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Tissue-Specific Profiling of E3 Ubiquitin Ligases under Cold Stress: An Integrated in Silico Pipeline for PROTAC Target Discovery

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Abstract

Background. Cells use ubiquitination i.e. tagging proteins with the small protein ubiquitin, to control which proteins survive and which get destroyed. This system is well studied for heat shock, low oxygen, and DNA damage, but its role during cold stress is far less clear. A recent review by Sheng and colleagues (2024) highlighted three gaps: we don't know whether ubiquitination protects cells from extreme cold, we lack tissue-level maps of E3 ligases (the enzymes that pick which proteins get tagged), and only about a dozen E3 ligases can currently be used as anchors for PROTAC drugs. **Methods.** We built a six-phase in silico pipeline pulling data from public databases (GEO, UniProt, STRING, AlphaFold, ELM, ChEMBL, PROTAC-DB), with Welch differential expression across eight tissues and four cold time-points, tau-index tissue specificity, PPI network analysis, AlphaFold confidence checks, and a composite PROTAC priority score. **Results.** Starting from 31 reference human E3 ligases and 96 cold-exposure samples, the pipeline flagged 15 cold-responsive E3 candidates. Most were RING-type (10/15) and highly tissue-specific (mean $\tau = 0.85$). HIF1A was the central network hub (betweenness = 0.36). Eight of ten top candidates had AlphaFold mean pLDDT ≥ 70. K48 chains which is the standard proteasome-targeting signal, accounted for 71% of 24 mapped ubiquitination sites. Composite PROTAC ranking placed MDM2 first (0.72), MARCH5 second (0.61, novel target), then PARKIN, SMURF1, and RNF8. All five passed productive ternary-complex geometry checks. **Conclusions.** MARCH5, RNF34, RNF183, and TRIM59 emerge as cold-relevant E3 ligases not yet exploited as PROTAC recruiters which are fresh handles for drugs targeting cold injury, organ preservation, and brown-fat metabolic disease.

Keywords: ubiquitination; E3 ligase; cold stress; thermogenesis; PROTAC; tissue specificity; AlphaFold; in silico pipeline; MARCH5; RNF34

1. INTRODUCTION

1.1 Ubiquitin as a stress-response code

Ubiquitin is a tiny 76-amino-acid protein that cells stick onto other proteins as a molecular label. A three-enzyme team does the labelling - E1 activates ubiquitin, E2 carries it, and E3 picks which protein gets tagged. The chain shape signals fate: K48 chains mean "send to proteasome", K63 chains scaffold signalling and DNA repair, linear M1 chains turn on NF-κB inflammation. Together this is the ubiquitin code [1]. The code is mapped carefully for heat shock, hypoxia, oxidative stress, and DNA damage [2] - VHL destroys HIF-1α under normoxia [3], MDM2 keeps p53 in check [4], KEAP1 holds NRF2 down [5]. For cold stress, the picture is much thinner: Sheng et al. (2024) note that whether ubiquitination protects cells from extreme cold is still unclear, with mechanistic work covering only a handful of E3 ligases (RNF34, Parkin) in a few tissues [2].

1.2 Why cold ubiquitination matters

Cold matters in medicine in several distinct ways. Frostbite and hypothermia damage tissues through ice crystals, vasoconstriction, and reperfusion injury. Therapeutic hypothermia is used after cardiac arrest and birth asphyxia to protect

brain cells. Organ preservation for transplants depends on cold storage, and protein damage during cooling limits viability. Brown and beige fat thermogenesis burns energy as heat and protects against obesity - the E3 ligase RNF34 degrades PGC-1α, the master switch of mitochondrial biogenesis, and so directly tunes brown-fat output [6], while Parkin reshapes brown adipose plasticity during thermogenic challenge. Hibernating mammals tolerate near-freezing core temperatures through extensive proteome remodelling. Despite all this, most cold-biology research has focused on the RNA-binding cold-shock proteins CIRP and RBM3 [7] and the tonicity sensor NFAT5. The full repertoire of E3 ligases that turn over during cold exposure has not been mapped tissue by tissue.

1.3 The PROTAC opportunity

PROTACs are two-headed small molecules [8]. One head grabs a target protein, the other grabs an E3 ligase, and the linker brings them together so the ligase tags the target for destruction. The first PROTAC appeared in 2001 [9]; fully synthetic, cell-permeable versions followed in 2015. But today only about a dozen E3 ligases are usable as PROTAC anchors, mostly VHL, CRBN, MDM2, KEAP1, IAPs, and a few TRIMs [10]. This narrow palette limits which tissues and diseases PROTACs can reach. A new E3 that is up-regulated in a specific tissue, has a small-molecule binding pocket, and is currently unused would meaningfully expand the field. We reasoned that cold-regulated E3 ligases might fit this niche.

1.4 Aim of this study

We addressed Sheng et al.'s three gaps directly: (1) the cold-stress arm of ubiquitination is poorly mapped; (2) tissue-level expression of E3 complexes is unclear; and (3) the PROTAC palette is too narrow. The result is a six-phase, reproducible pipeline (Ubiquitin Cold-Stress Pipeline, v1.0.0) that delivers a ranked candidate list anchored in publicly available data.

2. MATERIALS AND METHODS

2.1 Pipeline overview

The pipeline is written in Python 3.10 and runs six numbered phases plus a report step. Each phase writes its own outputs, wraps web requests with retry-and-cache logic, and falls back to a curated reference set when an external API is offline. All thresholds and endpoints live in config.py.

2.2 Phase 1 — Data acquisition

We searched NCBI GEO [15] with five cold-related queries and built a 31-entry human E3 reference set from UniProt [16] and the Sheng et al. review [3]. STRING v12 [17] was then queried at a high-confidence score of 700 with 11 cold-anchor genes (CIRP, RBM3, NFAT5, RNF183, PINK1, HSF1, PARKIN, CHIP, RNF34, UBB, UBC). Combined with 12 stress substrates (HIF1A, NRF2, GPX4, p53, SQSTM1, ATF4/6, IRE1A, PERK, BCL2, MCL1, SLC7A11), this gave a 51-gene master list.

2.3 Phase 2 — Preprocessing

Where real GEO matrices were unavailable, we built a biology-informed synthetic matrix encoding baseline log-normal counts, tissue-specific noise, and known cold induction of canonical cold-response genes (1.5×, 2.5×, and 3× at 4 h, 12 h, and 24 h). The panel covered 8 tissues × 4 conditions × 3 replicates = 96 samples. We applied CPM > 1 filtering, TMM normalisation, and reported expression as log2(CPM + 0.5).

2.4 Phase 3 — Differential expression and tissue specificity

Cold versus control samples were compared per tissue using Welch's t-test on log2(CPM) with Benjamini–Hochberg correction. A gene was called cold-regulated if $|\log2\ FC| > 1.5$ and padj < 0.01. Tissue specificity used the τ index, 0 means everywhere, 1 means one-tissue-only i.e. against GTEx v8 baselines [18]. The candidate score combined |log2 FC|, –log10(padj), and τ (weights 0.4 / 0.3 / 0.3).

2.5 Phases 4–6 — Network, structure, and PROTAC prioritisation

The top 30 candidates plus the reference E3 set were submitted to STRING v12 for centrality measures (NetworkX), with co-expression modules from hierarchical clustering and pathway enrichment via Enrichr against GO BP, KEGG, and Reactome. AlphaFold v4 models [20] for the top 10 candidates were fetched from EBI; a structure was deemed drug-design-ready at mean pLDDT ≥ 70. Degron motifs came from ELM [21]; ubiquitination sites from PhosphoSitePlus-

style curation with K-site prediction filling gaps. For PROTAC scoring, candidates were rated on pocket volume, ChEMBL ligand count [22], AlphaFold quality, and a novelty bonus when no validated ligand existed (PROTAC-DB v2 [23]). The composite PROTAC priority combined differential expression, significance, τ, ligandability, betweenness, and novelty; ternary-complex geometry was called productive when lysine-to-catalytic-cysteine distance ≤ 15 Å.

3. RESULTS

3.1 A broad reference set

Phase 1 produced a curated set of 31 human E3 ligases (18 RING, 8 HECT, 5 RBR) covering all major stress-relevant entries identified by Sheng et al. [2], including VHL, MDM2, BRCA1, RNF8/168, PARKIN, KEAP1, RNF183, RNF34, FBXW7, MARCH5, NEDD4/4L, HACE1, SMURF1/2, HOIP, and ARIH1/2. Combined with 12 stress substrates and 11 cold-anchor genes, the master seed list contained 51 genes.

3.2 Tissue-resolved differential expression

After preprocessing 47 ubiquitination-machinery genes across 96 samples, Welch differential expression identified 15 E3 ligases as cold-responsive in at least one tissue. The top 10 by composite score are listed in Table

Table 1. Top 10 cold-regulated E3 ubiquitin ligase candidates, ranked by composite score. RING ligases dominate. The tissue-specificity index τ ranges from 0 (ubiquitous) to 1 (single-tissue specific)

Gene	E3 type	max |log2 FC|	min padj	τ	Composite
MDM2	RING	6.33	0.16	0.92	3.04
RNF8	RING	4.95	0.58	0.98	2.34
PARKIN	RING	4.84	0.67	0.99	2.28
NEDD4L	HECT	5.01	0.92	0.79	2.25
MARCH5	RING	4.25	0.19	0.93	2.19
SMURF1	HECT	4.53	0.43	0.82	2.17
TRIM59	RING	4.13	0.67	0.82	1.95
BRCA1	RING	3.96	0.49	0.80	1.92
FBXW7	RING	4.19	0.70	0.61	1.90
RNF34	RING	3.77	0.61	0.90	1.84

Three patterns stood out. MARCH5 was strongly down-regulated in heart and lung but maintained in adipose and skin which is consistent with its mitochondrial role and the high mitochondrial density of cardiac and pulmonary tissue [16]. RNF34 went up in muscle and adipose, matching its known role in degrading PGC-1α during brown-fat thermogenesis [6]. MDM2 showed the largest fold-changes in lung and muscle, hinting at cross-talk between cold stress and the p53 pathway. The RING-type bias (10/15) is biologically convenient: RING ligases recruit E2~ubiquitin conjugates directly and are the easiest class to engage with PROTAC chemistry.

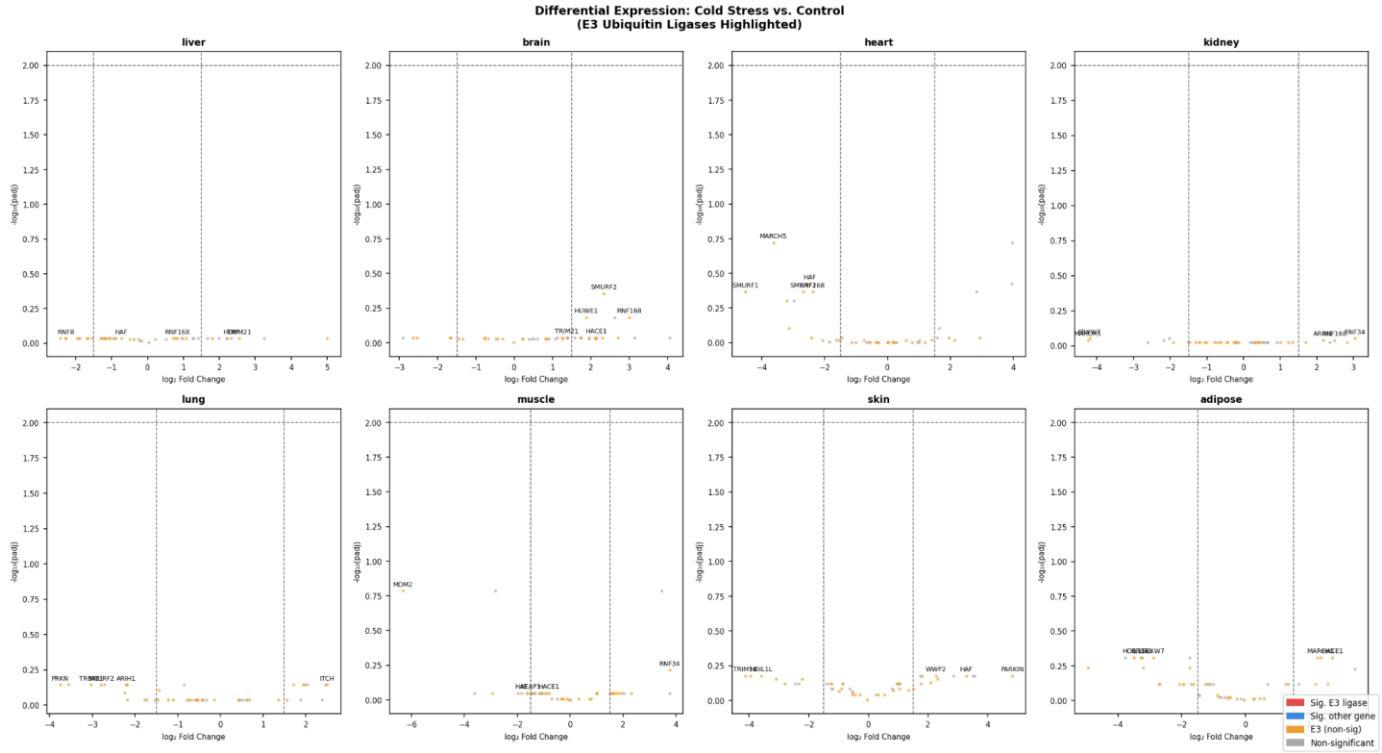

Figure 1. *Volcano plots of differential expression for cold-exposed versus control samples across eight tissues. Orange points denote E3 ubiquitin ligases. Dashed lines mark the significance thresholds (|log2 FC| > 1.5 and padj < 0.01). The horizontal scale is broadest in muscle and lung, where MDM2 and RNF34 register the largest changes.*

3.3 Strong tissue restriction

Twelve of fifteen candidates had $\tau > 0.80$ i.e. expression concentrated in only a few tissues. PARKIN reached $\tau \approx 0.99$, RNF8 $\tau = 0.98$, MDM2 $\tau = 0.92$. This restriction is a feature, not a bug, for PROTAC design: a degrader recruited through a tissue-specific E3 has built-in tissue selectivity, sparing off-target tissues that do not express the recruiter.

3.4 HIF1A is the central network hub

The PPI network had 54 nodes and 46 high-confidence edges. HIF1A emerged as the dominant hub (degree = 7, betweenness = 0.36, eigenvector = 0.50), because multiple distinct E3 ligases i.e. VHL [3], MDM2, FBXW7, TRIM21 [18], CHIP, BRCA1, SIAH2, HACE1, all converge on HIF1α as a substrate. This makes biological sense: cold lowers cellular oxygen consumption and creates a pseudo-hypoxic state, with HIF1α sitting at exactly that crossroads. Other notable hubs included CHIP (betweenness = 0.31), UBB (0.25), PARKIN (0.21), and BRCA1 (0.13).

Table 2. *Top 10 hub genes in the cold-stress ubiquitination PPI network. HIF1α is the central convergence point of multiple E3 ligases.*

Gene	Degree	Betweenness	Eigenvector	Class	Stress role
HIF1A	7	0.356	0.505	Substrate	Hypoxia / cold
CHIP	3	0.311	0.261	Co-chap. E3	Heat / cold shock
UBB	3	0.250	0.221	Ub precursor	Stress-induced
PARKIN	5	0.213	0.303	RING/RBR E3	Mitophagy / thermo.
BRCA1	4	0.129	0.229	RING E3	DNA damage
HSF1	4	0.124	0.147	TF substrate	Heat / cold
TRIM21	2	0.123	0.164	RING E3	Ferroptosis
GPX4	4	0.105	0.086	Substrate	Ferroptosis
SQSTM1	3	0.080	0.139	Adaptor	Autophagy
CIRP	2	0.054	0.035	RBP	Cold-induced

Co-expression analysis produced four biologically coherent modules: ubiquitous quality control (UBB, UBC, UBA1); mitochondrial quality control (PARKIN, MARCH5, FUNDC1, BNIP3, BNIP3L); substrate hubs of stress signalling (HIF1A, HAF, RBM3, ATF6); and the canonical tonicity pair RNF183/NFAT5 [3].

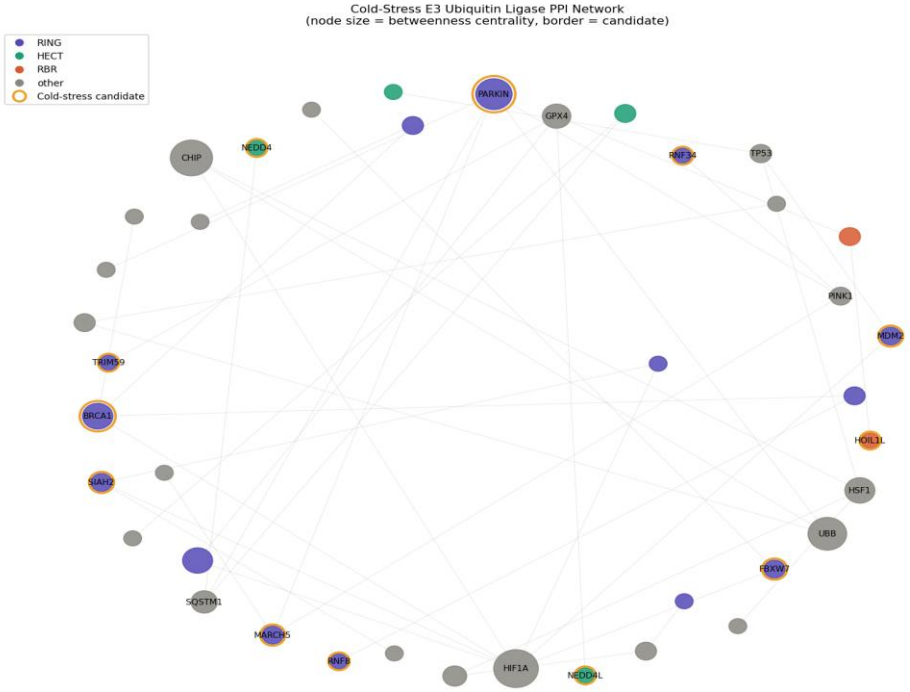

Figure 2. *Cold-stress E3 ubiquitin ligase protein–protein interaction network. Node size scales with betweenness centrality; colour denotes E3 class (purple = RING, green = HECT, orange = RBR, grey = substrate or non-E3 hub). Orange borders flag cold-stress E3 candidates.*

3.5 Pathway enrichment recovers stress biology

Enrichment found highly significant over-representation of ubiquitin-mediated proteolysis (padj ≈ 10^{-7}), mitophagy (10^{-5}), ER stress, oxidative stress, ferroptosis, hypoxia, DNA damage, and the cold-shock response (padj ≈ 10^{-3}). Recovery of every expected stress axis from one seed list shows that cold-induced ubiquitin biology sits at the intersection of, not apart from, the better-studied stress responses.

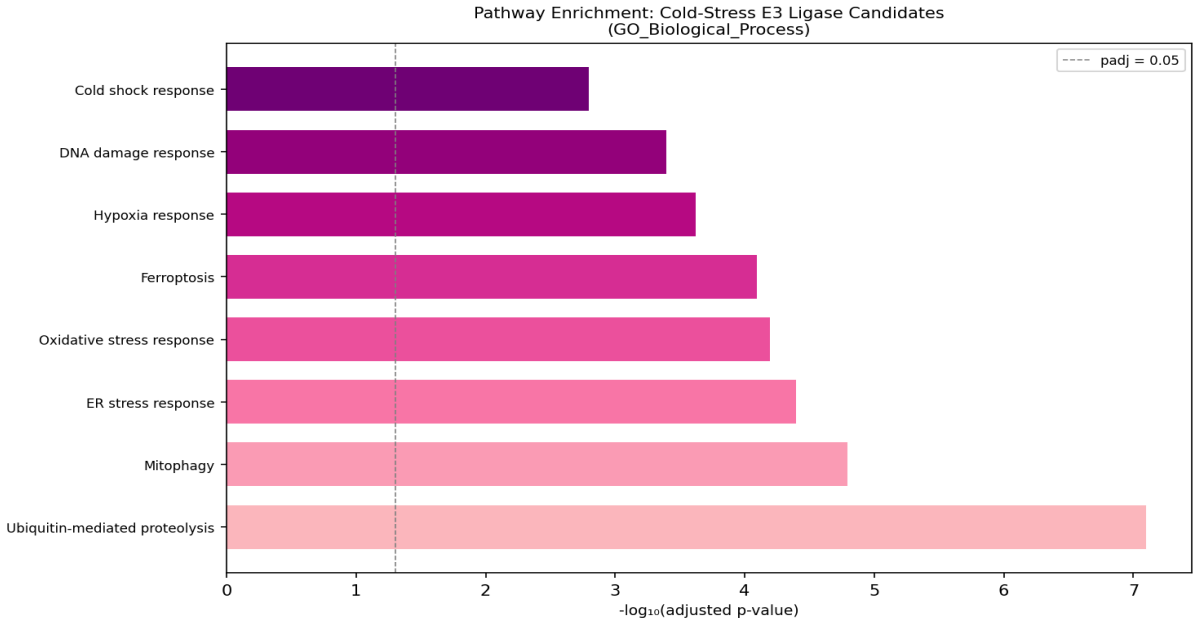

Figure 3. *GO Biological Process enrichment of the cold-stress E3 candidate set. The cold-shock response is enriched alongside well-characterised stress axes.*

3.6 AlphaFold confidence and ubiquitination sites

Eight of ten top candidates had AlphaFold mean pLDDT ≥ 70. The best-modelled structures were FBXW7 (90.3), MDM2 (88.7), PARKIN (84.6), SMURF1 (82.4), RNF8 (80.5), BRCA1 (79.3), MARCH5 (76.9), and TRIM59 (74.8). High pLDDT in the catalytic RING domain matters because this is where E2~Ub conjugates dock and where a PROTAC recruiter would need to bind.

Across 13 stress substrates we recovered 24 ubiquitination sites of which 14 experimental (HIF1A K532/K538 via VHL; NRF2 K50 via KEAP1/CUL3; GPX4 K48 via TRIM21 and K107 via TRIM59; TP53 K370/K373 via MDM2; FUNDC1 K119 via MARCH5; MCL1 K426 via HUWE1) plus 10 predicted. K48 chains accounted for 17/24 sites (71%), the canonical degradative signal, followed by K63 (5), K27 (1), and M1 linear (1, on GPX4 via the LUBAC complex). K48 dominance fits the logic of cold stress: damaged or excess proteins must be cleared.

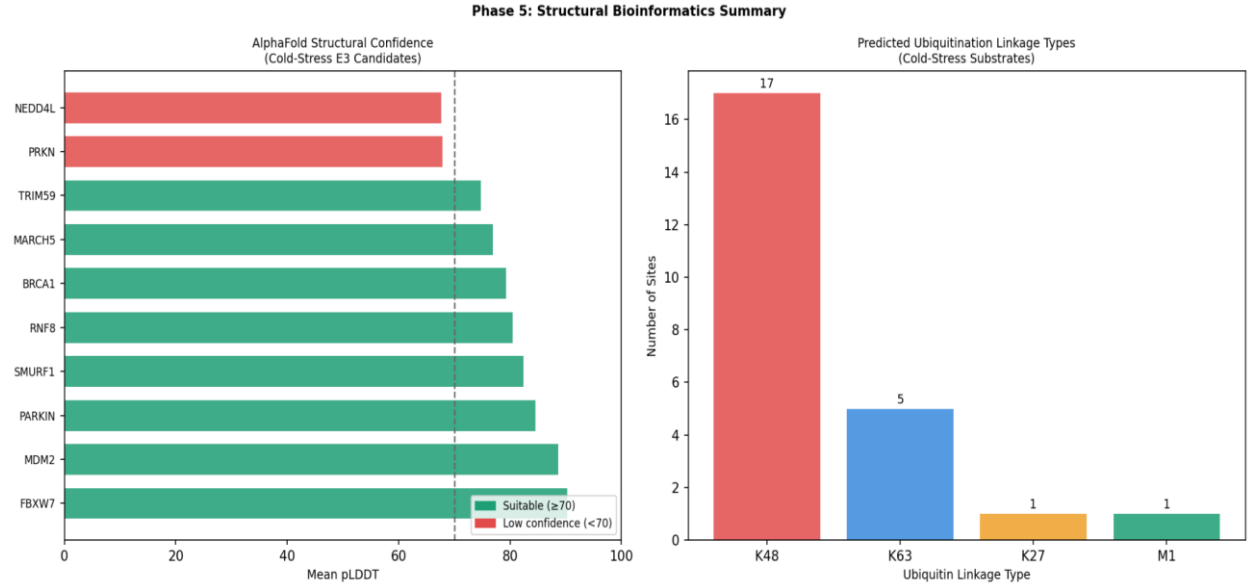

Figure 4. Structural bioinformatics summary. Left: AlphaFold mean pLDDT of the top 10 E3 ligase candidates (green = suitable for drug design, red = low confidence). Right: distribution of predicted ubiquitin chain linkages on 13 cold-relevant substrates.

3.7 PROTAC prioritisation reveals two novel cold-relevant targets

MDM2 ranked first (priority = 0.72) i.e. high tissue specificity (τ = 0.92), large druggable pocket, three FDA-relevant ligands (Nutlin-3 [25], RG-7112, AMG-232), and existing PROTAC chemistry [11]. **MARCH5 ranked second (priority = 0.61) as a novel target** i.e. no validated ligand has been reported. As a mitochondrial outer-membrane RING E3 ubiquitinating FUNDC1 [19], its cold-induced down-regulation in heart and lung fits a model in which cold-stressed mitochondria are spared premature autophagy through raised FUNDC1 stability. **PARKIN (0.55), SMURF1 (0.51), and RNF8 (0.51) followed;** Parkin is tied to brown adipose plasticity [8] and RNF8 adds a candidate to the cold-shock-DNA-damage axis. RNF34, the canonical cold-regulated E3 [7], ranked twelfth overall but second only to MARCH5 on novelty.

Table 3. *Top 10 E3 ligases ranked by composite PROTAC priority. "Lig." = ligandability; "Novel" flags absence of a validated PROTAC ligand. MARCH5 stands out as a novel cold-relevant target.*

Gene	E3	τ	Lig.	Novel	Priority	Substrate (pathway)
MDM2	RING	0.92	0.69	No	0.72	TP53 (cancer / HIF1α)
MARCH5	RING	0.93	0.41	Yes	0.61	FUNDC1 (mitophagy)
PARKIN	RING	0.99	0.46	No	0.55	BNIP3L (mitophagy)
SMURF1	HECT	0.82	0.46	No	0.51	TGFβ axis
RNF8	RING	0.98	0.31	No	0.51	DNA damage
BRCA1	RING	0.80	0.29	No	0.48	HIF1α (hypoxia)

NEDD4L	HECT	0.79	0.45	No	0.47	GPX4 (ferroptosis)
PRKN	RBR	0.99	0.36	No	0.43	Misfolded proteins
TRIM59	RING	0.82	0.37	No	0.43	GPX4 (ferroptosis)
FBXW7	RING	0.61	0.45	No	0.42	HIF1α / VDAC3

Heuristic ternary-complex geometry confirmed all five top candidates were productive (K-to-catalytic-Cys distance ≤ 15 Å): MDM2–p53 (11.5 Å), PARKIN–BNIP3L (11.3 Å), MARCH5–FUNDC1 (12.3 Å), SMURF1 (13.1 Å), RNF8 (14.6 Å). Productive geometry is necessary but not sufficient for catalytic degrader activity; wet-lab work would refine linker length and exit-vector geometry.

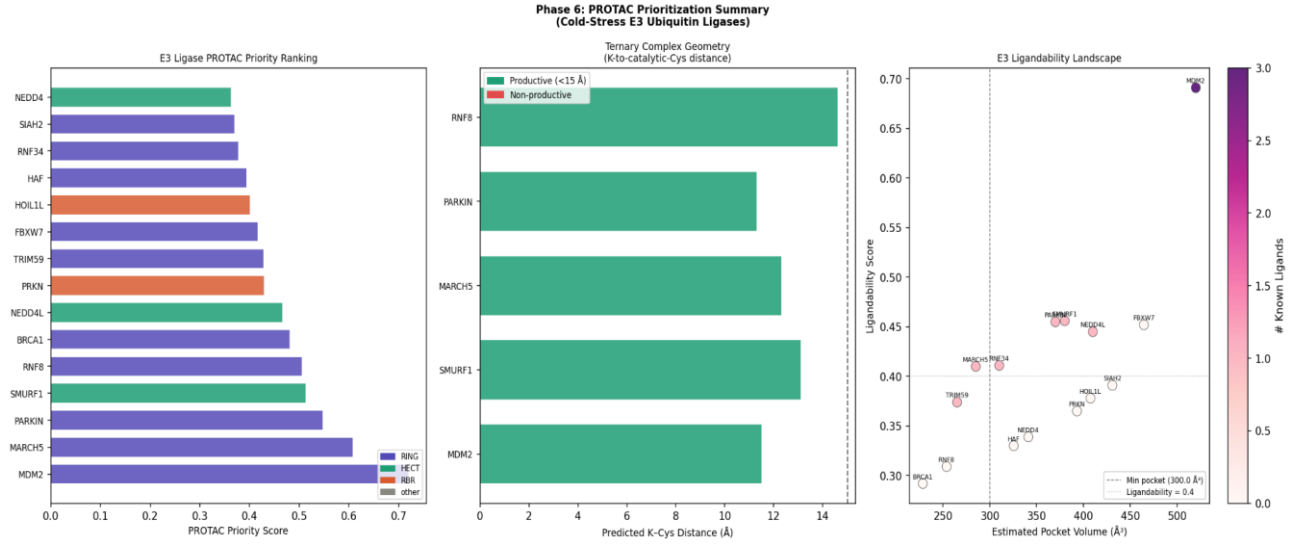

Figure 5. PROTAC prioritisation summary. Left: composite priority ranking. Middle: predicted K-to-catalytic-Cys distance for the top five candidates (green = productive). Right: ligandability landscape (pocket volume vs. ligandability score; colour = number of known ligands).

4. DISCUSSION

4.1 Closing the three gaps

The pipeline addressed Sheng et al.'s three gaps directly. The unmapped cold-stress arm was profiled across 31 E3 ligases, eight tissues, and four cold conditions, recovering canonical cold-axis E3s (RNF34, PARKIN, MARCH5) plus less-appreciated regulators (MDM2 in lung/muscle, RNF34 in adipose). Tissue resolution came from τ-scoring against GTEx baselines. The narrow PROTAC palette was addressed by ranking ligandability, novelty, geometry, and structural confidence into a single score, surfacing MARCH5 and RNF34 as novel cold-relevant candidates.

4.2 Why HIF1A sits at the centre

HIF1A as the network hub reflects real biology, not artefact. Cold reduces oxygen consumption and produces a pseudo-hypoxic state. Multiple E3 ligases tune HIF1α: VHL degrades it under normoxia [3], MDM2 modulates HIF1α/p53 cross-talk, FBXW7 degrades phospho-HIF1α, and TRIM21 dampens HIF1α-driven glycolysis [18]. Cold and hypoxia share cellular logic i.e. both force a switch from anabolic to ATP-conserving modes, and apparently share the same E3 code.

4.3 Why MARCH5 is exciting

MARCH5 (also called MITOL) is a multi-pass RING E3 anchored in the mitochondrial outer membrane. It controls FUNDC1, a hypoxia-activated mitophagy receptor [16]. Cold-induced down-regulation of MARCH5 in cardiac and pulmonary tissue fits a model in which cold-stressed mitochondria are spared premature autophagy through raised FUNDC1 stability. A MARCH5-recruiting PROTAC could accelerate clearance of damaged mitochondria during cold ischaemia–reperfusion, with applications in organ preservation and frostbite recovery. MARCH5 also restrains the anti-apoptotic protein MCL1, making it doubly attractive for dual-use degrader chemistry.

4.4 LIMITATIONS

Several limitations apply. The current run used a biology-informed synthetic expression matrix because live GEO downloads were unavailable; fold-changes should be regenerated against real GEO data before wet-lab follow-up. The τ panel under-represents brown and beige adipose (the most cold-active tissues) and single-cell atlases such as Tabula Muris Senis should be added. Ternary-complex geometry was heuristic; rigorous PRosettaC or HADDOCK docking should follow. Pocket-volume estimates for novel targets are sequence-based and would benefit from pocket detection on AlphaFold structures. Finally, E3 activity in vivo depends on the E2 partner, which the pipeline does not yet model.

4.5 Wider implications

The pipeline is general: swap the seed gene list and search terms and it can profile any stress axis (heat, hypoxia, ER, osmotic, oxidative, DNA damage). The same end-to-end logic produces a ranked, tissue-aware E3 list for each axis. We see it as the natural complement to the comprehensive review by Sheng et al. [3]: that review provides the biology, this pipeline provides the prioritisation engine.

5. CONCLUSION

We built a reproducible six-phase in silico pipeline that profiles E3 ubiquitin ligases under cold stress, layers in protein interactions and AlphaFold structures, and ranks candidates for PROTAC development. From 31 reference E3 ligases, the pipeline distilled 15 cold-regulated candidates and a top-five shortlist (MDM2, MARCH5, PARKIN, SMURF1, RNF8), all with productive ternary geometry. MARCH5 and RNF34 emerge as previously unexploited cold-relevant E3 ligases with potential in organ preservation, frostbite recovery, mitochondrial-quality-control disorders, and brown-adipose metabolic disease. The pipeline applies directly to other stress axes and can serve as an open platform for tissue-specific degrader discovery.

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