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TP53 Gain-of-Function Mutations and Metabolic Adaptation in Prostate Cancer: A Comprehensive Review

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ABSTRACT:

The tumor suppressor TP53 is frequently mutated in advanced prostate cancer, and certain TP53 gain-of-function (GOF) variants paradoxically promote tumor growth by acquiring oncogenic activities that reprogram cellular metabolism, enhance proliferation, and drive therapeutic resistance. This review synthesizes current mechanistic and translational evidence linking TP53-GOF mutations (notably R175H, R273H, and related hotspot variants) to metabolic rewiring in prostate cancer, including altered glucose handling, lipid and cholesterol metabolism, and amino acid-dependencies such as asparagine biosynthesis. It highlights how these changes create targetable vulnerabilities. We place particular emphasis on (i) molecular routes by which mutant p53 acquires new activities (dominant-negative effects, altered DNA binding, and novel protein–protein interactions), (ii) mutation-specific versus shared GOF phenotypes in metabolic pathways, and (iii) clinical translation, from small molecules that reactivate or destabilize mutant p53 (e.g., APR-246 / eprenetapopt and aggregation-disrupting peptides) to metabolic strategies that exploit mutant p53 dependencies (for example, co-targeting asparagine biosynthesis). We critically appraise the preclinical and early clinical evidence, identify important gaps (heterogeneity of mutation effects, limited clinical validation, and the interplay between TME and metabolism), and propose prioritized experimental and clinical strategies to accelerate translation. By integrating mechanistic insight with emerging therapeutic approaches, this review aims to provide a concise roadmap for leveraging mutant-p53-driven metabolic liabilities in lethal, therapy-resistant prostate cancer.

KEYWORDS:

TP53 gain-of-function mutation, prostate cancer, metabolic adaptation, asparagine synthetase (ASNS), squalene epoxidase (SQLE), androgen receptor resistance, tumor microenvironment, biomarker-driven therapy.

1. Introduction

Prostate cancer remains a leading cause of cancer morbidity and mortality among men worldwide and is responsible for a substantial fraction of cancer deaths in high-income countries. Population and registry data document rising numbers of advanced and therapy-resistant cases, and integrated genomic studies have repeatedly identified TP53 alteration as a key event associated with disease progression and poor outcome (1).

TP53 encodes the p53 protein, a multifunctional tumor suppressor that coordinates DNA damage responses, cell cycle checkpoints, apoptosis, and various aspects of cell metabolism. In cancer, non-synonymous TP53 mutations commonly produce stable, aberrant p53 proteins that not only lose their canonical tumor-suppressor activity but, in many cases, display gain-of-function (GOF) properties, acquiring novel oncogenic activities that actively promote malignancy. GOF mechanisms include (i) dominant-negative inhibition of wild-type p53 (when heterozygous), (ii) altered DNA-binding specificity that reprograms transcriptional networks, (iii) neomorphic protein–protein

interactions that engage oncogenic transcription factors and chromatin remodellers, and (iv) biochemical behaviors such as aggregation or altered isoform expression that create new cellular phenotypes. For a modern synthesis of these molecular mechanisms, see Chen et al. (2022) and related reviews (2,3).

A central and emerging theme is that many GOF p53 mutants rewire cancer cell metabolism in ways that promote survival under stress and create targetable dependencies. These metabolic effects are multifaceted: mutant p53 can shift glycolysis/mitochondrial balance, alter lipid and cholesterol synthesis, and change amino-acid handling; thereby supporting anabolic growth, redox balance, and therapy resistance. Importantly, several recent studies report mutation and context-specific outcomes rather than a single uniform metabolic program: for example, TP53-altered castration-resistant prostate cancers show upregulation of asparagine biosynthesis (ASNS) and functional dependency on asparagine in preclinical models (a therapeutic vulnerability identified in 2024), whereas other work highlights p53-dependent control of cholesterol biosynthesis via SQLE that connects p53 status to sterol metabolism and tumour growth (4–6).

Despite an expanding literature, the field faces important gaps and that this revised review aims to address: (i) many prior reviews summarize studies without critically synthesizing whether different TP53 hotspot mutations (e.g., R175H vs R273H vs R248W) cause overlapping or distinct metabolic phenotypes; (ii) mechanistic depth is often uneven; pathways (PI3K/AKT, Myc, AMPK, STAT3, etc.) are listed without clear molecular routes connecting mutant p53 to specific metabolic enzymes or transporters; and (iii) interactions with the tumour microenvironment (immune cells, stromal metabolism, nutrient competition) are underrepresented despite their likely importance to clinical translation.

In response to these gaps, this review (i) defines and exemplifies GOF mechanisms of mutant p53, (ii) organizes current data on how GOF TP53 mutants reprogram glucose, lipid/cholesterol and amino-acid metabolism in prostate cancer: distinguishing mutation-specific findings where possible, (iii) examines cross-talk with the tumour microenvironment and implications for immune and stromal compartments, and (iv) evaluates translational strategies (p53-reactivating agents, metabolic enzyme inhibitors, and combination approaches), highlighting outstanding questions and concrete experimental/clinical priorities. Subsequent sections synthesize mechanistic data, critically discuss controversies, and propose prioritized next steps for preclinical and clinical validation.

2. METHODOLOGY

2.1 Protocol and reporting

This review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) principles to ensure transparency and reproducibility. Where applicable, recommendations from the Cochrane Handbook for Systematic Reviews of Interventions were applied to study selection, data extraction, and synthesis. A PRISMA flow diagram and the full PRISMA checklist are provided in the Supplementary Materials.

2.2 Eligibility criteria

We included peer-reviewed primary research articles, preprints (clearly identified), reviews providing novel synthesis, and clinical-trial reports that addressed relationships among TP53 / mutant-p53, prostate cancer biology, metabolism, therapeutic strategies, or tumor microenvironment interactions. Studies were eligible if they provided original data on one or more of the following: (a) molecular mechanisms of TP53 gain-of-function (GOF) or loss-of-function (LOF) in prostate cancer, (b) metabolic reprogramming linked to TP53 alterations (glucose, lipid/cholesterol, amino-acid metabolism), (c) preclinical/intervention studies testing metabolic or p53-targeted agents, or (d) translational/clinical evidence (biomarker, ctDNA, trial outcomes) relevant to TP53 strata. Exclusion criteria: non-English language papers without an English abstract (unless a translation was provided), conference abstracts without accessible data, and purely computational/modeling studies without experimentally validated data (exceptions noted case-by-case). For preclinical assays, the focus was on studies in prostate cancer models (cell lines, organoids, PDXs, genetically engineered mouse models); when mechanisms were demonstrated in other tumor types, we flagged them as supportive but down-weighted them in synthesis.

2.3 Information sources and search strategy

We searched the following bibliographic databases from inception to 30 September 2025: PubMed/MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library. Trial registries (ClinicalTrials.gov, EU Clinical Trials Register)

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were checked for ongoing/terminated trials of p53-targeted or metabolic agents. Preprint servers (bioRxiv, medRxiv) were searched, and preprints were included but flagged as non-peer-reviewed. Reference lists of key reviews and included articles were hand-searched for additional studies.

A representative search string for PubMed (adapt to other databases and report full strings in Supplementary Table S1) was:

("TP53" OR "p53" OR "mutant p53" OR "p53 mutant")

AND ("prostate cancer" OR "prostatic neoplasm" OR "castration-resistant prostate cancer" OR "CRPC")

AND ("metabolism" OR "metabolic" OR "glycolysis" OR "oxidative phosphorylation" OR "OXPHOS" OR "lipid" OR "cholesterol" OR "asparagine" OR "ASNS" OR "SQLE" OR "asparaginase")

All database searches and date ranges, plus the full, reproducible search strings for each platform, are provided in Supplementary Table S1.

2.4 Study selection and screening

Search results were imported into a reference manager and deduplicated. Title/abstract screening was performed in the Covidence platform by two independent reviewers (F.J.U. & K.B) against the eligibility criteria. Full-text screening of selected records was also performed independently by two reviewers; disagreements were resolved by discussion and by adjudication with a third senior reviewer (A. J. A). Reasons for exclusion at the full-text stage are reported in the PRISMA flow diagram (Supplementary Fig. S1). For transparency, a table of excluded full texts with reasons is provided in the Supplementary Materials.

2.5 Data extraction

A standardized extraction form was developed and piloted on a sample of included studies. For each study we extracted: author, year, study type (in vitro, in vivo, clinical), model system (cell line with parental background, organoid, PDX, GEMM), TP53 status/allele (if reported), experimental interventions (drugs, genetic perturbations), key metabolic endpoints (e.g., ECAR/OCR, 13C flux results, sterol profiling), outcome measures (proliferation, apoptosis, tumor growth, PSA response), sample sizes/replicates, and main conclusions/limitations. For clinical studies, we additionally extracted patient numbers, line of therapy, biomarker methods (tumor sequencing/ctDNA), safety, and efficacy endpoints. When necessary, corresponding authors were contacted for missing or clarifying data; contact attempts and outcomes are recorded in Supplementary Table S2.

2.6 Quality assessment and risk-of-bias appraisal

Given the heterogeneous nature of the literature (preclinical mechanistic studies, animal models, and clinical reports), we applied distinct, appropriate risk-of-bias tools:

- **Clinical intervention and observational studies:** assessed using the Newcastle–Ottawa Scale (for cohort/case-control designs) or an appropriate Cochrane risk-of-bias tool for randomized trials. Where adequate, we applied the GRADE approach to judge the overall certainty of evidence for clinically relevant outcomes.

- **Animal studies:** assessed using the SYRCLE risk-of-bias tool adapted for preclinical in vivo experiments (randomization, blinding, outcome reporting, sample-size calculation).

- **In vitro / mechanistic studies:** because no single validated universal tool exists for bench studies, we used a pragmatic checklist adapted from best-practice recommendations: (i) clear reporting of cell-line provenance and authentication, (ii) use of appropriate controls (WT, null, isogenic alleles), (iii) reporting of biological vs technical replicates and sample sizes, (iv) independent validation in orthogonal models (organoid/PDX) where available, and (v) appropriate statistical testing. Each study received a qualitative rating (low/moderate/great concern) for internal validity on the adapted checklist.

Two reviewers independently assessed risk-of-bias; disagreements were resolved by consensus. Summary risk-of-bias tables and study-level ratings are provided in Supplementary Tables S3–S5.

2.7 Data synthesis

Because the included literature combined mechanistic laboratory studies and heterogeneous clinical reports, the primary synthesis was narrative and thematic: we grouped findings into metabolic axes (glucose/OXPHOS, lipid/cholesterol, amino-acid metabolism), allele-specific phenotypes (contact vs conformational mutants and common hotspot alleles), TME interactions, and translational implications.

For preclinical experimental outcomes that reported comparable quantitative metrics (for example, ECAR, OCR, tumor volume change), we considered pooled analyses where appropriate; a formal meta-analysis was performed only when ≥3 comparable, homogeneous data sets with extractable numeric outcomes were available. Heterogeneity for pooled analyses would be quantified using I^2 statistics and random-effects models (DerSimonian–Laird or REML) implemented in R (metafor) or RevMan; sensitivity and subgroup (allele, model type) analyses were pre-specified. For small-study or mechanistic datasets without comparable metrics, we summarized direction and effect size qualitatively and highlighted consistency across models.

2.8 Preclinical evidence appraisal and translational grading

For translational recommendations, we graded the preclinical evidence for each candidate vulnerability (e.g., ASNS/asparagine, SQLE/cholesterol) using a pragmatic three-tier scheme:

- **Tier 1 (High translational priority):** replicated in ≥2 model systems (isogenic lines + organoid or PDX), mechanistic causality demonstrated (genetic + pharmacologic perturbations with rescue), and at least one correlative clinical observation (tumor expression or ctDNA association).

- **Tier 2 (Moderate):** reproduced in multiple in vitro models and one in vivo model, but with limited clinical correlation.

- **Tier 3 (Exploratory):** single-model evidence or primarily observational signal without mechanistic perturbation.

This grading guided prioritization of candidate combinations and the proposed early-phase trial designs in Section 3.4.

2.9 Software and reproducibility

Data management and analyses were performed using EndNote/Zotero (reference management), Rayyan (screening), Excel/Google Sheets (data extraction templates), and R (version unspecified in text; specify exact version in final manuscript) or RevMan for any quantitative synthesis. All extraction templates, analytic scripts, and the full search strings are provided in the Supplementary Materials and will be shared publicly on request (or deposited in an open repository such as GitHub/Zenodo) to facilitate reproducibility.

2.10 Limitations of the methods

We acknowledge several methodological constraints: (i) inclusion of heterogeneous preclinical and clinical studies limits the ability to perform comprehensive quantitative meta-analysis; (ii) potential publication bias toward positive mechanistic findings in preclinical work; (iii) language restriction to English may omit relevant non-English studies; and (iv) inclusion of preprints introduces non-peer-reviewed evidence that was labelled and interpreted with caution. These limitations were considered when grading translational priority and making recommendations.

3. DISCUSSION

3.1 TP53 mutation and metabolic alteration in prostate cancer

Mutations in TP53 commonly produce stable mutant-p53 proteins that not only lose canonical tumor-suppressor functions but also gain oncogenic activities that reprogram cellular metabolism to support survival, proliferation, and therapy resistance. These *gain-of-function* (GOF) activities occur through several mechanisms: dominant-negative inhibition of remaining wild-type p53, altered DNA-binding/transcriptional programs, novel protein–protein interactions (for example, with transcription factors or metabolic regulators), and non-transcriptional interactions with metabolic enzymes and sensors. The literature shows that GOF mutant p53 rewires multiple metabolic axes in a context-dependent and mutation-specific manner(3).

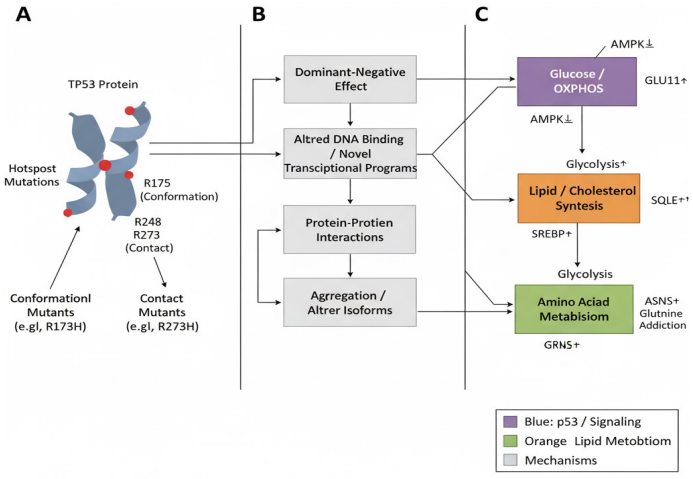

Figure 1: Allele-aware mechanisms by which mutant p53 reprograms tumor metabolism.

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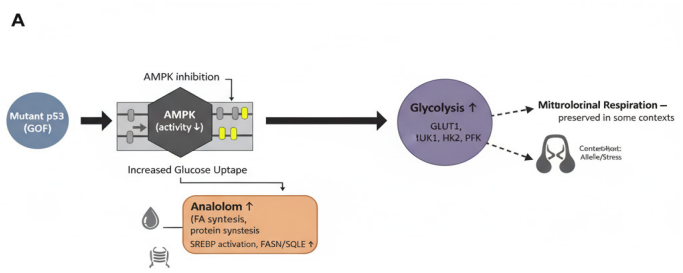
Schematic overview of TP53 gain-of-function mechanisms and their impact on tumor metabolic pathways, including glucose/OXPHOS balance, lipid/cholesterol synthesis, and amino acid metabolism.

3.1.1 Glucose handling, glycolysis, and mitochondrial metabolism

GOF mutant p53 promotes glycolytic reprogramming (the "Warburg effect") while also enabling metabolic plasticity that preserves mitochondrial fitness under stress. Mechanistically, mutant p53 has been shown to (i) increase glucose uptake by promoting GLUT1 translocation via RhoA/ROCK signalling, thereby enhancing aerobic glycolysis; (ii) interact with and activate transcriptional programs (directly or via partners) that upregulateupregulate glycolytic enzymes and regulators; and (iii) paradoxically enhance mitochondrial oxidative phosphorylation (OXPHOS) in certain contexts by stabilizing PGC-1α or other mitochondrial effectors: a dual program that permits adaptation to fluctuating nutrient/oxygen supply and supports metastasis. These basic points are supported by genetic and functional studies in cell lines and mouse models showing that mutp53 both stimulates glycolysis and, depending on the allele and context, preserves mitochondrial capacity to favor invasion/metastasis(7).

At the signaling level, one clear route is mutant-p53 inhibition of the energy sensor AMPK: several GOF p53 variants bind AMPKα and prevent its activation under energy stress, removing a brake on anabolic metabolism (fatty-acid synthesis, protein synthesis) and blunting autophagy/mitophagy responses that would otherwise constrain tumor growth. This transcription-independent interaction explains how mutp53 can acutely shift metabolic setpoints in energy stress conditions (8).



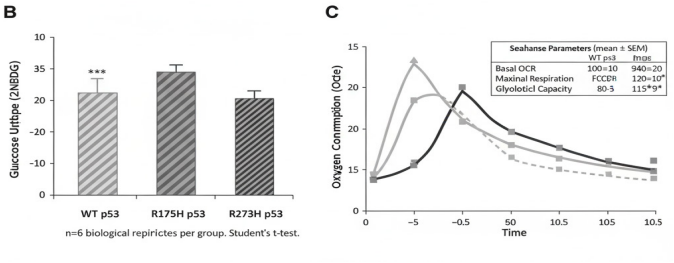


Figure 2: GOF p53 promotes glucose uptake and glycolysis through AMPK inhibition while preserving mitochondrial respiration in specific contexts.

(A) Schematic representation showing how gain-of-function (GOF) mutant p53 inhibits AMPK activity, leading to increased glucose uptake, enhanced glycolysis, and anabolic lipid synthesis via SREBP-mediated activation of FASN and SQLE. (B) Representative 2-NBDG assay illustrating elevated glucose uptake in R175H and R273H mutants compared with wild-type p53 (n = 6 biological replicates per group; Student's t-test). (C) Seahorse extracellular flux analysis demonstrating altered oxygen consumption and glycolytic capacity in mutant-p53–expressing cells. Data are presented as mean ± SEM. P < 0.05, P < 0.01, P < 0.001 vs. WT p53.

Translational note. Because mutant p53 enables both high glycolytic flux and preserved mitochondrial function, single-agent metabolic inhibitors (glycolysis *or* OXPHOS alone) may be insufficient; preclinical data support rational combination strategies (for example, glycolysis inhibitors with mitochondrial poisons or with modulators of AMPK signaling) (9).

3.1.2 Lipid and cholesterol metabolism

Mutant p53 often moves lipid metabolism toward anabolic lipid synthesis and cholesterol accumulation; metabolic programs that supply membranes for proliferation and generate signaling lipids that promote survival. A mechanistic exemplar is p53 regulation of squalene epoxidase (SQLE): wild-type p53 represses SQLE transcriptionally, decreasing cholesterol synthesis, whereas p53 loss or certain GOF contexts lead to increased SQLE activity and higher sterol production that supports tumor growth. Pharmacologic SQLE inhibition (e.g., terbinafine) reduces proliferation in p53-deficient models, indicating a therapeutically actionable axis (5).

Mutant p53 also cooperates with oncogenic drivers (MYC, PI3K/AKT) to enhance lipogenesis (acetyl-CoA and NADPH supply) and fatty-acid desaturation, producing membranes for rapid proliferation and lipid signaling that promotes invasion. Because prostate tumors are frequently lipogenic, these p53-driven shifts have particular

relevance to prostate cancer biology (9).

Translational note. SQLE and downstream cholesterol esterification enzymes represent candidate metabolic targets in TP53-altered prostate tumors, but patient-level validation (correlating TP53 alleles with SQLE expression/activity and response to inhibitors) is currently limited and a priority for clinical translation (5).

3.1.3 Amino-acid metabolism: asparagine, aspartate, and others

Recent work has defined a compelling amino-acid vulnerability in TP53-altered castration-resistant prostate cancer (CRPC): increased *asparagine synthetase* (ASNS) expression creates dependence on de novo asparagine biosynthesis and flux through asparagine–aspartate homeostasis. Yoo et al. (2024) combined transcriptomics, metabolomics, and functional perturbations to show that TP53-altered CRPCs upregulate ASNS and are sensitive to strategies that reduce intracellular and extracellular asparagine (genetic ASNS suppression, asparaginase, or combination approaches). This represents a concrete metabolic vulnerability tied to TP53 alterations and validates earlier mechanistic links between p53, ASNS transcriptional control, and stress responses (4).

Broader amino-acid control is also implicated: mutant p53 affects serine/glycine and glutamine pathways (through transcriptional and indirect regulatory networks), and p53 status alters aspartate/asparagine availability that feeds nucleotide synthesis and redox balance. However, the degree to which these dependencies are allele-specific (different for R175H vs R273H, etc.) remains incompletely resolved (3).

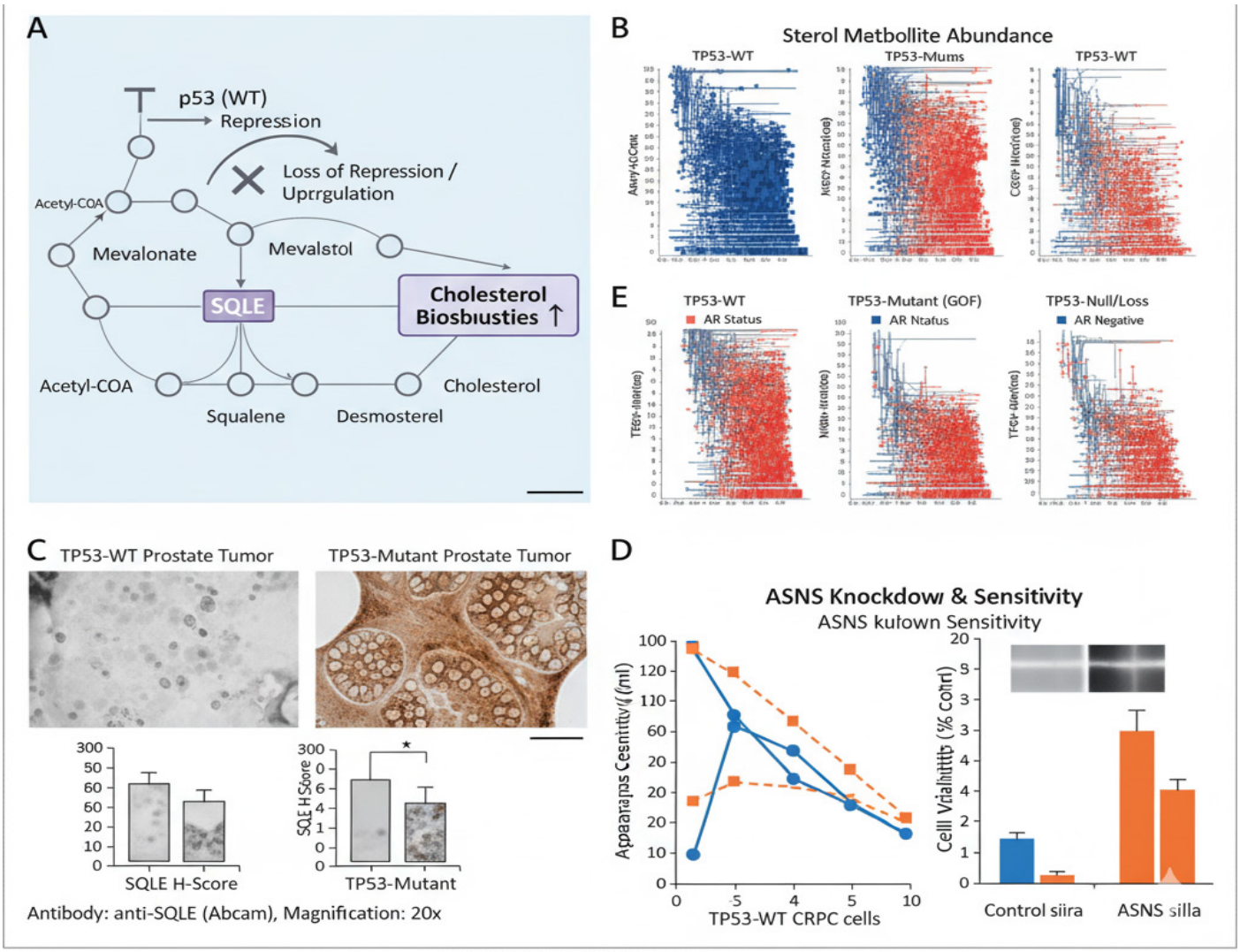


Figure 3: Lipid/cholesterol and amino acid rewiring in TP53-altered prostate cancer.
(A) Schematic illustrating how the loss of wild-type p53 (WT) or the presence of a gain-of-function (GOF) mutant p53 represses the enzyme SQLE, leading to a downstream cholesterol enrichment in TP53-altered prostate tumor cells.

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Translational note. The ASNS/asparagine axis is a high-priority target for translation in TP53-altered CRPC; clinical strategies could combine asparaginase or ASNS inhibitors with ARSIs or p53-reactivating agents, but toxicity and tumor heterogeneity must be addressed (4).

3.1.4 Mutation specificity, context dependence, and the tumor microenvironment (TME)

A recurring theme and a major reviewer point is that GOF effects are not uniform: different hotspot mutations (conformational vs contact mutants; e.g., R175H vs R273H) can produce overlapping but also distinct transcriptional and non-transcriptional outputs that alter metabolic phenotypes. Some alleles preferentially engage transcriptional reprogramming (e.g., forming aberrant complexes with NF-Y or SREBP family factors), while others act via cytosolic interactions (for example, with AMPK) or by forming aggregation-prone oligomers that sequester partners. The literature, therefore, argues for allele-aware analyses (cell models and patient cohorts stratified by specific TP53 alleles) rather than collapsing all TP53 alterations into a single group (10).

The TME (immune cells, fibroblasts, adipocytes, vascular supply) further modifies metabolic dependencies: mutant p53 can alter tumor–stromal signaling and cytokine profiles that change nutrient availability and immune cell metabolism, while nutrient competition in the TME can amplify tumor-intrinsic dependencies (for example, asparagine exported/imported between compartments). These bidirectional interactions make ex vivo and in vivo models (co-culture, organoids, PDXs) essential for translational validation beyond cell-line mechanistic work.

3.2 Proliferation and drug resistance driven by TP53 mutation in prostate cancer

3.2.1 Mutant-p53 mechanisms that directly increase proliferation

Mutant p53 proteins promote tumor cell proliferation by acquiring new biochemical activities that reprogram transcriptional networks, alter cell-cycle control, and blunt apoptotic responses. Mechanisms include: (i) transcriptional activation of pro-growth programs via novel interactions with transcription factors and chromatin remodelers; (ii) dominant-negative inhibition of any residual wild-type p53, removing cell-cycle checkpoints; (iii) stabilization of oncogenic signaling cascades such as PI3K/AKT and Myc; and (iv) direct non-transcriptional modulation of cell-cycle kinases and checkpoint proteins (for example, by interfering with AMPK and DNA-damage signaling). Together, these actions shorten G1/S control, increase S-phase entry, and reduce programmed cell death: molecular outcomes that accelerate tumor growth and increase clonogenic survival (3).

Practically, these activities manifest as increased proliferation indices, higher Ki-67, and enhanced clonogenicity in cell lines and xenografts expressing hotspot GOF alleles (for instance, R175H, R273H), supporting the concept that mutant p53 is an active driver rather than a passive marker of aggressive disease (11).

3.2.2 Mutant p53 and resistance to androgen receptor-targeted therapies (ARSIs)

Clinical and translational data increasingly link TP53 alteration to poor response and earlier progression on androgen receptor signaling inhibitors (enzalutamide, abiraterone) and castration-resistant evolution. TP53 mutation correlates with worse outcomes and shorter progression-free intervals following ARSI therapy, although the effect size is modulated by co-occurring alterations and tumor stage. Mechanistically, mutant p53 contributes to ARSI resistance through several, not mutually exclusive routes: (i) promoting lineage plasticity and neuroendocrine trans-differentiation that bypasses AR dependency; (ii) cooperating with transcriptional and epigenetic regulators to maintain alternative growth programs; and (iii) enabling survival under androgen deprivation by enhancing metabolic plasticity and DNA-repair adaptations. These mechanisms help explain why TP53 alterations are over-represented in more therapy-resistant, advanced prostate cancers (12).

Because ARSI resistance is multifactorial, TP53 status alone is not a perfect predictor, but in combination with RB1 and PTEN loss (the AVPC signature), it defines a high-risk group more likely to exhibit lineage plasticity and rapid progression. This highlights the need for multi-gene biomarker panels (including ctDNA) to stratify patients in trials (12).

3.2.3 Mutant p53 and resistance to cytotoxic and targeted agents

Mutant p53 promotes resistance to DNA-damaging chemotherapies and to certain targeted agents by diminishing apoptosis and altering DNA-damage response (DDR) pathways. GOF alleles can (i) down-regulate pro-apoptotic mediators and upregulate survival factors, (ii)

rewire DDR signaling to tolerate replication stress, and (iii) engage antioxidant and metabolic programs that blunt therapy-induced stress. Preclinical studies also show that mutant p53 can reduce sensitivity to mitotic kinase inhibitors and other targeted compounds, sometimes via allele-specific interactions, meaning p53 status can condition not only chemosensitivity but also responses to newer targeted agents (13).

The complete loss of TP53 and specific gain-of-function (GOF) missense mutations can lead to different treatment responses. For instance, some mutations mainly enhance resistance to cell death, while others activate gene programs that strengthen DNA repair. Therefore, grouping all 'TP53-mutant' tumors can hide important allele-specific differences in their clinical behavior (3).

3.2.4 Co-occurring tumor-suppressor losses, lineage plasticity, and aggressive variant prostate cancer (AVPC)

TP53 mutation frequently co-occurs with loss of RB1 and PTEN in aggressive prostate cancer phenotypes. The combined loss of these tumor suppressors promotes lineage plasticity, a shift from AR-dependent luminal epithelial programs to AR-indifferent or neuroendocrine-like states, which confers intrinsic resistance to ARSIs and often to conventional cytotoxics. Clinically, AVPC, defined by defects in RB1/PTEN/TP53, is associated with rapid progression and poor prognosis; mechanistically, concurrent pathway losses amplify chromatin and transcriptional reprogramming that enables adaptive survival programs. Therefore, therapeutic strategies for TP53-altered tumors must consider co-alterations and the resulting plasticity phenotype (12).

3.2.5 Therapeutic implications and candidate strategies

Given the central role of mutant p53 in proliferation and resistance, several therapeutic approaches merit priority testing:

1. **Direct reactivation/destabilization of mutant p53:** Small molecules that covalently modify mutant p53 (e.g., APR-246/eprenetapopt) or peptides that disrupt mutant-p53 aggregation (ReACp53) can restore tumor-suppressor function or reduce oncogenic activity in preclinical models and early-phase trials. APR-246 has shown clinical activity in hematologic malignancies and is in multiple combination trials; ReACp53 showed promising preclinical activity in prostate cancer models by reversing aggregation and restoring p53 function. Translating these agents to prostate cancer (especially allele-stratified cohorts) is a rational next step (14).
2. **Synthetic-lethal and pathway-targeting approaches:** Exploiting vulnerabilities that arise when p53 function is compromised: for example, targeting cell-cycle kinases (PLK1, WEE1), checkpoint kinases (CHK1), or altered metabolic dependencies (asparagine/ASNS, SQLE), can selectively kill TP53-altered cells. Preclinical data support PLK1/WEE1/CHK1 inhibition in TP53-compromised contexts, but the efficacy can depend on the specific allele and co-mutations, so preclinical validation in allele-aware models is essential (15).
3. **Combination strategies with ARSIs and DNA-damage agents:** Combining mutant-p53 reactivators or synthetic-lethal drugs with ARSIs, PARP inhibitors (in DNA-repair-deficient contexts), or chemotherapy may overcome resistance phenotypes. Rational combos should be guided by molecular biomarkers (TP53 allele, RB1/PTEN status, DDR markers) and validated in organoids/PDXs with preserved TME interactions (12).
4. **Biomarker-driven trial design and ctDNA monitoring:** Because allele specificity and co-alterations critically affect phenotype, clinical trials should use ctDNA or tumor sequencing to enroll and stratify patients by TP53 allele and co-occurring alterations. Window-of-opportunity trials with pre-/post-biopsies and metabolic/flux readouts will accelerate translation (12).

3.2.6 Prioritized experimental needs

1. **Allele-aware preclinical pipelines.** Use isogenic panels with major hotspot alleles (R175H, R248W, R273H) and patient-derived organoids/PDXs to test therapy responses and identify allele-specific synthetic lethals (11).
2. **Modeling co-alterations.** Explicitly test TP53 alterations together with RB1/PTEN loss to model AVPC biology and therapy resistance (12).
3. **Integrated biomarker strategies.** Develop ctDNA assays for TP53 allele tracking, combine with functional biomarkers (IHC for p53, Ki-67, SQLE/ASNS; metabolic flux/

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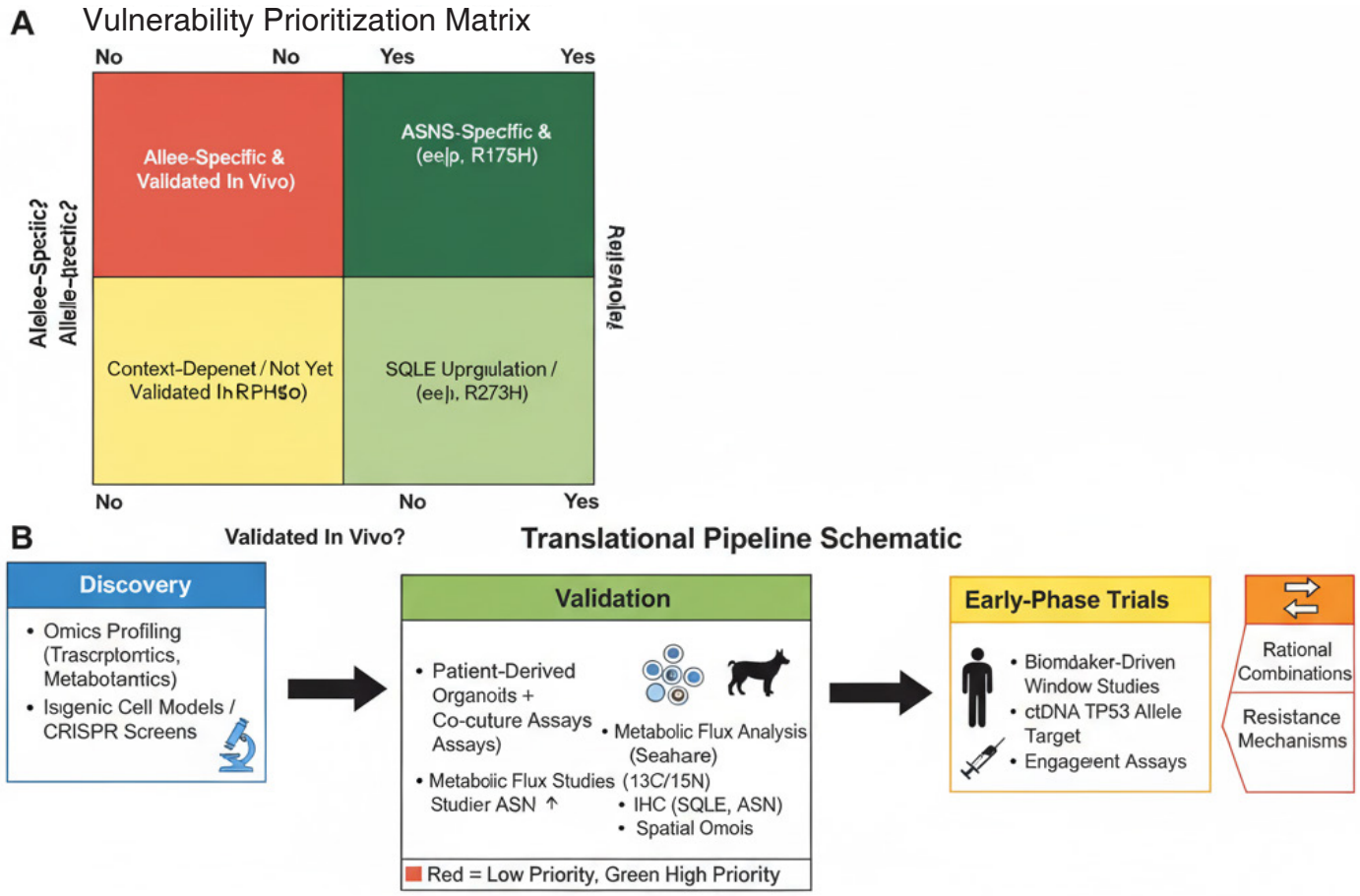
tracer studies) in early-phase trials to link mechanism to clinical signal (4–6,16).



C Candidate Therpauetics & Combinations

Drug Candidate	Mechanism	Clinical Status	Potential Combinations	Biomamer / Context
Asparaginasse	ASNS Inhibition	Phase 1/2 Solid Tumos)	ASNS High, Chemo	APHS High, Chemo
SQLE Inhbitor (ee.þ. **Lovastatin**		Repurossing / Pre-crinical	Phase 2/3 (MDS, Ov Ca)	SQLE High, Azi-CIR.
SQLE Inhibitor (Cholse Synth. Blockade		Asparagianited Axis Inh.	SQLE High (MDS, Ov Ca)	APR-A-tiitat ?
Azi-CDR (Azacicltine+Dectabialion (Hecitaibhated)		FDA-Approved (MB{, AML	FDA-Approved (all)	DDA-Mut, DNA Hyperphhated
Venetoloax		BCL-2 Inhibition	F53-High, (CLL, AML	BCL-Mutt, BCL2 High

Figure 4: Translational strategies and prioritized experimental pipeline

3.3 Tumor microenvironment (TME), immune–metabolic crosstalk, and mutant-p53

Mutant p53 reshapes the tumor microenvironment through both cell-intrinsic and secreted factors that together create an immunosuppressive, metabolically altered niche favoring tumor survival and therapy resistance. Mechanisms include (i) altered tumor secretome and exosome content that reprogram neighboring stromal and immune cells, (ii) transcriptional induction of chemokines and cytokines that favor suppressive myeloid populations, (iii) metabolic competition for nutrients (glucose, amino acids such as asparagine) and accumulation of immunosuppressive metabolites (lactate), and (iv) modulation of antigen presentation and immune-checkpoint pathways. These TME effects magnify the clinical impact of TP53 alterations and are therefore critical for translational strategies (17).

3.3.1 Mutant-p53, the secretome, and stromal remodeling

Mutant p53 alters the tumor secretome (cytokines, chemokines, growth factors, and extracellular vesicle cargo) in ways that promote cancer-associated fibroblast (CAF) activation, extracellular matrix remodeling, and pro-

tumorigenic inflammation. Recent literature shows that mutant-p53 can drive the secretion of factors that convert stromal fibroblasts to a more supportive phenotype and may alter ECM stiffness and collagen deposition, changes that favor invasion and therapeutic resistance. These secretome changes also modify local nutrient handling (for example, CAFs can supply metabolites to tumor cells), creating a reciprocal metabolic crosstalk that strengthens mutant-p53–driven metabolic programs (17).

3.3.2 Immune suppression: myeloid cells, T cells, and checkpoint biology

Multiple studies indicate that TP53 mutations promote an immunosuppressive microenvironment. Mechanisms include upregulation of immunosuppressive chemokines and PD-L1 in some contexts, reduced antigen presentation, and recruitment/education of suppressive tumor-associated macrophages (TAMs) and myeloid populations. Exosome-mediated delivery of mutant-p53 or related factors can directly impair T cell function and promote regulatory programs in macrophages, reducing antitumor immunity and limiting checkpoint inhibitor efficacy in preclinical models. These effects help explain clinical observations linking TP53 alterations to poor immunotherapy responsiveness in some tumor types and argue for combining metabolic or p53-targeted therapy with immune modulation in TP53-altered tumors (18).

3.3.3 Metabolic competition and immunometabolism

Metabolic reprogramming by mutant p53 affects available nutrients in the TME and thereby directly influences immune cell function. Two clinically relevant examples are: (a) asparagine metabolism: TP53-altered prostate cancers show ASNS upregulation and increased asparagine utilization, which may alter local asparagine availability and affect lymphocyte function or stromal support; and (b) lactate accumulation: enhanced glycolysis and poor lactate clearance polarize TAMs to an immunosuppressive phenotype and impair cytotoxic T-cell effector function. Thus, tumor-intrinsic metabolic shifts driven by mutant p53 have non-cell autonomous consequences that can be targeted to restore immune competence (4).

3.3.4 Therapeutic implications: combining metabolic, p53-directed, and immune strategies

Because mutant p53 both creates metabolic dependencies (e.g., ASNS/asparagine) and suppresses antitumor immunity, rational combinations should be prioritized. Examples include asparagine-depleting strategies (asparaginase or ASNS inhibition) combined with p53-reactivating agents (to re-sensitize tumor cells) and myeloid-modulating therapies (CSF1R inhibitors or lactate-targeting approaches) to re-enable T-cell function. Preclinical work also suggests that reversing lactate-mediated macrophage suppression enhances responses to PD-1 blockade in PTEN/TP53-deficient prostate cancer models, a paradigm readily adaptable to TP53-altered cohorts. Careful staging (window PD studies with paired biopsies) is required to show target engagement and immune reprogramming before larger efficacy trials (19).

3.3.5 Prioritized experimental approaches to validate TME effects

To translate TME-centric hypotheses into the clinic, we recommend allele-aware, TME-inclusive preclinical workflows:

• Use co-culture systems and organoids with matched CAFs, macrophages, and autologous T cells to measure how specific TP53 alleles alter stromal/immune phenotypes and metabolite exchange (e.g., conditioned media experiments, isotope tracing across compartments)(17).

• Employ extracellular vesicle (EV) profiling and proteomics to define mutant-p53-dependent secretome changes and test EV depletion or secretion inhibitors as modulators of the TME (18).

• Apply spatial transcriptomics and multiplexed IHC/IF on paired pre-/post treatment biopsies to map immune cell states (T cells, TAMs) and metabolic enzyme expression (ASNS, SQLE) relative to TP53 allele status (4)

• Use metabolic tracer research (13C/15N tracers in organoids/PDXs and PET tracers where available) to quantify intercellular nutrient flux and to confirm on-target metabolic effects of interventions (e.g., reduction in intra-tumoral asparagine) (4).

3.4 Therapeutic strategies & clinical evidence

Delivering clinically useful therapies for TP53-altered prostate cancer requires both agents that act on mutant p53 itself and strategies that exploit the metabolic and synthetic-lethal vulnerabilities created by TP53 loss or GOF. Below, we review the principal classes of therapies, summarize available clinical and preclinical evidence, and

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lay out concrete recommendations for allele-aware translation.

3.4.1 Direct p53-targeting approaches

Covalent reactivators / small molecules (eprenetapopt / APR-246): APR-246 (eprenetapopt) is a small molecule that modifies thiol groups in mutant-p53 proteins and can restore wild-type-like folding and transcriptional activity in some alleles; it has advanced furthest in clinical development. In haematologic malignancies, APR-246 combined with azacitidine produced high response rates and molecular remissions in TP53-mutant MDS/oligoblastic AML, although a large phase-3 readout for frontline MDS did not meet its primary endpoint, underscoring the need for careful patient selection and combination strategies. Early phase studies and a Phase I/IB program have shown on-target biological effects and tolerability across tumor types, including limited prostate cancer cohorts, supporting further exploration in allele-stratified CRPC cohorts. Clinical biomarkers such as SLC7A11 expression have been proposed as predictors of APR-246 sensitivity and may refine patient selection (6).

Aggregation-disrupting peptides (ReACp53) and protein-destabilizers: Peptide agents designed to disrupt mutant-p53 amyloid/aggregation (for example, ReACp53) restore nuclear localization and p53 transcriptional function in preclinical prostate cancer models and sensitize cells to apoptosis and to standard agents. ReACp53 has demonstrated tumor growth inhibition in xenografts and represents an orthogonal approach to small-molecule reactivation that may be particularly valuable for conformational/aggregation-prone alleles (e.g., R175H). These agents remain at preclinical/early-development stages in prostate cancer, but the available data support advancing allele-matched evaluation (20).

Clinical-development lessons: Clinical experience with APR-246 highlights two translational lessons: (i) single-agent activity in solid tumors has been limited, arguing for rational combinations (epigenetic agents, chemotherapies, metabolic drugs) and (ii) tumor-intrinsic determinants (for example, SLC7A11) and tumor heterogeneity materially affect activity; therefore, biomarker-driven, allele-aware trial designs are essential. Early phase prostate cancer programs should prioritize short window PD endpoints and molecularly stratified expansion cohorts rather than broad unselected populations (6).

3.4.2 Metabolic targeting: exploiting mutant-p53 dependencies

Asparagine/ASNS axis. The most concrete, recently validated metabolic vulnerability in TP53-altered CRPC is increased dependence on asparagine biosynthesis driven by ASNS upregulation. Yoo and colleagues used transcriptomics, metabolomics, and functional perturbation to show TP53-altered CRPCs rely on ASNS and are sensitive to asparagine depletion strategies (genetic ASNS suppression, asparaginase), making the ASNS/asparagine axis a high-priority translational target in allele-selected CRPC. Clinical translation will require attention to toxicity (asparaginase side-effects) and to patient selection via tumor ASNS expression or TP53 allele (4).

Cholesterol biosynthesis / SQLE. Wild-type p53 directly represses SQLE (squalene epoxidase), a rate-limiting enzyme of cholesterol biosynthesis; loss or GOF activity of p53 derepresses this pathway, creating an actionable dependency in several tumor types. SQLE inhibition (terbinafine, NB-598 in preclinical work) reduces growth in p53-deficient models, and retrospective clinical observations and small case series have reported PSA declines or survival signals associated with incidental terbinafine use in prostate cancer cohorts. While these data are encouraging, prospective, biomarker-guided trials are lacking and should be pursued in TP53-altered, SQLE-high tumors (5).

Glycolysis / OXPHOS and metabolic plasticity. Mutant p53 frequently promotes metabolic plasticity (heightening glycolysis while preserving mitochondrial function), which reduces the likelihood that single-pathway metabolic inhibition will be effective. Preclinical models, therefore, support combination metabolic approaches (e.g., glycolysis inhibitor + OXPHOS inhibitor, or metabolic inhibitor + p53-reactivator) and integration of metabolic flux readouts in early trials. Comprehensive flux (13C tracer) studies accompanied by paired biopsies are recommended to confirm target engagement (9).

3.4.3 Synthetic-lethal and cell-cycle targets

TP53 loss impairs canonical checkpoint responses and creates reliance on alternative regulators of cell-cycle progression and replication stress responses. In preclinical prostate and other cancer models, inhibition of WEE1, PLK1, CHK1, and related effectors produces selective toxicity in TP53-defective contexts; these agents therefore represent attractive partners for combination

studies with p53-reactivators or metabolic agents. As with other strategies, allele specificity and co-occurring alterations (for example, RB1/PTEN) modulate responses and require testing in isogenic and organoid/PDX platforms before clinical translation (21).

3.4.4 Immune strategies and combinations

Mutant p53 fosters an immunosuppressive TME and metabolic reprogramming that can limit the efficacy of immune checkpoint inhibitors. Preclinical studies indicate that reversing tumor metabolic suppression (for example, reducing lactate accumulation or depleting tumor asparagine) can recondition myeloid populations and enhance checkpoint efficacy. Therefore, combining p53-directed or metabolic agents with immune modulators (CSF1R inhibitors, PD-1/PD-L1 blockade) is a rational translational path, but early trials must include paired immune and metabolic PD markers to demonstrate reprogramming before claiming synergy (21).

3.4.5 Biomarkers, patient selection, and trial design recommendations

Biomarker priorities: Trials should be allele-aware and biomarker-rich. Minimum candidate biomarker assays for inclusion/stratification and PD readouts are:

- Baseline tumor or ctDNA sequencing to define TP53 allele(s) and co-alterations (RB1, PTEN, DDR genes) (22).
- Tumor IHC (p53 pattern, ASNS, SQLE, Ki-67) and targeted transcriptomic signatures (ASNS high/low) (4).
- Predictive molecular markers for specific agents (e.g., SLC7A11 expression for APR-246 sensitivity) (23).
- Metabolic PD: tumor metabolomics (targeted LC-MS for asparagine, sterol intermediates) and 13C tracer studies in a subset of patients (4).

Trial design: For proof-of-mechanism and early efficacy testing, we recommend a staged approach:

1. Window PD cohorts (12–20 patients per allele cohort): Short (7–21-day) pre-operative or pre-treatment window studies that administer the investigational combination (e.g., APR-246 + asparaginase; or p53-reactivator + SQLE inhibitor for SQLE-high tumors) with mandatory paired biopsies for PD (IHC, metabolomics, ctDNA). Primary endpoint: predefined PD effect (e.g., ≥X% reduction in intratumoral asparagine / ASNS expression, or ctDNA TP53 VAF decline). Secondary endpoints: safety, PSA50, radiographic signal. Use paired analyses for improved power (4).

2. Signal-seeking expansions (30–40 patients) or randomized phase II biomarker-enriched designs. If PD signals and tolerability are acceptable, expand to exploratory efficacy cohorts powered to generate estimates of PSA response, ORR, and short PFS for go/no-go decisions. Consider randomized signal-seeking arms versus best-available control if feasible (6).

3. Correlative framework: Include ctDNA TP53 VAF dynamics, targeted transcriptomics, tumor metabolomics, and spatial immune profiling as mandatory correlative endpoints. Pre-specify statistical PD thresholds and stopping rules for toxicity and futility (4).

Limitations and proposed early-phase design.

A limitation of the current preclinical literature is that many studies collapse all TP53 alterations into a single "mutant" group and rely heavily on 2-D cell lines; this practice obscures allele-specific biology and the modifying influence of co-occurring lesions (RB1, PTEN) and the tumor microenvironment. Translationally, we therefore propose a staged, biomarker-driven early-phase program: begin with a window-of-opportunity (proof-of-mechanism) cohort in metastatic castration-resistant prostate cancer (mCRPC) enriched for validated TP53 hotspot alleles (separate cohorts for common hotspots where feasible, e.g., R175H and R273H) and with pre-specified stratification by RB1/PTEN status. Eligibility: mCRPC after ≥1 ARSI, measurable disease, and willingness for paired biopsies. Interventions should test a *mechanism-matched* combination (example: APR-246 or other p53-reactivator plus metabolic perturbation where preclinical data support the vulnerability, e.g., asparaginase or ASNS suppression in TP53/ASNS-high tumors). Primary endpoints should be pharmacodynamic (PD) proof-of-mechanism (paired baseline and on-treatment tumor biopsies assayed for ASNS expression, intratumoral asparagine by metabolomics, SQLE/IHC when applicable, and ctDNA TP53 VAF dynamics) and safety; secondary endpoints should include PSA50, objective response rate, and short-term radiographic PFS. Correlative assays should include targeted ctDNA for TP53

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allele tracking, tumor IHC for p53/SQLE/ASNS/Ki-67, bulk and single-cell RNAseq on paired biopsies, and tracer-based flux (where feasible) to confirm metabolic engagement. For sample size, a window PD cohort of approximately 12–20 patients per allele cohort is typically sufficient to detect large paired PD effects (paired analyses comparing baseline vs on-treatment, which improve power); if a robust PD signal is observed, expand to an exploratory efficacy cohort of approximately 30–40 patients (or use a randomized signal-seeking expansion) to obtain preliminary estimates of clinical activity. Statistical analyses should pre-specify paired tests for PD markers (paired t/ t/Wilcoxon) and clearly defined criteria for "go/no-go" to larger trials (e.g., pre-specified magnitude of ASNS reduction or ctDNA VAF decline plus acceptable safety). This allele-aware, biomarker-heavy design will maximize the chance of detecting true, targetable mutant-p53 metabolic vulnerabilities while minimizing heterogeneity that has confounded prior translational efforts.

4. Conclusion

TP53 Mutations, particularly gain-of-function (GOF) hotspot alleles, fundamentally reshape prostate cancer biology by reprogramming energy metabolism, altering lipid and amino-acid pathways, and modifying the tumor microenvironment. These changes sustain proliferation, drive therapeutic resistance, and create distinct metabolic vulnerabilities. This review highlights that TP53 alterations are not uniform: conformational and contact mutants differ in their molecular interactions and downstream metabolic effects. Recognizing these allele-specific differences is essential for developing effective, targeted therapies. Among the emerging opportunities, the ASNS/asparagine and SQLE/cholesterol represented promising metabolic targets for translation. The future progress depends on integrating mechanistic discoveries with clinical validation. Allele-aware preclinical models, biomarker-driven patient selection, and early-phase trials incorporating pharmacodynamic and metabolic readouts will be crucial. Therefore, combining p53-reactivating, metabolic, and immune-modulating strategies offers a rational path to improve outcomes in patients with therapy-resistant prostate cancer.

In summary, a precision approach that links TP53 allele type, metabolic dependencies, and microenvironmental context can transform our understanding of prostate cancer and accelerate the development of personalized therapies.

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