COMPUTATIONAL TARGET PROFILE

SCYL3

An Orphan Pseudokinase, Characterised Without An Experimental Structure

A predicted function call, a degenerate kinase pocket, and a modification map for a soluble pseudokinase with **no solved structure** and **no known substrate**.

UniProt Q8IZE3 · 742 aa · Soluble (cytoplasmic) · IDG tier: T_{bio} · PDB: none · July 2026

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At A Glance

Predicted Function	**Non-enzyme (p=0.99) — a pseudokinase.** Astra recognises a kinase-like fold but declines to call it an active enzyme, matching SCYL3's known catalytically-dead status.
Kinase Pocket	**Degenerate — medium confidence.** A pocket in the kinase N-lobe (residues 58–85), but a low ATP-binding signal (0.15) and only medium pocket confidence (0.68) — consistent with a non-functional active site.
Architecture	Soluble; an N-terminal (pseudo)kinase domain (2–245) followed by four HEAT repeats — a scaffolding / protein-interaction module, not a catalyst.
Modifications	N-myristoylation at Gly2 (membrane / partner targeting); scattered phosphosites.
Clean Signal	Predominantly ordered (only a short disordered C-terminus); no amyloid.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. The load-bearing result is the *Non-enzyme* call (amber): Astra sees kinase-like features but low ATP-binding signal, and predicts SCYL3 is not an active kinase.

1 The Gap

SCYL3 (PACE1) is a kinase that probably isn't one. It carries a canonical protein-kinase domain and four HEAT repeats, but **lacks the catalytic HRD motif** — so it is classed as a *pseudokinase*, thought to act as a scaffold rather than an enzyme. It has **no experimental structure in the PDB**, **no known substrate**, and is understudied (IDG T_{bio} [2]). Yet it is disease-relevant: SCYL3 binds the C-terminus of ezrin (hence "PACE1") and localises to the lamellipodia of metastatic cancer cells with F-actin and CD44, and drives hepatocellular-carcinoma progression as a binding partner and regulator of ROCK2 [3].

That combination — **a kinase-shaped protein that may not be a kinase** — is exactly where prediction earns its keep: everything below is computed from the canonical 742-residue sequence and derived structural predictions, with no experimental SCYL3 structure used as input. The first question — real enzyme or scaffold? — is one the sequence can answer.

2 Sequence Architecture And Function

SCYL3 has a clear two-part architecture: an N-terminal (pseudo)kinase domain followed by four HEAT repeats and a scaffolding C-terminus. The load-bearing question is not *where* the active site is but *whether there is one* — and Astra reads the degenerate catalytic machinery and predicts a non-enzyme.

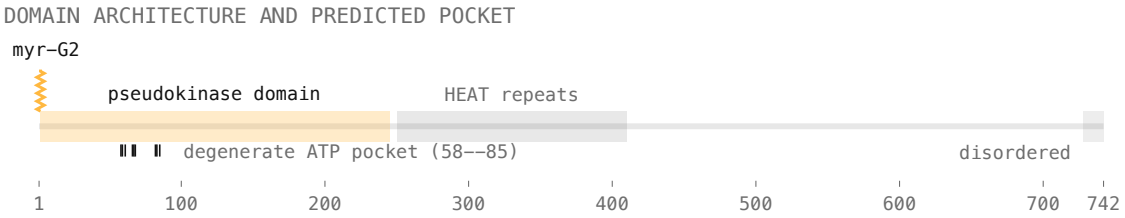

Figure 2. Sequence architecture. An N-terminal pseudokinase domain (amber) precedes four HEAT repeats; the predicted pocket (ticks) sits in the kinase N-lobe (residues 58–85) where ATP would normally bind — but at only medium confidence and with a low ATP-binding signal, consistent with a degenerate, non-catalytic site. N-myristoylation is predicted at Gly2.

3 Function: A Pseudokinase Call

The interesting question for a kinase-shaped protein is whether it is actually a kinase. Astra's answer is *no*: it classifies SCYL3 as a **Non-enzyme (p=0.99)**, with only a weak kinase-activity signal (0.62) and a low ATP-binding probability (0.15). The predicted pocket sits in the kinase N-lobe (residues 58–85) where ATP would normally bind, but at only medium confidence — the model recognises the fold yet calls the catalytic apparatus **non-functional**. That matches the biology: SCYL3 lacks the HRD catalytic motif and is classed a pseudokinase.

THE FUNCTION CALL

Function	Non-enzyme, p=0.99 — predicted *pseudokinase*
Kinase pocket	58–59, 61, 66–68, 82–83, 85 (N-lobe); ATP-binding signal only 0.15
Catalytic motif	HRD motif absent — the hallmark of a dead kinase

AlphaFold gives a fold; Astra tells you if it works. AlphaFold confidently models SCYL3's kinase fold — but a fold cannot tell you whether the kinase is alive or dead. Astra's function call does: it reads the degenerate catalytic machinery and predicts a non-enzyme — a scaffold. For a pseudokinase, that discrimination (real catalyst vs protein-interaction module) is **the whole question**, and it reframes any drug-discovery approach: target the fold for interaction disruption or allosteric control, not for ATP-competitive inhibition.

4 Post-Translational And Structural Features

The predicted modification map fits a membrane-associated scaffold, not a soluble enzyme:

- **N-myristoylation at Gly2.** An N-terminal lipid anchor that targets the pseudokinase to membranes and partner complexes — consistent with its reported lamellipodial localisation.
- **Dispersed phosphosites** across the HEAT-repeat and C-terminal regions — a likely regulatory layer over the scaffolding function.
- **Predominantly ordered; short disordered C-terminus (728–742).** No amyloid signal — the folded core is a viable target for structural work.

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
Non-enzyme / pseudokinase call	In-vitro kinase assay (± ATP, generic substrate)	Confirm absence of catalytic activity
Degenerate ATP pocket (58–85)	ATP-analogue binding / thermal-shift	Weak or no nucleotide binding
HEAT-repeat scaffold	Interaction proteomics (ezrin, ROCK2, actin/CD44)	Map the protein-interaction network
N-myristoylation at Gly2	G2A mutant	Mislocalisation — loss of membrane / lamellipodial targeting

Its role in cancer-cell migration and hepatocellular carcinoma [3] indicates where disrupting its scaffolding interactions 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 SCYL3 sequence (UniProt Q8IZE3 [1]). Modules used, with method publications cited where available: **AstraSUIT2** and **AstraROLE2** [4] (membrane and functional class, oligomeric state), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM2** [5] (modification sites) and **AstraBIND** [6] (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	SCYL3 · UniProt Q8IZE3, canonical isoform (742 aa)
Structure source	AlphaFold2 predicted model (no experimental PDB entry)
Feature inputs	ESM-2 embeddings + AlphaFold2-derived structural features [4–6]
Models	AstraSUIT2 · AstraROLE2 · AstraUNFOLD · AstraPTM2 · AstraBIND
Binding-site model	GATv2 detector trained on >250k protein–ligand complexes [6]
Confidence & calibration	Per-call model probability; per-model calibration, thresholds and benchmarks reported in [4]–[6]

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 pseudokinase call is a prediction.** Astra flags SCYL3 as a non-enzyme, consistent with its missing

HRD motif — but a direct kinase assay is needed to confirm it is catalytically dead. A residual or conditional activity cannot be excluded from sequence alone.

- **Biology caveats.** The disease role rests on cancer cell-line studies [3]; SCYL3's partners and the consequences of disrupting them are only partly mapped. Treat the therapeutic case as a hypothesis.

8 References

[1] UniProt Consortium. UniProtKB entry Q8IZE3 (SCYL3, human). uniprot.org.

[2] Pharos / Illuminating the Druggable Genome. SCYL3 (FAM188B) target record — T_{bio}. pharos.nih.gov/targets/Q8IZE3.

[3] SCYL3, as a novel binding partner and regulator of ROCK2, promotes hepatocellular carcinoma progression. *JHEP Reports* **4**(12) (2022). PMC9691429.

[4] 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.

[5] 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.

[6] 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.