AIGR Deep Research — sou1 / SPAC8E11.10 (Q9Y6Z9)

Hypothesis: NADP+-dependent arabitol (polyol) dehydrogenase (GO:0008106 + arabitol metabolic process)

Organism: *Schizosaccharomyces pombe* 972h- · **UniProt:** Q9Y6Z9 · **Gene:** sou1 (SPAC8E11.10) **Focus type:** computational_prediction (BioReason-Pro SFT) **Seed reference:** doi:10.64898/2026.03.19.712954

Executive Judgment

Verdict: PARTIALLY SUPPORTED at the activity-class level / OVER-ANNOTATED at the substrate level.

The prediction decomposes into three claims that must be judged separately:

1. **SDR-family NADP+-dependent CH–OH oxidoreductase → SUPPORTED.** Fold/family, the SDR glycine coenzyme fingerprint (TGGSGGIG), the catalytic Tyr-x-x-x-Lys tetrad (YHATK), and the cofactor-discriminating residues (basic cluster R42/K44/K45, no acidic Asp discriminator) all independently indicate a functional NADP-preferring SDR reductase. UniProt keyword *NADP* and the NADPH-dependent characterized ortholog agree.
2. **"Alcohol dehydrogenase (NADP+) activity" (GO:0008106) → WEAKLY / PARTIALLY SUPPORTED.** Defensible as a broad activity class, but it is *less informative and less precise* than the terms PomBase already carries (GO:0016616 CH–OH oxidoreductase; specific sugar/polyol reductase terms), and it remains experimentally unverified. Not the best available MF term.
3. **Arabitol substrate / "arabitol metabolic process" → REFUTED / UNSUPPORTED and technically defective.** No assay links SPAC8E11.10 to arabitol; the closest characterized ortholog acts on L-sorbose/fructose; and the proposed BP is a GO housekeeping problem: the seed cites **GO:0019677, which is actually "NAD+ catabolic process," not arabitol**,

while the genuine "arabitol metabolic process" term (GO:0051161) is **OBSOLETE**. The arabitol call is best read as a paralog/substrate misassignment.

Most important caveat: the enzyme is officially *"conserved unknown"* (uncharacterized). No S. pombe enzymatic assay exists, so every substrate assignment — sorbose, mannitol, xylulose, **or arabitol** — is inference. The prediction is not "correct"; at best it names a plausible-but-unproven pentitol within the right chemical class, wrapped in an obsolete/mis-cited GO term.

Evidence Matrix

#	Citation	Evidence type	Supports/ Refutes/ Qualifies	Claim tested	Key finding	Context
1	UniProt Q9Y6Z9 (database)	Structural/ evolutionary	Qualifies	Fold/ family	SDR family; InterPro IPR002347, Pfam PF13561, CDD cd05352, Rossmann Gene3D 3.40.50.720; kw **NADP**; EC 1.1.1.-	S. pombe protein record
2	This analysis (computational, sequence)	Computational	Supports (NADP), Confirms (SDR)	Motifs/ cofactor residues	Glycine fingerprint **TGGSGGIG** (res 11–22); catalytic **YHATK** (res 163–167); βB region res 33–46 has basic **R42/K44/K45**, **no acidic Asp** → NADP signature	255-aa sequence
3	P 16134116 (primary)	Direct assay (ortholog)	Qualifies / Competing	Substrate & cofactor of ortholog	*C. albicans* SOU1 (P87219) is an **NADPH sorbose reductase**: L-sorbose→D-sorbitol; also fructose→mannitol; **not arabitol**	Purified FLAG-Sou1 C. albicans
4	UniProt CAUTION, ECO:0000269 P 31132130	Mutant/ physiology (species trait)	Refutes	Sorbose reductase function in S. pombe	S. pombe **cannot assimilate L-sorbose** → sorbose-reductase role rejected	Fission-yea carbon-assimilatio physiology
5	PomBase SPAC8E11.10 (database)	Review/ database	Qualifies	Current curation state	Product = "**mitochondrial** oxidoreductase … CH–OH … NAD or NADP acceptor, implicated in carbohydrate assimilation"; **characterisation_status = conserved unknown**;	S. pombe curation

#	Citation	Evidence type	Supports/ Refutes/ Qualifies	Claim tested	Key finding	Context
					MF GO:0016616, GO:0050085 (mannitol 2-DH NADP+), GO:0032115 (sorbose reductase); CC GO:0005739	
6	PANTHER PTHR43008:SF13 (database)	Computational	Competing (alt. substrate)	Substrate class	Nearest subfamily = "**L-xylulose reductase-related**" (dicarbonyl/ xylulose→xylitol, NADPH)	Family classificati
6a	P 11882650 (primary)	Direct assay (subfamily)	Competing / Supports (NADP)	Subfamily substrate & cofactor	DCXR = **NADPH**-linked homotetramer, oxidoreduces **xylitol⇌L-xylulose** and α-dicarbonyls	Mammalia recombina DCXR
6b	P 23661708 (primary)	Direct assay (subfamily)	Competing	Subfamily substrate	Human DCXR reduces α-dicarbonyls and L-xylulose (SDR superfamily)	Recombina human DC
7	QuickGO/GO (database)	Database	Refutes term validity	Arabitol BP term	Seed's **GO:0019677** = **"NAD+ catabolic process"** (mis-cited); real "arabitol metabolic process" **GO:0051161 is OBSOLETE** (also GO:0051162/0051163)	GO ontolog

GO Curation Implications (leads — require curator verification)

- **GO:0008106 "alcohol dehydrogenase (NADP+) activity" (MF):** Do **not** add as a specific experimental call. If any MF is asserted computationally, prefer the more accurate, already-present **GO:0016616** ("oxidoreductase activity, acting on the CH–OH group of donors, NAD or NADP as acceptor") with an ISS/IEA evidence code and a "conserved unknown" caveat. GO:0008106 is an acceptable-but-suboptimal generalization; it is neither wrong nor the most informative supported term.
- **Arabitol metabolic process (BP): Reject.** The cited GO:0019677 is the wrong term (NAD+ catabolism) and the intended arabitol term (GO:0051161) is obsolete. There is no substrate-level evidence. Do not annotate an arabitol BP.
- **Sorbose reductase (GO:0032115) / mannitol 2-dehydrogenase NADP+ (GO:0050085):** These orthology- transferred terms should be retained only as low-confidence predictions with the existing CAUTION; the sorbose role is explicitly disfavored at species level.
- **Recommended framing:** Retain the gene as an uncharacterized NADP-preferring SDR CH–OH oxidoreductase (carbohydrate assimilation, mitochondrion). The BioReason arabitol/NADP-ADH output should **not** upgrade the annotation beyond the current predicted state.

Mechanistic Scope

Immediate molecular function under test = a single-domain, cytosolic/mitochondrial **NADP(H)-dependent short-chain oxidoreductase** that reversibly interconverts a sugar/polyol CH–OH group with the corresponding carbonyl (ketose ⇌ polyol), using the Tyr/Lys catalytic couple and an NADP cofactor. This is a *direct* enzymatic activity claim. "Arabitol metabolic process" and "carbohydrate assimilation" are *pathway/physiology-level* consequences that would follow only if the true substrate were arabitol/a pentitol — which is not established. No loss-of-function phenotype, localization-driven, or developmental inference is invoked by the prediction; the CC (mitochondrion) is itself predicted.

Conflicts and Alternatives

- **Paralog/ortholog substrate transfer:** The "sou1" name and arabitol/sorbose reasoning derive from *C. albicans* SOU1, whose measured activity is sorbose/fructose (not arabitol). Transferring a substrate across ~1 billion years of fungal divergence is unreliable, and UniProt already flags this.
- **Competing subfamily assignment:** PANTHER places the protein closest to **L-xylulose reductase / DCXR** (P 11882650 P 23661708 P 21300042), an NADPH-dependent pentose/pentitol/α-dicarbonyl reductase (xylitol⇌L-xylulose). This is a different (though chemically adjacent) substrate space than arabitol, and — together with the Candida SOU1 sorbose/fructose data — gives **two independent comparators that are NADPH-dependent but not arabitol-specific**.
- **Species physiology:** S. pombe does not use L-sorbose, directly conflicting with a sorbose-reductase reading and casting doubt on naive polyol-substrate transfers generally.
- **Cofactor caveat:** The NADP signature is a sequence heuristic; some SDRs with basic βB residues retain measurable NAD activity. Without a holoenzyme structure or kinetics, NAD+ cannot be fully excluded, though NADP+ is the better-supported call.

Knowledge Gaps

Gap	What was checked	Why it matters	What would resolve it
True physiological substrate	Orthology (sorbose/fructose), PANTHER (L-xylulose), UniProt/PomBase (unknown)	Determines whether *any* specific MF/BP is annotatable	Purified-enzyme substrate screen across polyols/ketoses (arabitol, sorbose, xylulose, mannitol, fructose)
NAD vs NADP kinetics	Sequence fingerprint + kw + ortholog	Distinguishes GO:0008106 (NADP+) from an NAD+ term	Cofactor-titration kinetics on recombinant Q9Y6Z9
Subcellular location	PomBase CC=mitochondrion (predicted)	Affects CC annotation and pathway context	Fluorescent-tag / fractionation localization
Arabitol relevance in S. pombe	GO term status (obsolete), literature (none found)	If S. pombe lacks arabitol metabolism, BP is moot	Metabolomic/growth assay on arabitol as C source

Discriminating Tests

1. **Recombinant enzyme substrate panel** (most decisive): assay purified Q9Y6Z9 for reductase activity on D-/L-arabitol-linked ketoses (D-xylulose, L-xylulose, ribulose), L-sorbose, D-fructose, and corresponding polyol oxidation, with NADPH and NADH side-by-side. Directly separates arabitol vs sorbose vs xylulose specificity and NAD vs NADP.
2. **AlphaFold holo-modeling + docking** of NADP vs NAD and candidate polyols into the active site to corroborate the cofactor fingerprint and rank substrates.
3. **Δsou1 growth phenotyping** on arabitol, sorbose, xylitol, mannitol as sole carbon sources.
4. **Phylogenetic reconciliation** of the fission-yeast SDR clade vs Candida SOU1 vs DCXR/L-xylulose reductase to test whether "sou1" orthology actually implies sorbose/arabitol substrate.

Curation Leads (require curator verification)

- **Action change:** Do not adopt the BioReason arabitol/NADP-ADH prediction as a specific annotation. Keep gene as uncharacterized NADP-preferring SDR CH–OH oxidoreductase.
- **Candidate MF (if any):** GO:0016616 (ISS/IEA) preferred over GO:0008106; both experimentally unproven.
- **Reject BP:** arabitol metabolic process — wrong/obsolete GO ID (GO:0019677 = NAD+ catabolic; GO:0051161 obsolete).
- **Candidate references to verify:**

  P 16134116
  (ortholog assay);

  P 31132130
  (species carbon physiology, basis of UniProt CAUTION); UniProt Q9Y6Z9; PomBase SPAC8E11.10; PANTHER PTHR43008:SF13.
- **Suggested question for curators:** Is there any S. pombe experimental evidence (kinetics, phenotype, metabolomics) for arabitol metabolism at all? If not, the BP prediction cannot stand.
- **Suggested experiment:** recombinant substrate/cofactor panel (Discriminating Test 1).

Provenance artifacts: `sou1_evidence_matrix.png` (computed SDR motif / cofactor-residue analysis and evidence table) and `sou1_GO_decision_table.png` / `sou1_GO_decision_table.csv` (per-term curation decision table). All computational results above are sequence/database-derived inference, explicitly distinguished from direct assays (P 16134116 on the *C. albicans* ortholog and P 11882650 / 23661708 on the DCXR/L-xylulose reductase subfamily — none performed on Q9Y6Z9 itself, which remains enzymatically uncharacterized).

GO Decision Table (leads — curator verification required)

GO term	Aspect	Source	Verdict	Curation action	Rationale
GO:0008106 alcohol dehydrogenase (NADP+) activity	MF	BioReason	Weakly/ partially supported	Generalize / keep only as low-conf ISS	Fold+NADP signature fit broad class; no assay; less precise than GO:0016616
"arabitol metabolic process" (seed cited GO:0019677 = *NAD+ catabolic process*)	BP	BioReason	Refuted / defective	**Do NOT add**	No substrate evidence; comparators = sorbose/fructose & xylulose/xylitol; GO:0051161 obsolete; GO ID mis-cited
GO:0016616 oxidoreductase, CH-OH donor, NAD/NADP acceptor	MF	PomBase ISS/IEA	Retain	Keep as best-supported MF	Matches fold+cofactor; conservative
GO:0032115 sorbose reductase activity	MF	PomBase ISS(ortholog)	Disfavored	Retain only with CAUTION	S. pombe cannot assimilate L-sorbose (P 31132130)
GO:0050085 mannitol 2-dehydrogenase (NADP+) activity	MF	PomBase ISS	Uncertain	Keep as low-conf prediction	Ortholog fructose→mannitol side-activity; unproven
GO:0005739 mitochondrion	CC	PomBase predicted	Uncertain	Keep as predicted	Localization not experimentally confirmed