COMPUTATIONAL TARGET PROFILE

GPR160

An Orphan Class A GPCR, Characterised Without An Experimental Structure

The dark oncology / pain orphan with a high-priority pocket hypothesis. No solved structure, no confirmed ligand, contested CARTp biology — resolved into a topology, a residue-level orthosteric-pocket hypothesis, and a validation plan.

UniProt Q9UJ42 · 338 aa · Class A (rhodopsin-like) · IDG tier: T_{dark} · PDB: none · July 2026

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At A Glance

Fold	Seven transmembrane helices; multi-pass plasma-membrane receptor; non-enzyme; likely monomeric.
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 validated small-molecule ligand; the CARTp pairing is contested in human systems.
Structural Anchors	Conserved TM3–ECL2 disulfide (C94–C173); C-terminal S-palmitoylation (C316); N-terminal N-glycosylation (N7).
Flexible Regions	Short disordered N-terminus (1–22), disordered ICL3 (211–231), disordered C-tail (301–338) — the natural truncation boundaries for construct design.
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. GPR160 remains largely dark: an IDG T_{dark} [2] class A GPCR with **no experimental structure in the PDB**, **no confirmed endogenous ligand**, and a thin primary literature. The proposed CART-peptide pairing is disputed in human cells [3], so even its pharmacology is unsettled. Yet interest is real: GPR160 is over-expressed across prostate-cancer cohorts [4] and has been tied to neuropathic-pain signalling.

That combination — **high interest, near-zero structural information** — is exactly where prediction earns its keep: everything below is computed from the canonical 338-residue sequence and derived structural predictions, with no experimental GPR160 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.

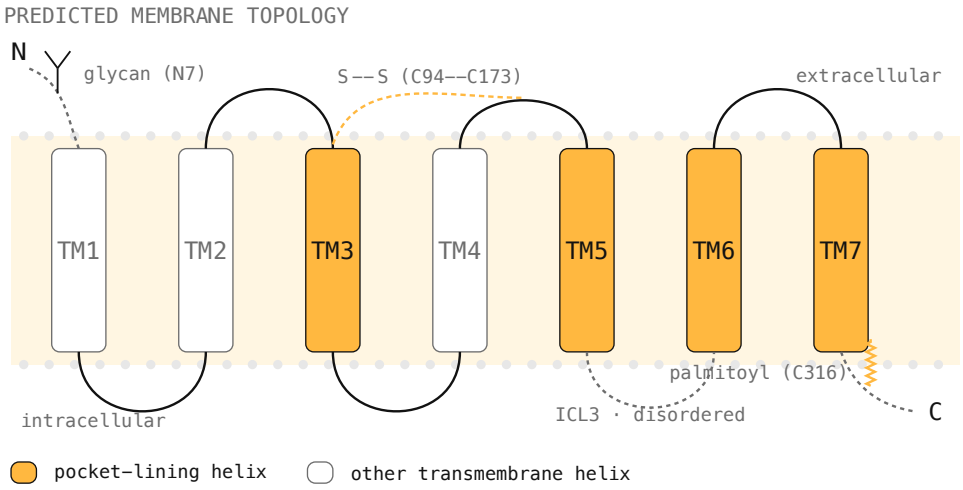

Figure 2. Predicted membrane topology. Seven transmembrane helices with an extracellular N-terminus and intracellular C-terminus; amber marks the four pocket-lining helices. The conserved C94–C173 disulfide, N7 glycosylation, C316 palmitoylation and the disordered ICL3 are drawn in place.

Element	Residues	Note
N-terminus	1–23	Short, extracellular; disordered 1–22; glycosylated at N7.
TM1–TM7	see figure	24–44, 58–79, 97–118, 140–157, 183–204, 241–264, 273–294.
ECL2	158–182	Carries C173 of the conserved disulfide; contributes to the pocket.
ICL3	205–240	Disordered core 211–231; clustered phospho-sites (putative GRK/PKC).
C-terminus	295–338	Disordered 301–338; palmitoylation anchor at C316.

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. GPR160 has *no validated small-molecule ligand*; the CARTp pairing remains contested in human systems.

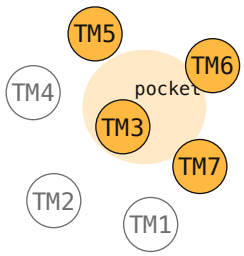

Figure 4. Schematic extracellular (top-down) view. Amber helices line the pocket; ECL2 caps it.

POCKET-LINING RESIDUES

TM3	101, 102, 103, 105, 106
ECL2 / TM5	174, 175, 176, 177, 179, 183–189, 191
TM6	252, 255, 257, 259
TM7	275, 279–284, 286

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of GPR160 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 GPR160 pocket is a like-for-like prediction rather than an extrapolation into empty space. The net effect: GPR160 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:

- **Conserved disulfide C94–C173.** Links the extracellular tip of TM3 to ECL2 — the bridge that caps the orthosteric pocket in class A GPCRs. Its presence is a structural sanity check and a mutagenesis handle.
- **S-palmitoylation at C316.** In the C-terminal tail, consistent with a membrane-anchored helix 8 that forms a fourth intracellular loop — relevant to trafficking and G-protein coupling.
- **N-glycosylation at N7.** On the short extracellular N-terminus.
- **Phosphorylation clusters** in ICL3 (222–231) and the C-tail (333) — the expected footprint of GRK/PKC regulation and a starting point for signalling studies.

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
Orthosteric-pocket residues (TM3, TM6, TM7)	Alanine scan + docking / fragment screen at the predicted site	Ligand binding or SAR at the predicted pocket
Conserved disulfide C94–C173	Cys→Ala mutagenesis (C94A, C173A)	Expression / fold loss — fold-integrity check
S-palmitoylation at C316	C316A point mutant	Trafficking / signalling shift
Disordered ICL3 (211–231)	Fusion-partner insertion or loop deletion	Expression / stability improvement
Disordered C-tail (301–338)	C-terminal truncation	Improved amenability to cryo-EM / crystallography

The receptor's reported prostate-cancer expression [4] indicates 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 GPR160 sequence (UniProt Q9UJ42 [1]). Modules used, with method publications cited where available: **AstraSUIT2** and **AstraROLE2** [5] (membrane and functional class, oligomeric state), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM2** [6] (modification sites) and **AstraBIND** [7] (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	GPR160 · UniProt Q9UJ42, canonical isoform (338 aa)
Structure source	AlphaFold2 predicted model (no experimental PDB entry)
Feature inputs	ESM-2 embeddings + AlphaFold2-derived structural features [5–7]
Models	AstraSUIT2 · AstraROLE2 · AstraUNFOLD · AstraPTM2 · AstraBIND
Binding-site model	GATv2 detector trained on >250k protein–ligand complexes [7]
Confidence & calibration	Per-call model probability; per-model calibration, thresholds and benchmarks reported in [5]–[7]

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.** The CART-peptide pairing for GPR160 is disputed in human systems [3], and the disease rationale rests on expression data [4]. Treat the therapeutic case as a hypothesis.

8 References

[1] UniProt Consortium. UniProtKB entry Q9UJ42 (GPR160, human). uniprot.org.

[2] Pharos (Illuminating the Druggable Genome). GPR160 target record — T_{dark}. pharos.nih.gov.

[3] Ye C., Zhou Q., Lin S., et al. High expression of GPR160 in prostate cancer is unrelated to CARTp-mediated signaling pathways. *Acta Pharm. Sin. B* **14**(3), 1467–1471 (2024). doi:10.1016/j.apsb.2023.11.025.

[4] Guo W., Zhang J., Zhou Y., et al. GPR160 is a potential biomarker associated with prostate cancer. *Signal Transduct. Target. Ther.* **6** (2021). doi:10.1038/s41392-021-00583-7.

[5] 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.

[6] 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.

[7] 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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