white-matter pathology, is well documented. Direct medical costs, productivity loss, and caregiver burden for overweight and obesity alone exceeded US$2.5 trillion in the USA in 2019, with global costs projected to rise significantly by 2030.[p32]

Within this HEOR framework, GPR149 offers a unique value proposition. By addressing both the 'firing' (neuronal reward) and the 'wiring' (glial-mediated repair), a GPR149-targeted inverse agonist moves beyond the popular 'satiety-only' model of current incretin therapies. This dual-action approach targets the high-cost

'comorbidity tail' of addiction and neurodecline, providing a mechanism for true disease modification.

The premium price logic: infrastructure repair justifies higher QALY valuation

From a health economics perspective, 'infrastructure repair' (remyelination) commands a premium valuation over symptomatic relief. By demonstrating durable disease modification, measured as reduced relapse rates, sustained weight loss, and delayed disability progression, a GPR149-targeted therapy would justify higher quality-adjusted life year (QALY) thresholds. This aligns with payer demands for demonstrable reductions in total cost of care across obese, addicted, and demyelinating populations. The therapeutic goal is not merely symptom management, but a reduction in the aggregate economic burden of illness across comorbid populations.[p32]

A therapeutic drug that addresses both a metabolic anchor (e.g., obesity or metabolic syndrome) and its CNS sequelae (reward dysregulation, addiction liability, or neuroprotection in demyelination) supports a reimbursement logic that single-indication agents cannot. The dual metabolic–CNS treatment could support reduced downstream hospitalization, disability, and relapse across comorbid populations. However, value capture and resource utilization would depend on long-term durability of the effect of the drug.

Therefore, payer value demonstration hinges on evidence that GPR149 modulation drives negative neuroplasticity toward unhealthy choices and positive neuroplasticity toward healthy choices, restored setpoints, and glial repair, rather than symptomatic relief alone. For a drug that treats both a metabolic anchor and its CNS comorbidities, reimbursement logic rests on demonstrating that the agent reverses the maladaptive neural consolidations underlying chronic obesity and addiction, thereby reducing the aggregate economic burden of leading illnesses across large segments of the population.

Rational pipeline design and option value

Rational pipeline design follows from this HEOR logic. Early behavioral and metabolic assays must capture cross-domain efficacy and plasticity-relevant readouts that single-focus screens would miss, identifying compounds with a broader therapeutic profile from the outset. Bias engineering offers an additional differentiator: ligands can be deliberately designed with specific signaling profiles (e.g., $G_{i/o}$ versus β-arrestin) to independently modulate metabolic, motivational, and glial pathways, potentially yielding multiple development candidates from a single target.[p33] This approach increases the chances of finding compounds useful for obesity, addictive disorders, MS, and depression with comorbid metabolic syndrome, spreading regulatory and market risk across high-cost populations and diversifying the net present value of the asset.

The concept of option value is central here. In financial terms, an option is the right, but not the obligation, to pursue a future opportunity. In drug discovery, the integrated parallel-track strategy builds in option value: if ligand discovery for one indication stalls, structural and circuit-level insights continue to deliver fundamental biological value, preserving the potential of the asset for other applications. The glial mechanism provides a separate, validated therapeutic axis to pursue even if the metabolic indication encounters hurdles. This strategy ensures the discovery program remains a viable investment regardless of single-indication challenges.

These factors establish GPR149 as a prototype for next-generation GPCR targets the value of which is measured by integrated roles across physiological domains and by a reimbursement logic that rewards treatment of both metabolic anchor and CNS comorbidities. The progression from metabolic to addiction-related to neuroprotective indications is captured in Figure 4.

Integrated path to the clinic: circuit validation and disease modification

Translating GPR149 modulation into predictable clinical outcomes requires knowledge of which neural circuit is modulated followed by testing for disease modification. Neuroimaging studies have demonstrated that craving engages a distributed network of brain regions, including the brainstem, NAcc, VTA, dorsal striatum, amygdala, and prefrontal cortex (PFC).[p34],[p35] Durable disease modification grounds the mechanism of action in the circuit network that perpetuates or reverses disease and bridges cellular assays with whole-organism physiology. Three core principles guide this integration.

Circuit architecture determines functional impact: the path to negative neuroplasticity

The overall clinical effect of a ligand depends not only on its signaling bias (e.g., $G_{i/o}$ versus β-arrestin) but also on how that signaling propagates through specific hypothalamic and mesolimbic circuits that develop maladaptive patterns in obesity. Central to this energy-balance 'tug-of-war' are two specialized cell populations in the hypothalamic arcuate nucleus: anorexigenic proopiomelanocortin (POMC) neurons and orexigenic agouti-related peptide (AgRP) neurons.[p36] POMC neurons are the primary satiety-promoting cells of the brain; when activated by signals such as leptin or insulin, they release alpha-melanocyte-stimulating hormone to suppress food intake. By contrast, AgRP neurons are specialized hunger-promoting cells. Activated by energy deficit and ghrelin, these GABAergic/NPY neurons induce voracious eating by directly inhibiting POMC signaling and the paraventricular hypothalamus.[p37] In chronic obesity, this balance is often locked into the maladaptive positive neuroplasticity defined above, a state where AgRP overactivity and POMC suppression become the pathological baseline, reinforcing the cycle of weight gain.

The functional outcome of a $G_{i/o}$-biased GPR149 modulator, especially an inverse agonist aimed at reducing baseline inhibitory tone, will vary depending on the cellular context. Disinhibiting POMC neurons, which means removing the molecular brake on satiety, would promote homeostatic balance, whereas the same action in AgRP neurons could unintentionally increase hunger. Similarly, the effects on D1 versus D2 medium spiny neurons (MSNs) in the nucleus accumbens will determine whether the treatment shifts reward-seeking behavior or unintentionally amplifies it.[p38] D1- and D2-type MSNs in the NAcc are distinct, often complementary groups that regulate reward, motor functions, and learning behaviors. D1 MSNs, typically linked to promoting reward and motivation, and D2 MSNs, associated with aversion, work together

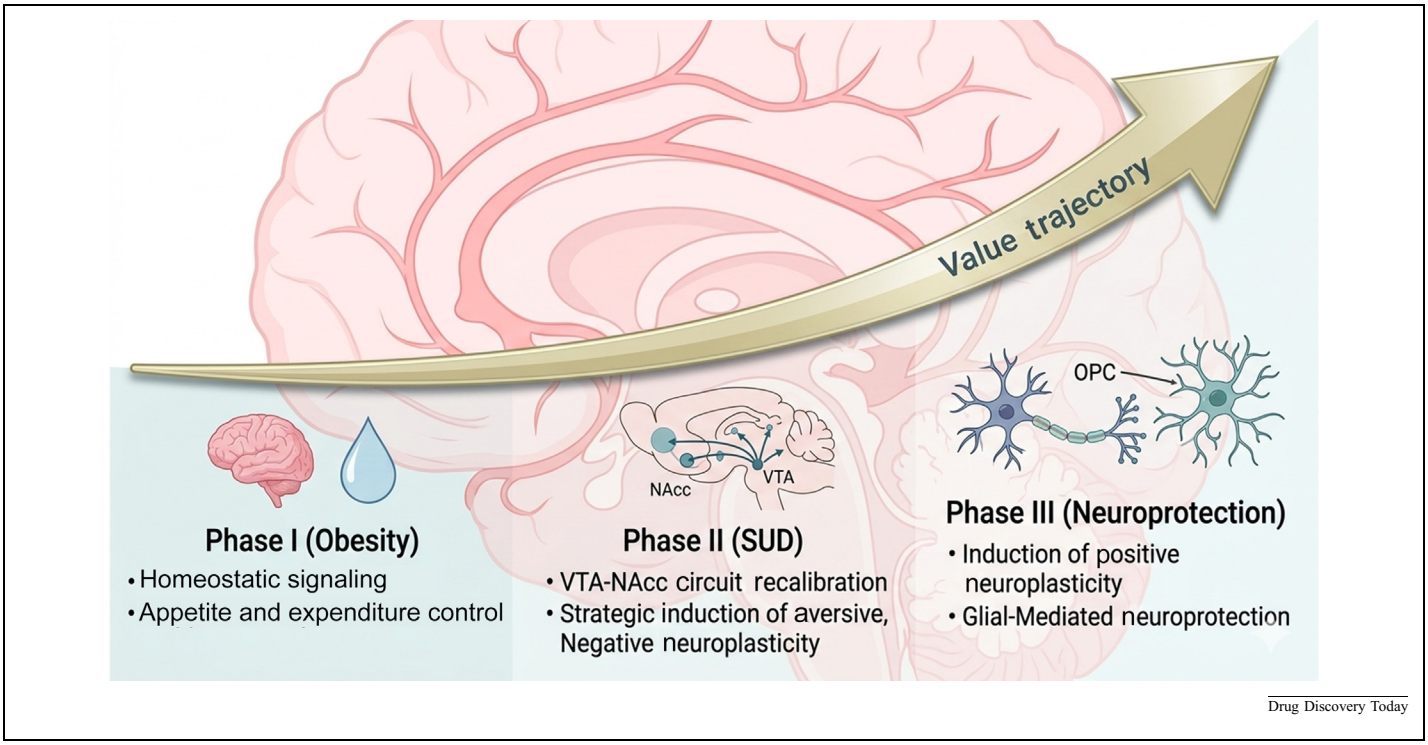

FIGURE 4

Strategic prioritization and value expansion for GPR149. This roadmap illustrates the progression of GPR149 from a single-indication metabolic target into a multi-asset neurorestorative platform. **(a)** The metabolic anchor: initial discovery efforts focus on reversing the predicted baseline $G_{i/o}$ inhibitory tone of GPR149, addressing acute satiety and reward signaling ('firing'). **(b)** Dual-domain value escalator: utilizing the Integrated Four-Pillar Framework, the campaign causally validates the glial-selective role of GPR149 in oligodendrocyte progenitor cell (OPC) differentiation and remyelination ('wiring'). This 'directed neuroplasticity' mechanism supports long-term recovery and differentiates GPR149 from Class B GLP-1R agonists. **(c)** Health Economics & Outcomes Research (HEOR) value demonstration: This final phase represents the value expansion strategy, expanding the target product profile (TPP) into demyelinating diseases. This 'two-for-one' capability maximizes market potential, creates a robust Blue Ocean strategy (uncontested market space), and supports premium value-based pricing by demonstrating multimorbid utility across high-economic-burden populations (e.g., obesity, multiple sclerosis, and substance-use disorder). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

rather than strictly against each other to control behavior and adapt to environmental stimuli.

Targeting the NAcc-resident GPR149 population must be contextualized within the broader, distributed neurocircuitry of addiction. Addiction is not a disease restricted to a single node; it involves complex, reciprocal crosstalk between the PFC, the VTA, and the extended amygdala.[p35] Recent evidence emphasizes that effective intervention in substance use disorders requires modulating these interconnected nodes to restore homeostatic balance.[p34] GPR149 is uniquely positioned for this task, because its expression across these reward-relevant nuclei suggests a role in 'tuning' the overall circuit tone rather than acting as a binary switch.

To predict whether GPR149 engagement will promote the desired negative neuroplasticity, and to interpret behavioral data within a true disease-modification framework, we must move beyond bulk assays. Mapping the cell type-specific actions of GPR149 using single-nucleus RNA sequencing (snRNA-seq) and projection-specific manipulations is necessary to ensure that the drug 'unlocks' the obesity-consolidated circuit. This circuit-level resolution is the ultimate de-risking step, providing the mechanistic 'ground truth' needed to justify the long-term value demonstration required by payers and HTA bodies in a crowded, post-GLP-1RA market.

Biased agonism as a path to functional specificity and improved safety

Ligands with distinct bias profiles offer a direct chemical strategy to tune clinical outcomes and to steer plasticity toward negative rather than positive endpoints. For GPR149, this can be utilized to separate desired from adverse effects: a $G_{i/o}$-biased compound might preferentially drive acute metabolic benefits and restoration of homeostatic set-points via cAMP inhibition, whereas an arrestin-biased ligand, potentially promoting greater receptor internalization, might favor long-term remodeling of reward circuits (negative neuroplasticity in VTA–NAcc and related nodes) or distinct glial effects.[p33] Quantifying signaling bias early in lead optimization, using platforms such as PRESTO-Tango[p10] alongside canonical pathway assays, allows medicinal chemistry to steer toward a tailored product profile, potentially enhancing efficacy and minimizing side-effect liabilities linked to specific pathways.

Beyond traditional orthosteric and allosteric ligands, emerging pharmacological strategies, such as molecular glues, which stabilize specific receptor-transducer complexes to fine-tune signaling, represent a promising frontier for achieving unprecedented selectivity for GPCRs such as GPR149.[p39]

Furthermore, a modern drug discovery lens necessitates moving beyond canonical functional assays. As highlighted elsewhere,[p40] successful GPCR targeting requires integrated assessment of pharma-

cological parameters, such as internalization/recycling rates, desensitization profiles, and the potential for compartmentalized (e.g., endosomal) signaling. For GPR149, explicitly screening tool compounds for these properties, particularly the relationship between residence time and sustained intracellular signaling, could identify ligands with optimized profiles for chronic administration, where maintaining receptor responsiveness is paramount.

Multimodal validation to de-risk clinical translation

A tiered experimental approach bridges receptor biophysics and whole-animal behavior, thereby reducing translational uncertainty: (i) chemogenetic surrogates (e.g., DREADDs): allow for the probing of circuit-specific roles before a high-affinity ligand exists, validating the therapeutic hypothesis and identifying sensitive behavioral readouts[p24]; (ii) optogenetics: provides causal, temporally precise validation of circuit manipulations, distinguishing acute modulation from developmental or compensatory effects[p41]; (iii) computational modeling: can integrate pharmacokinetic/pharmacodynamic (PK/PD) data with circuit maps to predict dosing regimens and effects on complex behaviors like decision-making or reward valuation. Furthermore, the integration of AI with quantitative systems pharmacology (AI-QSP) can generate predictive digital twins and virtual patient populations, enhancing the mechanistic interpretability and clinical translatability of circuit-aware pharmacodynamic models.[p42]

Together, these approaches form a robust, iterative loop between molecule design and systems pharmacology, ensuring that clinical candidates are selected for not only potency and selectivity, but also their predicted impact on the integrated brain circuits that underlie disease.

Proactively addressing peripheral on-target safety

A complete translational strategy for an orphan receptor must extend beyond the CNS to assess potential peripheral expression and on-target safety liabilities. Although CNS expression of GPR149 is well documented, a thorough de-risking plan requires definitive profiling of its expression in crucial human peripheral tissues (e.g., cardiovascular system, gastrointestinal tract, pancreas, and immune cells) using sensitive techniques, such as single-cell RNA-seq.[p1] The hypothesized $G_{i/o}$-mediated 'brake' function, if active in cardiac myocytes or the sinoatrial node, could theoretically pose a pro-arrhythmic risk, a recognized class effect of $G_{i/o}$-coupled receptors.

Therefore, the integrated strategy explicitly mandates early *in vitro* safety pharmacology profiling. This includes screening tool compounds against human stem cell-derived cardiomyocytes to assess effects on beat rate and field potential duration using comprehensive *in vitro* proarrhythmia assay (CiPA)-compliant assays as an integral part of the lead optimization cycle (Pillar II/III). Early *in vitro* pharmacology profiling demonstrates regulatory awareness and aligns with FDA's International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S7B guidelines.

Furthermore, creating a tissue-specific Gpr149 conditional knockout model would enable direct interrogation of potential hyperplasia or metabolic sequelae in peripheral organs, de-risking this concern long before candidate selection.

Peripheral expression and safety pharmacology

GPR149 (also known as *Igsl1*) was initially identified as an oocyte-enriched transcript rather than a CNS or metabolic regulator. Research in murine models revealed that GPR149 is highly concentrated in the germinal vesicle and meiosis-II stage oocytes, but notably absent from surrounding granulosa cells.[p43] Although genetic ablation of *Gpr149* does not impair reproductive function, it paradoxically results in a 'superfertile' phenotype. This is characterized by a 10–20% increase in ovulation rates and larger litter sizes, suggesting that GPR149 acts as a negative regulator of follicular maturation.[p43]

From a drug development perspective, this peripheral expression profile presents a strategic double-edged sword. A GPR149 antagonist could serve as a novel agent in assisted reproductive technology (ART), representing a significant option value for the scaffold. Conversely, this same mechanism poses a potential off-target safety concern for patients not seeking fertility enhancement. Consequently, the Pillar III safety strategy must prioritize assessing reproductive impact, utilizing the high degree of CNS-to-peripheral selectivity or tissue-specific signaling bias inherent in candidate leads to mitigate these risks.

The predicted impact on female fertility

The primary impact of a GPR149 inverse agonist on the female reproductive system would likely include: (i) increased ovulation rates: in *Gpr149*-knockout mice, the absence of the receptor leads to a significantly higher number of oocytes being released during each estrus cycle. An inverse agonist would theoretically mimic this by 'unlocking' the follicle earlier or more frequently[p1]; (ii) enhanced fecundity (litter size): the 'superfertile' phenotype in mice is characterized by larger-than-average litters. In a clinical context, this could translate to a higher probability of multifollicular development and possible multiple gestation; and (iii) potential as an art adjunct: instead of a traditional 'drug,' a GPR149 inverse agonist might be positioned as a therapeutic for ART to improve egg yield in patients with low ovarian reserve.

Strategic risks and the 'selectivity' challenge

Although 'increased fertility' sounds like a positive outcome, it represents a significant on-target safety risk for the primary CNS/metabolic indications (obesity or addiction). If a patient is taking a GPR149 modulator for weight loss or sobriety, unintended 'superfertility' could lead to unplanned pregnancies or complications, such as ovarian hyperstimulation syndrome (OHSS). To mitigate this off-target consequence, I propose two specific medicinal chemistry strategies: (i) blood–brain barrier (BBB) restriction: designing the molecule to be highly CNS penetrant but peripherally restricted. Keeping the drug in the VTA-NAcc and hypothalamic circuits would avoid engaging the receptors in the oocytes; and (ii) tissue-specific bias: engineering a ligand that only targets the signaling pathways active in neurons (e.g., $G_{i/o}$ suppression) while remaining neutral toward the pathways that govern oocyte maturation.

Consequently, the discovery program must prioritize BBB-restricted scaffolds to decouple neurometabolic benefits from

peripheral reproductive effects, unless the asset is being specifically developed for fertility-related indications.

Impact on the male HPG axis

Based on recent mapping of *Gpr149* in male tissues, an inverse agonist or antagonist would likely have a complex, potentially stimulatory effect on the hypothalamic–pituitary–gonadal (HPG) axis in men. Recent evidence confirms that the highest Gpr149 expression in non-neuronal tissue is found in the pituitary gland of the male mouse.[p6]

Predicted impact on FSH and LH in men

If one extrapolates from the 'superfertile' knockout models, a GPR149 inverse agonist or antagonist would likely lead to: (i) increased pituitary sensitivity to gonadotropin-releasing hormone (GnRH): in female models, loss of GPR149 leads to increased levels of follicle-stimulating hormone (FSH) receptor and cyclin D2 mRNA.[p43] Given that GPR149 is enriched in male pituitary endocrine cells,[p8] blocking this signaling could lower the threshold for GnRH-induced secretion, potentially increasing FSH and luteinizing hormone (LH) pulse amplitude; (ii) reduced negative feedback inhibition: GPR149 is expressed in hypothalamic nodes, specifically the VMH, known to integrate metabolic and reproductive signals.[p8] Blocking this 'brake' might disrupt the normal negative feedback loop, causing the hypothalamus to perceive a 'low testosterone' state and subsequently increase GnRH pulsatility, which would drive up both LH (stimulating testosterone) and FSH (stimulating sperm production); (iii) spermatogenesis enhancement: given that FSH is the primary driver of Sertoli cell function and spermatogenesis in men, a GPR149 inverse agonist that increases FSH sensitivity or levels could be investigated as a therapeutic for male factor infertility (oligospermia); and (iv) increased testosterone production: LH primarily stimulates specialized steroid-producing cells in the gonads to regulate reproduction. In men, LH stimulates Leydig cells in the testes to produce testosterone. In principle, a GPR149 inverse agonist that increases LH production in men could be investigated as a therapeutic for male hypogonadotropic hypogonadism, a condition often associated with metabolic syndrome in the aging male. Although low serum testosterone levels can now be treated safely and conveniently with sublingual testosterone troches,[p44] GPR149 represents a potential upstream modulator of the entire HPG axis. This positioning differentiates GPR149 from traditional GnRH modulators, offering a potential path for treating male hypogonadism while simultaneously addressing the associated metabolic comorbidities.

Strategic prioritization and risk mitigation: justifying the investment

With over 100 orphan GPCRs competing for research and development resources, justifying a focused campaign on GPR149 requires a clear, multifaceted business and scientific case. This case rests on the unique combination of biological validation, therapeutic scope, and technical tractability.

A compelling case for prioritization: the four strategic attributes

GPR149 distinguishes itself from the typical orphan through four strategic attributes: (i) anatomically strategic expression: its localization to hypothalamic, striatal, and limbic hubs positions it as a master regulator at the intersection of metabolic, motivational, and affective processing, a nexus of high unmet medical need; (ii) validated, non-redundant physiological role: the clear metabolic phenotype of Gpr149-null mice[p8] and the direct inhibition of OPC differentiation[p9] provide two independent, strong lines of functional validation, reducing the risk of targeting a biologically inert protein; (iii) dual neuronal–glial function: this is its most powerful differentiator. It offers two potential therapeutic axes (circuit modulation and remyelination) from a single target, dramatically expanding the market potential and providing a built-in risk-mitigation strategy should one axis prove intractable; (iv) evolutionary conservation and technical tractability: high sequence conservation suggests an essential function; the ERY and DPxxF microswitch pair (functional specialization) and the feasibility of modern cryo-EM[p12] support a structural blueprint for rational design within the Integrated Four-Pillar Framework.

Together, these pillars frame GPR149 not as a curiosity but as a high-value regulator with plausible, multisystem impact. Table 2 consolidates this assessment into a target druggability scorecard, providing the structured feasibility evaluation that project teams and portfolio managers need to justify resource allocation. For a high-stakes industrial perspective, Table 2 evaluates GPR149 across four strategic dimensions: technical tractability, biological validation, clinical differentiators, and commercial HEOR value. The total score of 38/40 positions GPR149 as a Tier 1 orphan GPCR. Unlike typical orphans lacking phenotypic data, the dual-domain status of GPR149 acts as an inherent risk-mitigation tool: if the metabolic axis faces competition, the neurorepair (demyelination) axis remains a high-value, orphan drug-designated fallback.

A practical risk-mitigation framework for orphan GPCR campaigns

Orphan-receptor campaigns are inherently uncertain, but strategic design can systematically manage and mitigate risk in several ways: (i) parallel-track discovery: concurrent cryo-EM, screening, and *in vivo* circuit assays prevent single-point failures. Insights from one pillar continuously inform and de-risk the others; (ii) early surrogate tools: chemogenetics (DREADDs) and CRISPR-based *in vivo* manipulations yield crucial circuit-level efficacy and safety pharmacology data before a drug-like ligand is in hand, enabling early go/no-go decisions; (iii) agnostic screening and AI-enabled design: interrogating diverse chemical libraries avoids the trap of presupposing ligand class. AI-driven *de novo* design, even starting from modest-potency hits, can rapidly iterate toward optimized leads; (iv) tiered outcome framework: defining success to include 'productive failure' (e.g., definitive negative data, a new structural method, or refined prioritization criteria) ensures that the campaign delivers value to the portfolio regardless of the ligand outcome, protecting the overall R&D investment; and (v) glial safety profiling: the prodifferentiation and promyelination effects of GPR149 inhibition require specific safety studies to rule out uncontrolled proliferation or tumorigenic risk. The validated *in vivo* phenotype shows accelerated but self-limiting remyelination following demyelinating injury,[p9] not neoplastic transformation. The de-risking plan includes early *in vitro*

TABLE 2

GPR149 target druggability scorecard.

Strategic pillar	Target attribute	Score	Industrial R&D evidence
I. Technical tractability	Structural blueprint	4	ERY/DPxxF microswitch identified; high suitability for cryo-EM and AI-driven *de novo* ligand design
	Assay development	5	PRESTO-Tango and cAMP-centric readouts provide high-throughput, path-agnostic screening capability
II. Biological validation	Phenotypic proof	5	Gpr149-null mice show improved insulin sensitivity; validated inhibition of OPC differentiation
	Circuit logic	4	Anatomical localization in ARC, VMH, and NAcc aligns with 'missing link' ImP–behavioral axis
III. Clinical differentiator	Dual-domain efficacy	5	Simultaneous 'firing' (neuronal) and 'wiring' (glial) addresses both habit and infrastructure
	Bias potential	4	Ability to engineer $G_{i/o}$ vs. β-arrestin bias to decouple metabolic from neurorepair effects
IV. Commercial/HEOR value	Reimbursement logic	5	Multimorbid value (obesity + addiction + MS) supports premium price-to-value HEOR demonstration
	Market saturation	5	'Blue Ocean' strategy distinct from GLP-1R agonists via glial/CNS-reparative mechanism
Total score:		38/40	

assays to assess the proliferation kinetics of human OPCs under sustained GPR149 inhibition or knockout. Furthermore, pivotal *in vivo* toxicology studies in relevant species will incorporate long-term dosing regimens and detailed histological examination of white matter tracts and neural stem cell niches to monitor for any aberrant glial cell dynamics or ectopic differentiation, ensuring the therapeutic effect remains within a physiologically appropriate window.

Successful execution of such a parallel-track campaign requires not only technical innovation, but also an organizational commitment to implementing robust data science (DS) and AI strategies across R&D, addressing known challenges in integration, talent, and governance.[p45]

This layered strategy transforms GPR149 from a speculative venture into a manageable, milestone-driven discovery program with multiple paths to a positive return on investment, both financial and intellectual.

Concluding remarks: reversing Eroom's Law

The Integrated Four-Pillar Framework presented here (high-throughput screening, cryo-EM, bias-capable chemistry, and circuit-level validation) offers a reproducible, capital-efficient blueprint for transforming the dark GPCRome into a source of first-in-class therapeutics.[p46]

GPR149 is the prototype. Its strategic expression in metabolic and reward circuitry, its validated glial mechanism, and its non-canonical microswitch architecture make it the ideal test case. Deorphanizing GPR149 using this framework would do more than deliver a single asset: it would validate a scalable platform. If cryo-EM and circuit-level mapping can systematically de-risk GPR149, then the same logic applies to the 100+ remaining orphans.

The prize is not just a ligand. It is a new class of dual-domain therapeutics, agents that simultaneously recalibrate maladaptive reward circuitry ('firing') and repair damaged neural infrastructure ('wiring'). Such a profile would differentiate GPR149 from current incretin-based therapies, extending reach from metabolic disease into addiction, psychiatric disorders, and demyelinating conditions such as MS. This is the essence of reversing Eroom's Law: replacing sequential, high-attrition discovery with parallelized, intelligence-driven de-risking.

In an era of soaring R&D costs and shrinking margins, the framework that succeeds for GPR149 becomes the template for the industry. The dark GPCRome is no longer a graveyard of abandoned targets: it is a pipeline waiting to be unlocked.

Translating this framework into clinical success requires a disciplined roadmap. Lead candidate nomination should prioritize a GPR149-targeted inverse agonist with demonstrated $G_{i/o}$ bias, favorable ADMET, and proof-of-concept efficacy in DREADD-based models. Parallel biomarker development must align with dual-domain pharmacology: functional neuroimaging to assess engagement of hypothalamic and VTA–NAcc circuits; plasma metabolic markers (insulin sensitivity, lipid profiles); and, for the glial axis, diffusion tensor imaging to monitor white matter integrity and serum markers of OPC differentiation. Initial clinical trials should stratify patients by comorbid metabolic and CNS phenotypes, such as individuals with obesity and binge eating disorder, or metabolic syndrome with comorbid depression, thereby targeting the high-economic-burden populations that justify premium value-based reimbursement.

Declaration of interests

The author declares no competing interests.

References

1. Sriram K, Insel PA. G protein-coupled receptors as targets for approved drugs: how many targets and how many drugs? *Mol Pharmacol*. 2018;93:251–258.
2. Hauser AS et al. Trends in GPCR drug discovery: new agents, targets and indications. *Nat Rev Drug Discov*. 2017;16:829–842.
3. Zhou Q et al. Common activation mechanism of class a GPCRs. *Elife*. 2019;8, e50279.
4. Zhang M et al. Molecularly defined and spatially resolved cell atlas of the whole mouse brain. *Nature*. 2023;624:343–354.

5. Siletti K et al. Transcriptomic diversity of cell types across the adult human brain. *Science*. 2023;382, eadd7046.
6. Wyler SC et al. Gpr149 is involved in energy homeostasis in the male mouse. *PeerJ*. 2024;12, e16739.
7. Agirman G et al. The microbial metabolite imidazole propionate modulates hypothalamic activity and stress-induced behaviors. *Cell Host Microbe*. 2025;33:2030–2042.
8. Inoue A et al. Illuminating G protein-coupling selectivity of GPCRs. *Cell*. 2019;177:1933–1947.
9. Suo N et al. The orphan G protein-coupled receptor GPR149 is a negative regulator of myelination and remyelination. *Glia*. 2022;70:1992–2008.
10. Kroeze WK et al. PRESTO-Tango as an open-source resource for interrogation of the druggable human GPCRome. *Nat Struct Mol Biol*. 2015;22:362–369.
11. Russell IC et al. Cryoelectron microscopy as a tool for illuminating activation mechanisms of human class A orphan G protein-coupled receptors. *Pharmacol Rev*. 2025;77, 100056.
12. Shihoya W et al. Cryo-EM advances in GPCR structure determination. *J Biochem*. 2024;176:1–10.
13. Latorraca NR et al. GPCR dynamics: structures in motion. *Chem Rev*. 2017;117:139–155.
14. Skiba MA. Nanobodies unlock new mechanisms to target G protein-coupled receptors. *Mol Pharmacol*. 2026;108, 100110.
15. Rasmussen SG et al. Structure of a nanobody-stabilized active state of the β(2) adrenoceptor. *Nature*. 2011;469:175–180.
16. Hilger D et al. Structure and dynamics of GPCR signaling complexes. *Nat Struct Mol Biol*. 2018;25:4–12.
17. Kim J, Choi C. Orphan GPCRs in neurodegenerative disorders: integrating structural biology and drug discovery approaches. *Curr Issues Mol Biol*. 2024;46:11646–11664.
18. Qiao X et al. Identification of an unexplored dynamic allosteric site on the activation pathway of the vasopressin V2 receptor. *J Med Chem*. 2025;68:16766–16780.
19. Li N et al. Exploring the distinct activation mechanisms of neuromedin B receptor through multiple replica molecular dynamics simulations and Markov state modeling. *Acta Pharmacol Sin*. 2025;46:3190–3203.
20. Li M et al. Delineating the stepwise millisecond allosteric activation mechanism of the class C GPCR dimer mGlu5. *Nat Commun*. 2024;15:7519.
21. Zhang M et al. G protein-coupled receptors (GPCRs): advances in structures, mechanisms, and drug discovery. *Signal Transduct Target Ther*. 2024;9:88.
22. Reboul E et al. Improving the reliability of molecular string representations for generative chemistry. *J Chem Inf Model*. 2025;65:10221–10238.
23. van den Broek RL et al. In search of beautiful molecules: a perspective on generative modeling for drug design. *J Chem Inf Model*. 2025;65:9383–9397.
24. Roth BL. DREADDs for neuroscientists. *Neuron*. 2016;89:683–694.
25. Yao G et al. The landscape of innovative oncology drug targets. *Drug Discov Today*. 2026;31, 104571.
26. Puorro-Radzwill K et al. Reassessing GPR17 as a therapeutic target in remyelination. *BioRxiv*. Published online July 8, 2025. http://dx.doi.org/10.1101/2025.07.08.659146. [Pre-print].
27. Tzang CC et al. Metabolic rebound after GLP-1 receptor agonist discontinuation: a systematic review and meta-analysis. *EClinicalMedicine*. 2025;90, 103680.
28. Gunturu S. The potential role of GLP-1 agonists in psychiatric disorders: a paradigm shift in mental health treatment. *Indian J Psychol Med*. 2024;46:193–195.
29. Holst JJ. GLP-1 physiology in obesity and development of incretin-based drugs for chronic weight management. *Nat Metab*. 2024;6:12–25.
30. Cheng D et al. The role of glucagon-like peptide-1 receptor agonists (GLP-1 RA) in diabetes-related neurodegenerative diseases. *Drug Des Devel Ther*. 2022;16:665–684.
31. Godschall EN et al. A brain reward circuit inhibited by next-generation weight loss drugs. *BioRxiv*. Published online June 14, 2024. https://doi.org/10.1101/2024.12.12.628169. [Pre-print].
32. Okunogbe A et al. Economic impacts of overweight and obesity: current and future estimates for 161 countries. *BMJ Glob Health*. 2022;7, e009773.
33. Smith JS et al. Biased signalling: from simple switches to allosteric microprocessors. *Nat Rev Drug Discov*. 2018;17:243–260.
34. Paludetto LS et al. Mapping the neural substrates of cocaine craving: a systematic review. *Brain Sci*. 2024;14:329.
35. Volkow ND et al. The dopamine motive system: implications for drug and food addiction. *Nat Rev Neurosci*. 2017;18:741–752.
36. Cone RD. Anatomy and regulation of the central melanocortin system. *Nat Neurosci*. 2005;8:571–578.
37. Sternson SM, Eiselt AK. Three pillars for the neural control of appetite. *Annu Rev Physiol*. 2017;79:401–423.
38. Lüscher C, Slesinger PA. Emerging roles for G protein-gated inwardly rectifying potassium (GIRK) channels in health and disease. *Nat Rev Neurosci*. 2010;11:301–315.
39. Xing Y et al. Molecular glues as GPCR modulators: unveiling three distinct mechanistic pathways for signal regulation. *Drug Discov Today*. 2025;30, 104484.
40. Costa-Neto CM et al. Deciphering complexity of GPCR signaling and modulation: implications and perspectives for drug discovery. *Clin Sci*. 2025;139:463–477.
41. Tye KM, Deisseroth K. Optogenetic investigation of neural circuits underlying brain disease in animal models. *Nat Rev Neurosci*. 2012;13:251–266.
42. Goryanin I, Demin O. Revolutionizing drug discovery: integrating artificial intelligence with quantitative systems pharmacology. *Drug Discov Today*. 2025;30, 104448.
43. Edson MA et al. Deletion of the novel oocyte-enriched gene, Gpr149, leads to increased fertility in mice. *Endocrinology*. 2010;151:358–368.
44. Guth MAS. Compounded testosterone troches to optimize health and the testosterone controversy. *Int J Pharm Compd*. 2015;19:195–203.
45. Garzya V et al. Implementation of a data science and artificial intelligence strategy across pharmaceutical R and D: challenges and solutions. *Drug Discov Today*. 2025;30, 104527.
46. Tropsha A et al. The six Ds of exponentials and drug discovery: a path toward reversing Eroom's law. *Drug Discov Today*. 2025;30, 104341.

Michael A.S. Guth *

Institute for Neuroplasticity Research, Oak Ridge, TN, USA

* *Corresponding author.*
mike@michaelguth.com