COMPUTATIONAL TARGET PROFILE

GPR149

An Orphan Class A GPCR, Characterised Without An Experimental Structure

The oversized, disorder-dominated orphan where construct design is the product. An unusually large (731-aa), ~65%-disordered orphan GPCR — mapped into truncation boundaries, a pocket hypothesis, and a validation plan.

UniProt Q86SP6 · 731 aa · Class A (rhodopsin-like) · IDG tier: T_{bio} · PDB: none · July 2026

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At A Glance

Fold	Seven transmembrane helices; multi-pass plasma-membrane receptor; non-enzyme; likely monomeric — unusually large for a class A GPCR (731 aa).
Orthosteric Pocket	**High-priority hypothesis.** A residue-level pocket at the **canonical class A orthosteric site** (TM3, ECL2, TM5, TM6, TM7) — a concrete starting point for docking, mutagenesis and ligand-screen design. No known binder: a novel, structurally uncharacterised orphan pocket.
Structural Anchors	N-terminal N-glycosylation cluster (N6, N10, N20); a predicted disulfide-bond cysteine at C104 (TM3 tip); dense phosphorylation across the intracellular regions.
Flexible Regions	**~65% disordered by residue.** Short disordered N-terminus (1–27), a large disordered ICL3 (219–303) and an unusually long disordered C-terminal region (368–731) — the dominant construct-design consideration.
Clean Signal	No amyloidogenic segments predicted.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. The pocket (amber) is the load-bearing prediction that the rest of this profile builds on.

1 The Gap

Most therapeutically tractable receptor families have been structurally explored. GPR149 remains largely dark: an understudied (IDG T_{bio}) [2] class A GPCR with **no experimental structure in the PDB**, **no confirmed endogenous ligand**, and an atypical microswitch architecture — a degenerate DRY motif and an unusually long C-terminus. Its best-established biology is in reproduction (*Gpr149*-null mice show increased fertility [3]), and it has recently been repositioned as a neuro-metabolic target: knockouts partially resist diet-induced weight gain with improved insulin sensitivity [4], and the receptor negatively regulates myelination in the CNS [5].

That combination — **high interest, near-zero structural information** — is exactly where prediction

earns its keep: everything below is computed from the canonical 731-residue sequence and derived structural predictions, with no experimental GPR149 structure or validated ligand used as input. For a genuine orphan, there is nothing to look up.

2 Receptor Architecture And Topology

The receptor is a canonical class A seven-helix bundle. Helix boundaries and the intervening loops are resolved cleanly, with three flexible regions that matter for anyone planning to express, truncate, or crystallise the protein.

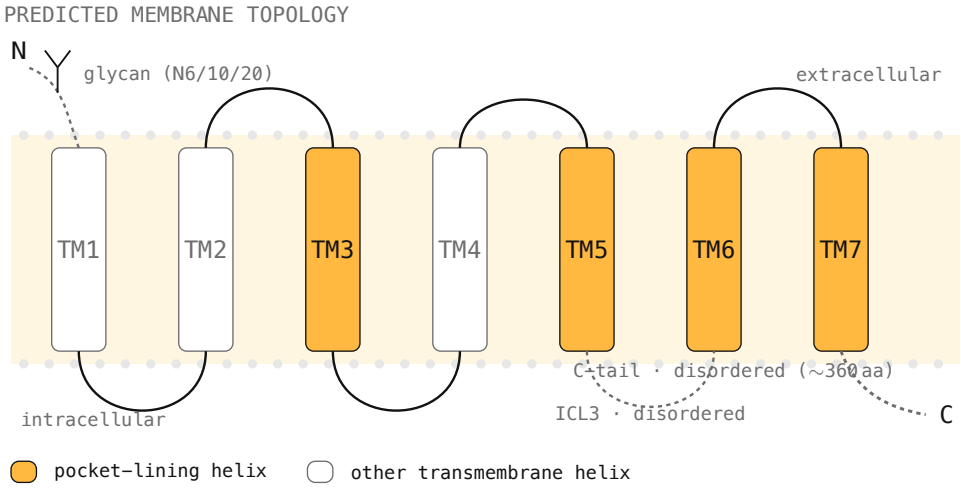

Figure 2. Predicted membrane topology. Seven transmembrane helices with an extracellular N-terminus and intracellular C-terminus; amber marks the four pocket-lining helices. GPR149 carries an N-terminal N-glycosylation cluster (N6/N10/N20), a large disordered ICL3, and an unusually long disordered C-terminal region.

Element	Residues	Note
N-terminus	1–35	Short, extracellular; disordered 1–27; N-glycosylation cluster (N6, N10, N20).
TM1–TM7	see figure	36–57, 69–90, 108–128, 151–170, 191–211, 312–332, 346–362.
ECL2	171–190	Contributes to the orthosteric pocket.
ICL3	212–311	Large disordered insert (219–303); dense phospho-cluster (putative GRK/PKC).
C-terminus	363–731	Unusually long; largely disordered (368–731); extensive phosphorylation.

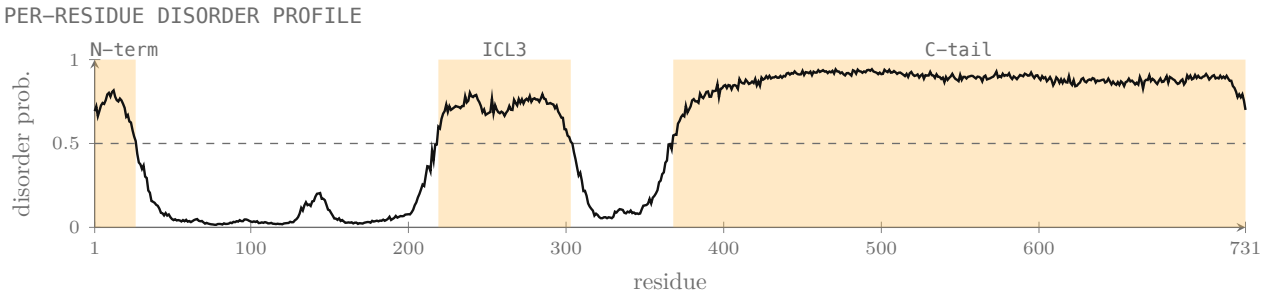

Figure 3. Predicted disorder across the sequence. Amber bands mark the three disordered regions (dashed line = 0.5 call threshold). The ordered seven-helix core between them is the region most amenable to structural work once the usual thermostabilisation and fusion strategies are applied.

3 The Predicted Orthosteric Pocket

Every class A GPCR has an orthosteric pocket, so its existence is not the finding. The useful question is *which residues line it* — the input a docking run or a selectivity argument actually needs, and the one thing you cannot read straight off the sequence. Astra resolves that residue set and places it at the **canonical class A orthosteric site** (TM3, ECL2, TM5, TM6, TM7): a **high-priority, residue-level hypothesis** — a concrete starting point for docking, mutagenesis and ligand-screen design, not a claim of proven ligandability. GPR149 is a genuine orphan with *no known binder* — a novel, structurally uncharacterised pocket.

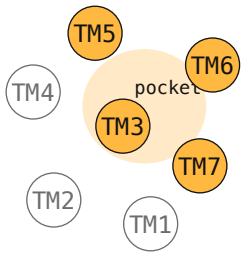

Figure 4. Schematic extracellular (top-down) view. Amber helices line the pocket; ECL2 caps it.

POCKET–LINING RESIDUES

TM3	109, 110, 112, 113, 116, 117
ECL2 / TM5	175, 182–183, 186, 192–195, 198
TM6	323–331
TM7	346–348, 350–351

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of GPR149 exists, and it is a useful input — but a fold alone does not tell you which cavity is the orthosteric pocket, where the modification and disordered boundaries fall, or how far to prioritise each for experiment. This profile is that annotation layer. As a control, the same pocket detection recovers the known orthosteric site on class A GPCRs whose structures *are* solved (e.g. the fatty-acid receptor GPR84), so the GPR149 pocket is a like-for-like prediction rather than an extrapolation into empty space. The net effect: GPR149 goes from an orphan sequence to a **ranked experimental hypothesis map**.

4 Post-Translational And Structural Features

The predicted modification map is coherent with a working class A receptor and points to specific, testable residues:

- **N-glycosylation cluster (N6, N10, N20).** Three sites on the short extracellular N-terminus — a surface-expression and trafficking handle.
- **Extensive phosphorylation** across the disordered ICL3 (219–303) and the long C-terminal region — an unusually large GRK/PKC-type regulatory surface, consistent with the atypical, extended C-terminus.
- **Predicted disulfide-bond cysteine at C104** (extracellular tip of TM3); the ECL2 partner is not confidently resolved, so the canonical class A bridge is only partially supported here.
- **No confident S-palmitoylation site** — unlike many class A GPCRs, consistent with GPR149's atypical C-terminus.

5 Recommended Experimental Follow-Up

This turns an orphan sequence into a ranked, executable plan: each prediction is paired with the experiment that would test it and the readout to watch for.

Prediction	Experiment	Readout
Long disordered C-terminal region (368–731)	C-terminal truncation for expression constructs	Improved amenability to cryo-EM / crystallography
Orthosteric-pocket residues (TM3, TM6, TM7)	Alanine scan + docking / fragment screen at the predicted site	Ligand binding or SAR at the predicted pocket
Large disordered ICL3 (219–303)	Fusion-partner insertion or loop deletion	Expression / stability improvement
N-glycosylation cluster (N6, N10, N20)	N→Q substitution	Surface expression / trafficking shift
Predicted disulfide cysteine C104	Cys→Ala mutant	Expression / fold-integrity check

The receptor's emerging metabolic and CNS roles [4, 5] indicate where a resulting tool compound would first be worth evaluating.

6 Where This Fits In A Discovery Workflow

Team	What they get from this profile
Target biology	Testable residue-level hypotheses and a validation plan
Structural biology	Construct boundaries, disordered regions, fusion / deletion ideas
Medicinal chemistry	Pocket / active-site residues for docking and SAR
BD / platform evaluation	Evidence Orbion can prioritise dark targets quickly

7 Methods

All predictions were generated with Orbion's Astra suite from the canonical GPR149 sequence (UniProt Q86SP6 [1]). Modules used, with method publications cited where available: **AstraSUIT2** and **AstraROLE2** [6] (membrane and functional class, oligomeric state), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM2** [7] (modification sites) and **AstraBIND** [8] (binding pocket). Reported values are model outputs; model internals are out of scope. Confidence scores are model-estimated probabilities (0–1) that rank and gate each call — not calibrated rates of experimental success.

PREDICTION PROVENANCE

Target & input	GPR149 · UniProt Q86SP6, canonical isoform (731 aa)
Structure source	AlphaFold2 predicted model (no experimental PDB entry)
Feature inputs	ESM-2 embeddings + AlphaFold2-derived structural features [6–8]
Models	AstraSUIT2 · AstraROLE2 · AstraUNFOLD · AstraPTM2 · AstraBIND
Binding-site model	GATv2 detector trained on >250k protein–ligand complexes [8]
Confidence & calibration	Per-call model probability; per-model calibration, thresholds and benchmarks reported in [6]–[8]

Scope And Limitations

- **Prediction, not experiment.** These are computational hypotheses to prioritise experiments — not a substitute for a structure or an assay. No result here has been validated in the wet lab.
- **The pocket is predicted; the ligand is not named.** For a genuine orphan the honest output is a residue-level pocket hypothesis, not a drug. We make no claim about ligandability or which chemotype binds.
- **Biology caveats.** GPR149's phenotypes derive from knockout-mouse models [3–5] and its neuro-metabolic

repositioning is recent; the endogenous ligand remains unknown. Treat the therapeutic case as a hypothesis.

8 References

[1] UniProt Consortium. UniProtKB entry Q86SP6 (GPR149, human). uniprot.org.

[2] Pharos / Illuminating the Druggable Genome. GPR149 target record — T_{bio}. pharos.nih.gov/targets/Q86SP6.

[3] Edson M.A., Lin Y.-N., Matzuk M.M. Deletion of the novel oocyte-enriched gene, *Gpr149*, leads to increased fertility in mice. *Endocrinology* **151**(1), 358–368 (2009). doi:10.1210/en.2009-0760.

[4] Wyler S., Surbhi, Cao N., et al. *Gpr149* is involved in energy homeostasis in the male mouse. *PeerJ* **12**, e16739 (2024). doi:10.7717/peerj.16739.

[5] Suo N., He B., Cui S., et al. The orphan G protein-coupled receptor GPR149 is a negative regulator of myelination and remyelination. *Glia* **70**(10), 1992–2008 (2022). doi:10.1002/glia.24233.

[6] Bozkurt Ç., Vasilyeva A., Goteti A. AstraROLE2 & AstraSUIT2: Multi-Task Annotation Models for Functional Profiling of Proteins. *bioRxiv* 2025.06.21.660734 (2025). doi:10.1101/2025.06.21.660734.

[7] Bozkurt Ç., Vasilyeva A., Goteti A. AstraPTM2: A Context-Aware Transformer for Broad-Spectrum PTM Prediction. *bioRxiv* 2025.10.03.680341 (2025). doi:10.1101/2025.10.03.680341.

[8] Goteti A., Vasilyeva A., Bozkurt Ç. AstraBIND: Graph Attention Network for Predicting Ligand Binding Sites. *bioRxiv* 2025.11.10.687555 (2025). doi:10.1101/2025.11.10.687555.

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