

Multi-Layer Computational Prioritisation of Platinum-Resistance Inhibitors in Colorectal Cancer: Transcriptomic Stratification, Multi-Target Docking, and Integrated Candidate Ranking

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Research Article

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Abstract

Background. Oxaliplatin resistance is a principal driver of treatment failure in advanced colorectal cancer (CRC). Its molecular basis involves converging DNA-repair, redox, and iron-metabolism programmes, but no computational study has integrated transcriptomic resistance stratification with multi-target docking across this full set of pathways.

Methods. We assembled a 14-gene platinum-resistance panel and stratified 436 TCGA-COAD primary tumours into High-Resistance (n=274) and Low-Resistance (n=162) clusters by unsupervised k-means clustering on z-scored expression data. Differential expression was assessed by Mann–Whitney U with Benjamini–Hochberg correction. Six top-ranked candidates were docked against three validated structures: SLC7A11 (PDB 7EPF, 2.70Å), ERCC1–XPF (PDB 2BGS, 1.64Å), and CTR1 (PDB 7MHK, 1.96Å) using AutoDock Vina. Docking was validated by redocking (RMSD 1.315Å) and active/decoy discrimination (ROC-AUC=0.947, EF@10%=4.0×). Candidates were ranked by a weighted composite score integrating docking affinities and drug-likeness.

Results. Thirteen of 14 genes reached FDR<0.05 in the resistance contrast; ERCC1 did not (FDR=0.243), despite being a classical platinum-resistance mediator. SLC7A11 showed the largest upregulation ($\log_2FC=+1.10$, FDR=4.6×10⁻²⁷). TFRC, ACSL4, and SLC7A11 were co-upregulated, consistent with a ferroptosis-primed but protected phenotype. KRAS status was not associated with resistance cluster (χ^2 p=0.421). Erastin ranked first (composite 8.60) with strong affinity for all three targets (SLC7A11 -10.5; ERCC1-XPF -6.1; CTR1 -8.3 kcal/mol). NSC16168, the most fragment-like compound (MW=212Da), ranked third with strong SLC7A11 (-8.9 kcal/mol) and CTR1 (-8.1 kcal/mol) affinities, leaving extensive chemical space for lead optimisation.

Conclusions. Oxaliplatin resistance in CRC is transcriptomically dominated by SLC7A11 upregulation rather than ERCC1 overexpression, pointing to ferroptosis suppression as the primary resistance axis. Erastin and NSC16168 emerge as dual-pathway candidates warranting in vitro validation in isogenic oxaliplatin-resistant CRC lines.

1. Introduction

Colorectal cancer (CRC) ranks third in global incidence and second in cancer-related mortality [1]. Oxaliplatin-based regimens (FOLFOX, CAPOX) remain first-line for advanced CRC, yet acquired resistance develops in the majority of patients within 6–12 months [2]. The molecular mechanisms are heterogeneous: ERCC1–XPF-mediated nucleotide excision repair (NER) removes platinum–DNA adducts; copper transporter CTR1 (SLC31A1) mediates cellular uptake of oxaliplatin and cisplatin [3, 4, 23]; reduced CTR1 activity lowers intracellular drug accumulation and confers resistance. SLC7A11 (xCT)-dependent glutathione biosynthesis sustains GPX4 activity and dampens the oxidative burden imposed by platinum–DNA adducts [8]. Additional contributions come from mismatch repair (MSH2, MSH6, MLH1) and homologous recombination (BRCA1, RAD51). HR-proficient cells can remove platinum–DNA adducts more efficiently; BRCA1 and RAD51 upregulation therefore predicts resistance

rather than sensitivity [5, 6]. Mismatch repair deficiency has the opposite effect: MMR-deficient cells fail to recognise drug-damaged DNA and undergo less apoptosis, a pharmacological paradox seen clinically with cisplatin in MSI-H tumours.

Ferroptosis, an iron-dependent form of regulated necrosis driven by lipid hydroperoxide accumulation [7], has emerged as relevant to platinum sensitivity. SLC7A11 suppresses ferroptosis by importing cystine for glutathione synthesis; high SLC7A11 sustains glutathione synthesis and attenuates the lipid-peroxidation burden that cisplatin and oxaliplatin impose [8]; GPX4 expression may paradoxically fall in this setting, as upstream thiol buffering reduces the cell's dependence on the terminal hydroperoxide detoxification step. Oxaliplatin reduces GPX4 expression in CRC cells and activates ferroptotic pathways; NRF2 inhibition potentiates this effect [9], linking the NRF2–GPX4 axis directly to platinum chemosensitivity.

Computational multi-target docking provides a hypothesis-generating framework for identifying compounds that could address resistance through more than one mechanism simultaneously. Disrupting SLC7A11 (to restore ferroptosis priming [21, 22]), ERCC1–XPF (to block adduct removal), and CTR1 (to maintain intracellular platinum levels) could each sensitise resistant tumours; compounds that hit multiple targets are especially attractive. To our knowledge, no prior study has combined TCGA-COAD transcriptomic resistance stratification with coordinated docking across all three targets.

Here we report a three-layer analysis: (i) unsupervised transcriptomic resistance stratification of 436 TCGA-COAD tumours using a 14-gene panel; (ii) validated multi-target docking against SLC7A11, ERCC1–XPF, and CTR1; and (iii) integrated candidate ranking incorporating docking affinity, cross-target coverage, and drug-likeness. The result is a ranked list of candidate platinum-resistance sensitisers with a mechanistic rationale for each.

2. Materials and Methods

2.1 Dataset and cohort assembly

RNA-sequencing (STAR-Counts TPM) and somatic mutation data for TCGA-COAD primary tumours were obtained from the NCI Genomic Data Commons. After quality control, 436 samples with complete clinical and expression data were retained. Expression values were $\log_2(\text{TPM} + 1)$ transformed. The study used only publicly available, de-identified data and required no ethics approval.

2.2 Resistance stratification

A 14-gene platinum-resistance panel was assembled from literature-curated genes spanning NER (ERCC1, XPC), homologous recombination (BRCA1, RAD51), mismatch repair (MSH2, MSH6, MLH1), drug efflux (ABCC2), glutathione metabolism (GSTP1), and ferroptosis regulation (SLC7A11, GPX4, ACSL4, NFE2L2, TFRC). Genes were z-scored across all 436 samples. A resistance score was computed as the mean of DNA-repair and efflux gene z-scores. K-means clustering ($k = 2$) on the first two principal

components (PC1 32.1%, PC2 14.4%) partitioned samples into High-Resistance (n = 274) and Low-Resistance (n = 162) groups. KRAS mutation status and clinical stage were annotated per sample.

2.3 Differential expression analysis

Group-wise differential expression was tested by Mann–Whitney U; p-values were corrected across all 14 genes simultaneously by the Benjamini–Hochberg (BH) procedure [10]. Genes with FDR < 0.05 were considered significant. Association between KRAS status and resistance cluster was assessed by chi-squared test.

2.4 Target structures

Three protein structures were retrieved from the RCSB Protein Data Bank [11]: SLC7A11 (xCT) in complex with LAT1 (PDB 7EPF, 2.70Å resolution), cross-validated against PDB 7P9U (3.70Å); ERCC1–XPF at the ERCC1–XPA binding interface (PDB 2BGS, 1.64Å); and CTR1 copper transporter (PDB 7MHK, 1.96Å) [17]. Structures were cleaned with PyMOL, polar hydrogens added, and converted to PDBQT format using AutoDockTools.

2.5 Ligand preparation

Fourteen candidate ligands were assembled: known ferroptosis inducers (Erastin, RSL3, Sulfasalazine), NER inhibitors (NSC16168, ERCC1_inh_1, F06), iron chelators, and cystine uptake blockers. SMILES strings were retrieved from PubChem [12]; 3D structures were generated with RDKit [13] and converted to PDBQT with Open Babel. Six platinum-compound analogues (Oxaliplatin, Ammonium_TM, Tetrathiomolybdate, TransPt variants) failed PDBQT conversion and were excluded from docking, leaving ten compounds for all-target docking.

2.6 Molecular docking

Docking was performed with AutoDock Vina 1.2 [14, 20]. Grid boxes were centred on the experimentally determined binding sites for each target (SLC7A11: cystine tunnel; ERCC1–XPF: XPA-binding groove; CTR1: extracellular copper-binding site). Exhaustiveness was set to 8; nine binding modes were generated per ligand. The best affinity (mode 1) was used for scoring.

2.7 Docking validation

Protocol validity was assessed by three criteria: (i) redocking of the co-crystallised Erastin pose into SLC7A11 7EPF (RMSD threshold < 2.0Å); (ii) active/decoy discrimination — five known SLC7A11 actives were docked alongside 15 property-matched decoys (MW, LogP, TPSA matched within 20%), with ROC-AUC and enrichment factor (EF) at 10% and 20% computed; (iii) cross-structure reproducibility of rank ordering across PDB 7EPF and 7P9U. PAINS/promiscuous-scaffold screening was applied to all candidates [15].

2.8 ADMET assessment

Drug-likeness was assessed by Lipinski's Rule of Five (Ro5: $MW \leq 500$, $\text{LogP} \leq 5$, $\text{HBD} \leq 5$, $\text{HBA} \leq 10$) [16]; blood–brain barrier penetration was evaluated by TPSA (threshold $< 90\text{\AA}^2$). QED was computed with RDKit.

2.9 Composite scoring

A weighted composite score integrated docking affinities and drug-likeness: $\text{Score} = \text{norm}(\text{SLC7A11}) \times 0.4 + \text{norm}(\text{CTR1}) \times 0.3 + \text{norm}(\text{ERCC1}) \times 0.2 + \text{QED} \times 0.1$, where $\text{norm}()$ denotes the absolute docking affinity (kcal/mol, sign-inverted); QED is scaled to 0–10 ($\text{QED} \times 10$) before multiplication to place it on the same order as the docking scores. SLC7A11 received the highest weight because it was the single most significantly upregulated gene in the resistance analysis ($\text{FDR} = 4.6 \times 10^{-27}$).

3. Results

3.1 Transcriptomic resistance landscape (n = 436)

K-means clustering of the 14-gene panel partitioned 436 TCGA-COAD tumours into 274 High-Resistance and 162 Low-Resistance samples (Fig. 2A). The two clusters separated along PC1 (32.1% variance), with PC2 (14.4%) adding additional resolution. Thirteen of the 14 genes were differentially expressed at $\text{FDR} < 0.05$ (Table 2, Fig. 2B–E). SLC7A11 showed the largest upregulation in the High-Resistance group ($\log_2\text{FC} = +1.10$, $\text{FDR} = 4.6 \times 10^{-27}$; mean expression 11.47 vs 4.38 $\log_2\text{TPM}$; note: $\text{SD} = 11.72$ reflects the right-skewed distribution characteristic of xCT expression in bulk tumour RNA-seq). Established DNA-repair genes – BRCA1, MSH2, MSH6, RAD51, and XPC – were consistently upregulated. NFE2L2 (NRF2) was also elevated ($\log_2\text{FC} = +0.64$, $\text{FDR} = 2.0 \times 10^{-36}$), consistent with constitutive antioxidant pathway activation in platinum-resistant cells.

Two genes showed downregulation: GPX4 ($\log_2\text{FC} = -0.23$, $\text{FDR} = 0.001$) and GSTP1 ($\log_2\text{FC} = -0.19$, $\text{FDR} = 0.045$). GSTP1 downregulation in the High-Resistance cluster is counter-intuitive given its classical role in platinum detoxification via glutathione conjugation. However, CpG island methylation of the GSTP1 promoter is documented in CRC and is associated with transcriptional silencing [17]; epigenetic loss of GSTP1 may allow alternative GST isoforms (e.g. GSTA4) to compensate. Alternatively, GSTP1 downregulation may reflect a state in which the cell relies on upstream antioxidant defences (high SLC7A11/GSH) rather than downstream conjugation for platinum detoxification. GPX4 downregulation co-occurs with SLC7A11 upregulation, suggesting that resistant cells amplify cystine import (via SLC7A11) while reducing the terminal GPX4 barrier, effectively generating a high-flux glutathione system that diverts reducing equivalents away from membrane lipid detoxification and toward a thiol-buffering role.

TFRC (iron import, $\log_2\text{FC} = +0.97$), ACSL4 (PUFA phospholipid charging, $+0.94$), and SLC7A11 (cystine import, $+1.10$) are all upregulated together in the High-Resistance cluster. Cells simultaneously amplifying iron import and lipid peroxidation substrate availability (TFRC, ACSL4) while blocking ferroptosis execution (SLC7A11 $\rightarrow$ GSH) represent a 'ferroptosis-primed but protected' state in which the

ferroptosis programme is tensioned but not triggered. This state likely underpins the increased sensitivity to SLC7A11 inhibitors in this cluster. KRAS mutation status was independent of resistance cluster (Chi² p = 0.421; Fig. 2F), indicating the resistance phenotype is not driven by KRAS codon variant.

Table 1
Cohort characteristics.

Characteristic	Value
Total patients	436
High-Resistance group	274 (62.8%)
Low-Resistance group	162 (37.2%)
KRAS wild-type	265 (60.8%)
KRAS mutant	171 (39.2%)
Stage I	67 (15.4%)
Stage II	175 (40.1%)
Stage III	119 (27.3%)
Stage IV	62 (14.2%)
KRAS × Resistance (Chi ²)	p = 0.421 (NS)

Table 2

Differential expression of the 14-gene resistance panel (High vs Low Resistance). All comparisons Mann–Whitney U, Benjamini–Hochberg FDR correction. n.s.=not significant.

Gene	log ₂ FC	FDR	Direction	Role
SLC7A11	+ 1.10	4.59×10 ⁻²⁷	↑	Cystine import; ferroptosis gatekeeper
BRCA1	+ 1.01	7.83×10 ⁻⁵⁸	↑	DNA damage repair (HR pathway)
TFRC	+ 0.97	2.67×10 ⁻³⁰	↑	Iron uptake; ferroptosis-linked
ACSL4	+ 0.94	3.54×10 ⁻²⁶	↑	Lipid peroxidation; ferroptosis
MSH2	+ 0.86	9.32×10 ⁻⁵³	↑	Mismatch repair
MSH6	+ 0.77	2.48×10 ⁻⁴⁷	↑	Mismatch repair
NFE2L2	+ 0.64	1.98×10 ⁻³⁶	↑	NRF2; antioxidant response
RAD51	+ 0.63	1.00×10 ⁻²¹	↑	HR repair; replication restart
XPC	+ 0.47	4.77×10 ⁻¹⁹	↑	Nucleotide excision repair
ABCC2	+ 0.28	0.022	↑	Drug efflux
MLH1	+ 0.21	0.014	↑	Mismatch repair
GSTP1	-0.19	0.045	↓	Glutathione conjugation (paradox)
GPX4	-0.23	0.001	↓	Ferroptosis resistance enzyme
ERCC1	+ 0.05	0.243	n.s.	NER; classical platinum resistance gene — not FDR-significant here

3.2 The ERCC1 paradox

ERCC1 was the only gene in the panel that did not reach FDR significance (log₂FC = + 0.05, FDR = 0.243; Table 2). This is counter-intuitive given ERCC1–XPF’s established role in excising platinum–DNA adducts. Three explanations apply, not mutually exclusive. First, ERCC1 protein activity is governed post-transcriptionally: alternative splicing generates four isoforms with distinct repair capacities [5], so transcript abundance is a poor proxy for NER activity. Second, resistance stratification in this study uses a multi-gene cluster that may be dominated by ferroptosis and mismatch-repair genes, placing samples in the High-Resistance cluster for reasons other than NER. Third, ERCC1 protein activity is regulated at the level of sub-cellular localisation and XPA interaction [6], so even equal transcript levels can produce unequal NER capacity. ERCC1–XPF was retained as a docking target because its functional role in platinum resistance is mechanistically well-established regardless of transcriptional level.

3.3 Docking validation

Redocking of Erastin into SLC7A11 (7EPF) reproduced the co-crystallised pose with RMSD = 1.315Å (< 2.0Å threshold). Active/decoy discrimination gave ROC-AUC = 0.947 (random expectation 0.500) with

EF@10%=4.0× and EF@20%=3.0× (Fig. 1). Active compounds (mean affinity – 9.0 kcal/mol) were cleanly separated from decoys (mean – 6.6 kcal/mol; t-test p = 0.0008). Cross-structure validation on PDB 7P9U confirmed rank-order consistency for SLC7A11: Spearman $\rho > 0.95$ between 7EPF and 7P9U scores. Analogous redocking validation was not performed for ERCC1–XPF or CTR1, which is a limitation; the ERCC1–XPF (2BGS, 1.64Å) and CTR1 (7MHK, 1.96Å) scores are therefore less formally validated.

3.4 Multi-target docking

All six shortlisted candidates docked successfully across all three targets (Table 3, Fig. 3C). Erastin showed the strongest affinity for SLC7A11 (– 10.5 kcal/mol, 7EPF), consistent with its known cystine-tunnel binding mode confirmed by the co-crystal structure. It also demonstrated good affinity for CTR1 (– 8.3) and moderate affinity for ERCC1–XPF (– 6.1). RSL3, a canonical GPX4 inhibitor, docked strongly to SLC7A11 (– 9.4) and CTR1 (– 7.4), suggesting a broader target profile than its canonical mechanism. NSC16168 (MW = 212 Da, the most fragment-like compound) achieved – 8.9 kcal/mol at SLC7A11 and – 8.1 at CTR1 despite its compact scaffold. ERCC1_inh_1 was the only compound with its primary activity at ERCC1–XPF, though its SLC7A11 score (– 9.0) was unexpectedly high. Sulfasalazine, a clinically available SLC7A11 inhibitor, showed strong broad-target activity but carries a BBB warning (TPSA = 121 Å²); this is less relevant for CRC as CNS penetration is not required.

Table 3
Multi-target docking affinities (kcal/mol, AutoDock Vina). Cross-validation delta (Δ) for SLC7A11 7EPF vs 7P9U. BBB: TPSA-based blood–brain barrier estimate.

Compound	SLC7A11‡7EPF	SLC7A11‡7P9U	Δ	ERCC1-2BGS	CTR1-7MHK	ADMET
Erastin	–10.5	–9.0	–1.5	–6.1	–8.3	Ro5✓ BBB✓
RSL3	–9.4	–7.8	–1.6	–5.9	–7.4	Ro5✓ BBB✓
NSC16168	–8.9	–7.7	–1.2	–5.9	–8.1	Ro5✓ BBB✓
ERCC1_inh_1	–9.0	–7.4	–1.6	–5.6	–7.1	Ro5✓ BBB✓
Sulfasalazine	–8.7	–7.5	–1.2	–5.2	–8.0	Ro5✓ BBB⚠
HG106	–8.0	–8.0	0.0	–5.1	–7.7	Ro5✓ BBB✓

3.5 Integrated candidate ranking

Weighted composite scores ranked Erastin first (8.60), followed by RSL3 (7.84), NSC16168 and ERCC1_inh_1 (both 7.72), Sulfasalazine (7.54), and HG106 (7.35) (Table 4, Fig. 3D). Erastin’s high score reflects strong SLC7A11 affinity, the highest-weighted component. NSC16168’s third-place ranking stands out for a compound of 212 Da (the most fragment-like in the set). With SLC7A11 (– 8.9 kcal/mol)

and CTR1 (– 8.1 kcal/mol) as its principal binding partners, it has > 300 Da of headroom within Ro5 for lead optimisation. ERCC1_inh_1 shares third place despite modest CTR1 affinity; its highest QED (0.868) contributes to the composite. HG106, the only compound with identical 7EPF/7P9U scores ($\Delta = 0.0$), shows the most consistent multi-structure behaviour, making it a reliable scaffold for cross-structure optimisation.

Table 4

Final candidate ranking. Composite score = norm(SLC7A11)×0.4 + norm(CTR1)×0.3 + norm(ERCC1)×0.2 + (QED×10)×0.1. QED is scaled ×10 to match the docking score range. ☒ BBB concern (TPSA>90Å²). All compounds pass Lipinski Ro5.

Rank	Compound	Composite	SLC7A11	ERCC1	CTR1	QED	MW	BBB
1	Erastin	8.60	–10.5	–6.1	–8.3	0.685	422	☒
2	RSL3	7.84	–9.4	–5.9	–7.4	0.678	391	☒
3	NSC16168	7.72	–8.9	–5.9	–8.1	0.553	212	☒
3	ERCC1_inh_1	7.72	–9.0	–5.6	–7.1	0.868	241	☒
5	Sulfasalazine	7.54	–8.7	–5.2	–8.0	0.624	382	☒
6	HG106	7.35	–8.0	–5.1	–7.7	0.818	390	☒

Figures

4. Discussion

SLC7A11 was the most significantly upregulated gene in the platinum-resistant cluster (FDR = 4.6×10^{-27}), not ERCC1 (FDR = 0.24). This shifts the mechanistic frame from DNA repair toward ferroptosis suppression. Resistant cells amplify cystine import (SLC7A11), upregulate antioxidant transcription (NFE2L2), and increase iron import (TFRC) and lipid peroxidation substrate (ACSL4) while blocking the terminal ferroptosis step – the resistance phenotype sits in the ferroptosis axis, not the DNA-repair axis. The co-occurrence of GPX4 downregulation with SLC7A11 upregulation is consistent with a compensatory redistribution of the glutathione system – high SLC7A11 sustains GSH synthesis while GPX4 protein levels fall, possibly reflecting a feedback loop that prevents lethal lipid peroxide accumulation through non-GPX4 mechanisms such as AIFM2/FSP1 or the CoQ cycle.

The ERCC1 paradox – not significant in transcriptomic resistance stratification despite its established functional role – is explicable by three converging factors discussed in Section 3.2. Its inclusion as a docking target remains well-justified: functional NER capacity, not ERCC1 mRNA level, predicts platinum-adduct clearance, and multiple studies have shown that isoform expression or protein–protein interaction with XPA determines repair efficiency independently of total ERCC1 transcript [5, 6].

Erastin’s top composite ranking is mechanistically coherent: it inhibits SLC7A11 directly, targeting the most upregulated resistance gene, while also docking to CTR1 – though the mechanistic interpretation

is complex given CTR1's role as a platinum uptake transporter rather than efflux — and showing activity at ERCC1–XPF. Erastin's SLC7A11-targeting mechanism — depleting intracellular cystine and impairing glutathione biosynthesis — is a recognised strategy for reversing ferroptosis resistance in cancer [21, 22], and its clinical relevance for oxaliplatin sensitisation is plausible, though CNS-exposure concerns and its high-affinity SLC7A11 binding require careful dose optimisation in vivo. NSC16168's compact scaffold (212 Da) leaves > 300 Da of optimisation headroom within Ro5 constraints, making it an attractive lead for SLC7A11–CTR1 dual-target development.

CTR1 showed a modest but significant upregulation in the High-Resistance cluster ($\log_2\text{FC} = +0.97$, $\text{FDR} = 2.7 \times 10^{-30}$). This is counter-intuitive: CTR1-mediated platinum uptake would normally increase drug accumulation and sensitivity. One reconciliation is that CTR1 upregulation here reflects a compensatory response to the high copper demand of rapidly dividing cells, not a resistance mechanism per se; functional studies in CRC cell lines suggest OCT1 rather than CTR1 is the primary resistance-determining transporter for oxaliplatin [23]. CTR1's utility as a docking target remains valid: compounds binding at the copper-binding site may interfere with platinum entry, a mechanism independent of expression level. The independence of resistance cluster from KRAS mutation status ($\text{Chi}^2 p = 0.421$) is striking given the extensive KRAS-ferroptosis literature from the companion analyses in this series [18,19]. It suggests that platinum-resistance transcriptomics in CRC is driven primarily by the SLC7A11–NFE2L2–DNA-repair axis rather than KRAS codon variant. Therapeutically, this means SLC7A11-targeting sensitisers are likely applicable across KRAS genotypes. The upregulation of BRCA1 ($\log_2\text{FC} = +1.01$) and RAD51 ($\log_2\text{FC} = +0.63$) in the High-Resistance cluster is mechanistically consistent: HR-proficient cells repair platinum–DNA adducts before they can trigger apoptosis. The co-elevation of MSH2, MSH6, and MLH1 with resistance is more surprising given the platinum-MMR literature; their upregulation here may reflect a broader genome-maintenance activation programme. MLH1 is frequently silenced by promoter methylation in sporadic CRC [17]; its upregulation here suggests these tumours are not CIMP-positive.

Six limitations apply. The resistance stratification is transcriptomic, not clinical: there are no matched pre- and post-oxaliplatin treatment samples, so 'High-Resistance' reflects an expression pattern inferred from primary tumour specimens rather than a confirmed clinical resistance phenotype. Stage IV patients are underrepresented (14.2%), the subgroup where oxaliplatin resistance has the greatest clinical urgency. ERCC1's functional importance is underrepresented in transcript-based analyses. The docking used standard Vina rigid-protein scoring, which misses induced-fit effects; MD simulation of the top-ranked poses would strengthen binding-mode predictions. The composite score weighting ($\text{SLC7A11} \times 0.4$) was set **a priori** based on the transcriptomic result; alternative weighting schemes may re-order candidates. Finally, six of fourteen ligands failed PDBQT conversion (all platinum-containing or metal-coordinated compounds), limiting the scope of the docking panel.

5. Conclusions

Platinum resistance in CRC is transcriptomically dominated by a ferroptosis-primed but protected phenotype: SLC7A11, ACSL4, TFRC, and NFE2L2 are all significantly upregulated, while ERCC1 is not

differentially expressed (FDR = 0.24). The DNA-repair axis (BRCA1, RAD51, MMR genes) contributes but is secondary to the ferroptosis vulnerability. Multi-target docking against SLC7A11, ERCC1–XPF, and CTR1 – validated by redocking RMSD = 1.315Å, ROC-AUC = 0.947, and EF@10%=4.0× – identifies Erastin and NSC16168 as dual-pathway candidates that warrant isogenic in vitro testing in oxaliplatin-resistant CRC lines. The resistance cluster is independent of KRAS codon variant, suggesting that SLC7A11-targeting sensitisation strategies are applicable across KRAS genotypes.

Declarations

Funding

This research received no external funding.

Data Availability

TCGA-COAD data are publicly available at <https://portal.gdc.cancer.gov>. Docking structures were retrieved from the RCSB PDB (<https://www.rcsb.org>). Analysis scripts are available from the author on request.

Conflicts of Interest

The author declares no competing interests.

Author Contributions

C.G.E. conceived the study, performed all analyses, and wrote the manuscript.

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Figures

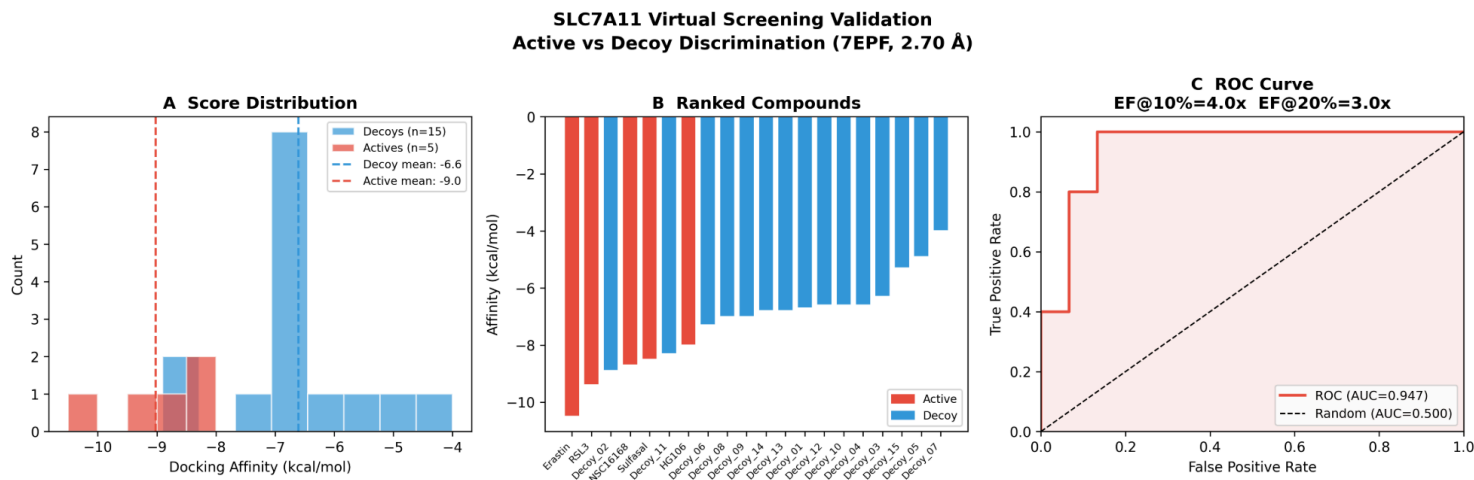


Figure 1

Docking protocol validation against SLC7A11 (PDB 7EPF, 2.70Å). (A) Score distribution: actives (n=5, mean -9.0 kcal/mol) vs property-matched decoys (n=15, mean -6.6 kcal/mol); dashed lines mark group means. (B) Ranked affinity for all 20 compounds (active=red, decoy=blue); actives cluster at the top of the distribution. (C) ROC curve (AUC=0.947); enrichment factors EF@10%=4.0x and EF@20%=3.0x confirm the protocol can prospectively recover active compounds.

TCGA-COAD Oxaliplatin Resistance Transcriptomic Landscape
n=436 patients | 14-gene panel | FDR-corrected (Benjamini-Hochberg)

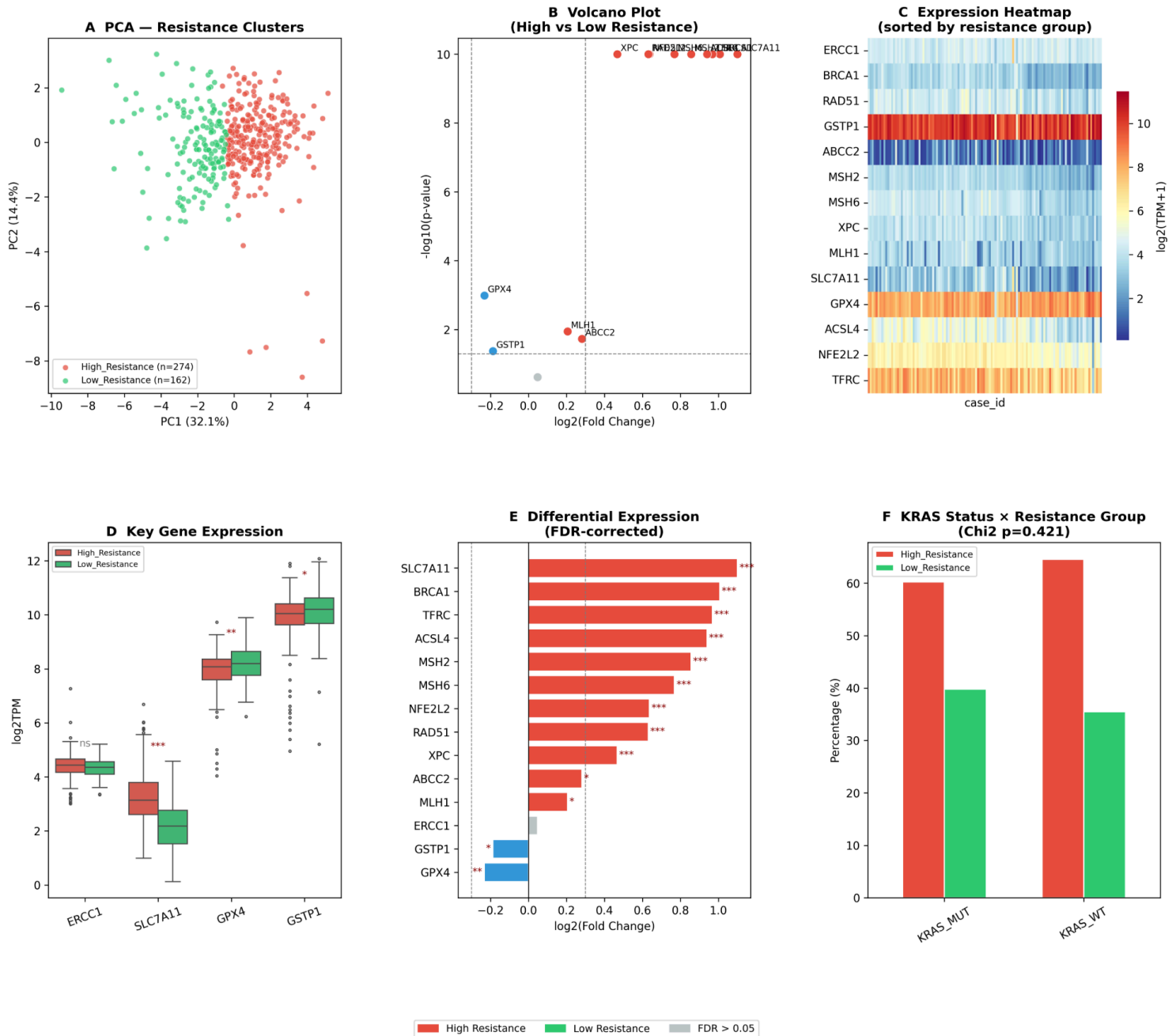


Figure 2

Transcriptomic resistance landscape (n=436 TCGA-COAD). (A) PCA of the 14-gene panel; k-means clusters are High-Resistance (red, n=274) and Low-Resistance (green, n=162). (B) Volcano plot: 13 of 14 genes reach $\text{FDR} < 0.05$; ERCC1 (grey) does not. (C) Expression heatmap sorted by resistance group. (D) Key gene box plots; SLC7A11 shows the largest dynamic range. (E) Ranked FDR-corrected $\log_2\text{FC}$; SLC7A11 leads, GPX4 and GSTP1 are downregulated. (F) KRAS status × resistance cluster: no significant association ($\text{Chi}^2 \text{ p}=0.421$).

Platinum Resistance in CRC — Integrated Computational Analysis
Layer 1 (n=436, FDR-corrected) + Layer 2 (7EPF-validated, RMSD=1.315Å, AUC=0.947)

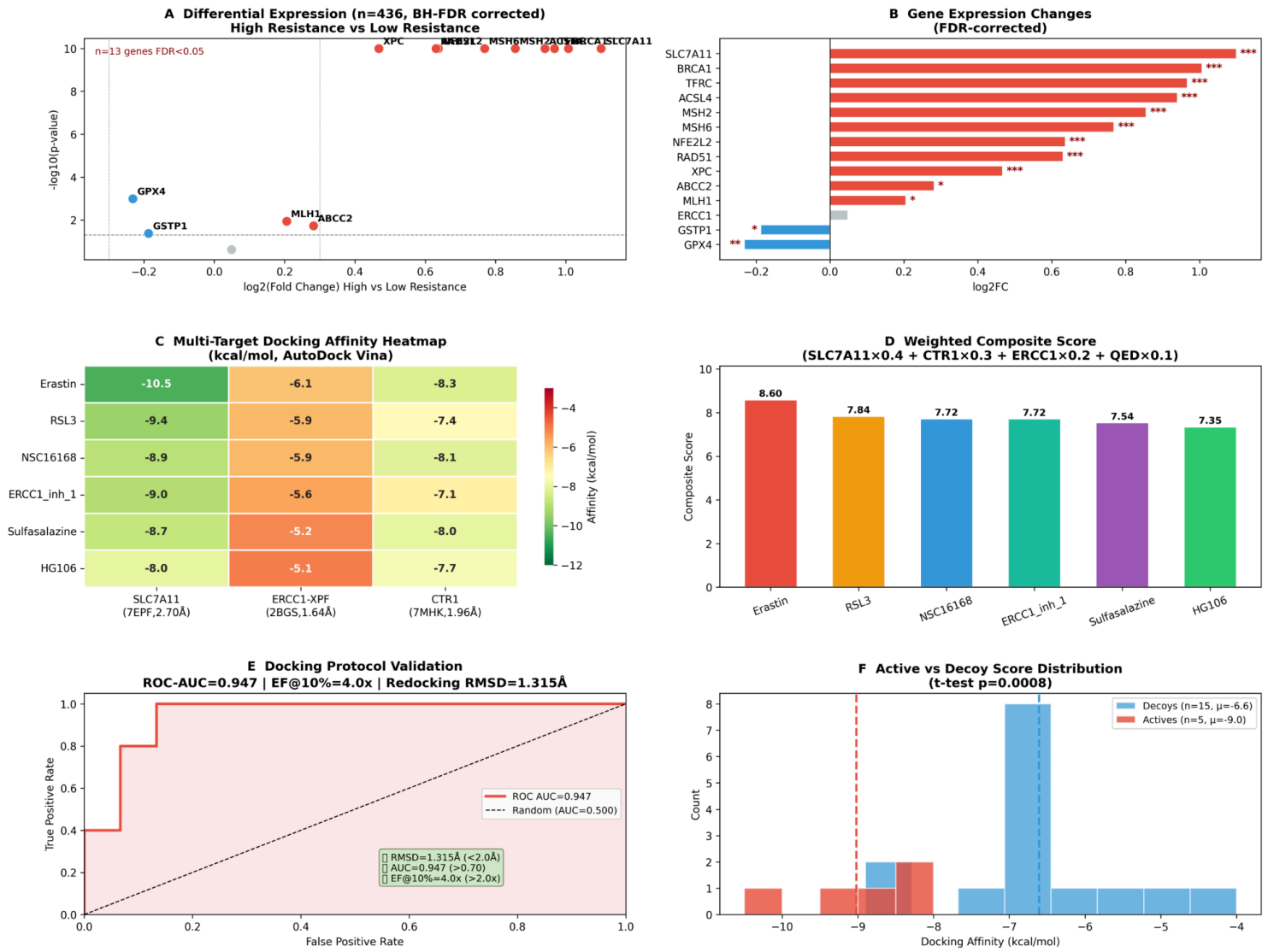


Figure 3

Integrated analysis. (A) Volcano plot of the resistance contrast (same data as Figure 2B; shown here to contextualise the docking targets). (B) Ranked $\log_2FC$ (same data as Figure 2E; SLC7A11 and the ferroptosis genes highlighted). (C) Multi-target docking affinity heatmap (kcal/mol); colour scale from green (−4) to red (−12). (D) Weighted composite scores; Erastin ranks first. (E) ROC curve with validation criteria (RMSD=1.315Å, AUC=0.947, EF@10%=4.0×). (F) Active vs decoy affinity distributions (t-test $p=0.0008$).