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Targeting mutant p53 in cancer: from mechanistic insights to therapeutic strategies

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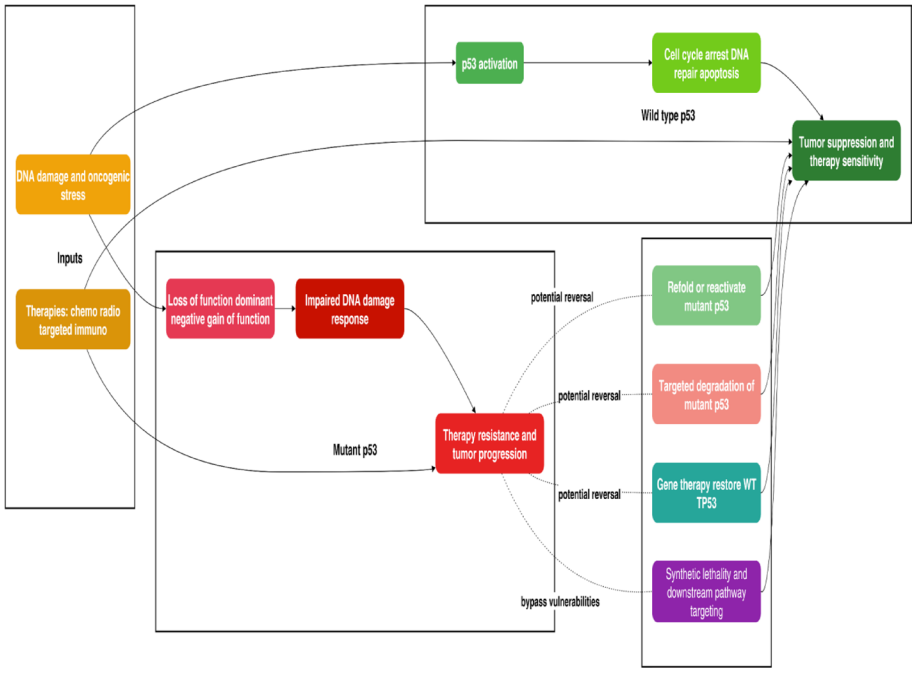
Abstract

The tumor suppressor p53, often referred to as the "guardian of the genome," is mutated in more than half of human cancers. These mutations have a significant impact on cancer biology and response to therapy. p53 mutations involve a range of changes that interfere with DNA binding, eliminate tumor suppressor functions, and, in many cases, confer dominant-negative or gain-of-function characteristics that actively promote oncogenesis. These mutations are closely linked to poor clinical outcomes and resistance to standard treatments. This review examines the impact of p53 mutations on cancer therapy in various ways. In chemotherapy and radiotherapy, loss of wild-type p53 impairs DNA damage responses, whereas mutant forms often contribute to treatment resistance. Additionally, p53 status influences responses to targeted therapies and immunotherapies, thereby affecting patient outcomes and prognoses. Importantly, ongoing clinical trials are beginning to integrate p53 mutational status as a predictive biomarker for therapy selection. Strategies aimed at restoring p53 activity are gaining increasing popularity in the development of treatments. These approaches include gene therapy to reintroduce the wild-type gene, targeted degradation of mutant p53 proteins, and small molecules designed to refold or reactivate mutant p53. In addition, synthetic lethality frameworks are being utilized to exploit vulnerabilities specific to tumors with p53 mutations, as well as interventions that target downstream effectors of p53 pathway. Together, these strategies represent a significant shift in precision oncology.

Keywords p53 tumor suppressor, Mutation, Gain-of-function, Cancer progression, Cancer therapy

Graphical Abstract



Introduction

The tumor suppressor protein p53, encoded by the *TP53* gene, plays a vital role in regulating cellular responses to stress and maintaining genomic integrity [1–3]. As a key transcription factor, p53 integrates signals from DNA damage, oncogenic stress, and metabolic imbalances to manage essential processes such as cell cycle arrest, DNA repair, cellular senescence, and apoptosis [4–7]. Through these functions, p53 acts as a crucial barrier against malignant transformation. The signals that trigger stress and activate p53, along with the resulting cellular outcomes, are illustrated in Fig. 1.

TP53 plays a crucial role in the body, but it is also the most frequently mutated gene in human cancer, with alterations found in about half of all tumors [1, 2]. Unlike many tumor suppressor genes that are often deleted or silenced, *TP53* is typically affected by missense mutations [4]. These mutations lead to the production of unstable proteins that still get expressed. As a result, mutant p53 proteins lose their normal tumor suppressor function and may exert dominant-negative effects on wild-type p53 family members. Additionally, these mutants can acquire gain-of-function properties that promote tumor progression, metastasis, and resistance to therapy [5].

The prevalence and functional diversity of *TP53* mutations have significant implications for cancer therapy. Tumors with *TP53* mutations are often linked to poor prognosis and resistance to chemotherapy, radiotherapy, and targeted treatments. However, the stability and persistence of mutant p53 proteins also present unique therapeutic opportunities. Over the past decade, considerable progress has been made in developing strategies to restore wild-type p53 function, eliminate mutant p53, or exploit vulnerabilities arising from p53 loss.

The purpose of this review is to critically evaluate emerging therapeutic strategies targeting p53. We will focus on how different *TP53* mutation types affect treatment

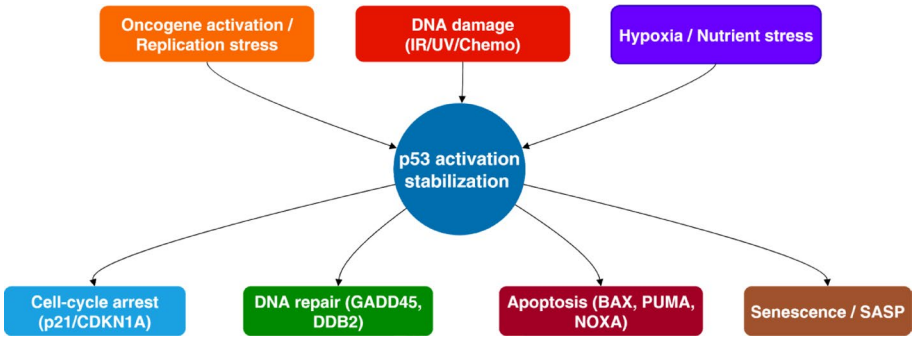


Fig. 1 Overview of p53-regulated stress responses and therapeutic entry points. Schematic illustration of the major cellular stress signals that activate p53, including DNA damage, oncogene activation, hypoxia, and metabolic stress, and the downstream transcriptional programs governing cell cycle arrest, DNA repair, senescence, and apoptosis. Central to these responses is the regulation of p53 stability and activity by post-translational modifications, particularly ubiquitination mediated by E3 ligases and deubiquitinases. This framework provides a conceptual reference for the therapeutic strategies discussed throughout this review, including p53 reactivation, mutant p53 degradation, exploitation of synthetic lethal vulnerabilities, and targeting of downstream p53-regulated pathways

responses and highlight recent advances in gene therapy, small-molecule reactivation, targeted degradation, synthetic lethality, and modulation of downstream pathways. Drawing on extensive research from our laboratory and others regarding the regulation of p53 stability by ubiquitin ligases and related pathways, we aim to provide a comprehensive framework for understanding how mutant p53 can be transformed from a contributor to poor prognosis into a viable therapeutic target [6–8]. Unlike many previous p53 reviews that emphasize canonical loss-of-function paradigms, this review highlights dominant-negative and gain-of-function mechanisms, structural and oligomerization-based interference, and their emerging therapeutic implications.

The guardian's dilemma: understanding p53 mutations

The integrity of the p53 pathway is crucial for maintaining genome stability and preventing malignant transformation. The *TP53* gene exhibits a distinctive mutation spectrum in human cancers, characterized by a high frequency of missense mutations clustered within the DNA-binding domain [4, 9, 10]. These alterations not only disrupt the canonical tumor suppressor functions of p53 but can also confer dominant-negative or gain-of-function activities that actively promote tumor progression. Understanding the diversity of *TP53* mutations, their structural consequences, and their biological impact is essential for appreciating how they reshape the cancer landscape and complicate therapeutic intervention. The structural domains of p53 and the distribution of hotspot mutations are illustrated in Fig. 2.

Types of p53 mutations

Mutations in *TP53* can be classified into several categories, each with distinct effects on the protein's structure and function. (1) p53 missense mutations account for approximately 75% of all *TP53* gene alterations [5]. These mutations typically occur within the DNA-binding domain, specifically in exons 5 to 8, and lead to single-amino acid substitutions that disrupt sequence-specific DNA recognition [11–15]. R175, G245, R248, R273, and R282 are significant p53 hotspot mutations that frequently occur across various tumor types. R175 refers to the substitution of arginine at position 175 with other amino acids, located within a loop that interacts with DNA. Mutations at R175

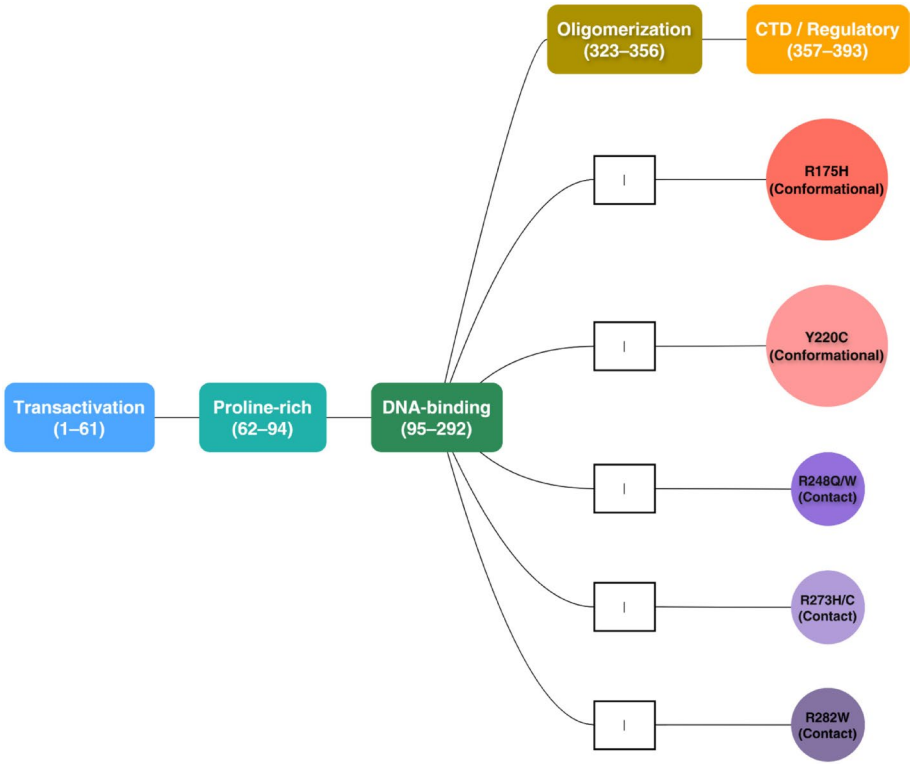


Fig. 2 Schematic representation of TP53 domains and recurrent cancer-associated mutations. Full-length TP53 (1–393 aa) is shown with major functional domains indicated: transactivation (1–61), proline-rich (62–94), DNA-binding (95–292), oligomerization (323–356), and C-terminal regulatory domain (357–393). Recurrent hotspot mutations within the DNA-binding domain are displayed using a lollipop plot, where vertical stems indicate mutation positions and circles denote individual mutations. Conformational mutations (R175H, Y220C) and DNA-contact mutations (R248Q/W, R273H/C, R282W) are highlighted in distinct colors. Collectively, these mutations disrupt normal p53 function and contribute to tumorigenesis

destabilize the DNA-binding domain, significantly impairing p53's ability to suppress tumors. The R175H mutation, which changes arginine to histidine, is common and is often associated with gain-of-function properties that promote invasion and metastasis [16]. G245 is located in the L3 loop of the DNA-binding domain, a crucial area for DNA interaction. Mutations like G245S (glycine to serine) can disrupt the loop's structure and hinder DNA binding [17]. R248 is a frequently mutated codon in the *TP53* gene, essential for binding to the major groove of DNA. Mutations such as R248Q (arginine to glutamine) and R248W (arginine to tryptophan) disrupt these interactions, preventing p53 from binding to its target genes. R248 mutants are known for their gain-of-function activities, which promote increased cell proliferation, survival, and metastatic potential [11, 18]. R249, located next to R248, is a key DNA-contact residue. The R249S mutation (arginine to serine) is common in hepatocellular carcinoma and linked to exposure to aflatoxin B1, a potent carcinogen. This mutation disrupts DNA binding and is often associated with more aggressive disease [19]. R273 is a key residue that interacts with the phosphate backbone of DNA, stabilizing the p53-DNA complex. Mutations at R273, such as R273H, significantly reduce DNA-binding affinity, thereby impairing p53's ability to activate target genes [20]. R282 is located in an alpha-helix of the DNA-binding domain and interacts non-sequence-specifically with DNA. Mutations such as R282W (arginine to tryptophan) disrupt the structure of this helix, compromising the

domain's stability and leading to loss of p53 function [21]. (2) Nonsense mutations of the *TP53* gene account for approximately 10–11% of all TP53 mutations. These mutations introduce a premature termination codon (PTC) into the messenger RNA (mRNA) sequence, resulting in the production of a truncated and inactive p53 protein [22]. These often result in complete loss of p53 activity and contribute to haploinsufficiency or null phenotypes. Here are two examples of nonsense mutations in the *TP53* gene: (a) *TP53* p.R213X (c.637 C > T). This common mutation converts arginine (R) to a premature stop codon (X) at amino acid position 213, resulting in a non-functional p53 protein [22]. (b) *TP53* p.R306X (c.916 C > T). This mutation introduces a premature stop codon at position 306, leading to a nonfunctional p53 protein and a failure to induce apoptosis in *TP53*-null cells [23]. **(3)** Frameshift mutations arise from insertions or deletions that alter the reading frame, leading to the production of unstable or misfolded proteins. For example, (a) The *TP53* c.216dup (p.Val73fs) mutation is a specific type of frameshift mutation characterized by the duplication of a single nucleotide (cytosine, C) at position 216 of the TP53 cDNA (c.216dupC). This mutation is predicted to lead to a loss of normal protein function and has been classified as pathogenic. It is associated with hereditary cancer syndromes, such as Li-Fraumeni Syndrome [24]. (b) *TP53* c.994_995delTC (p.Cys332Ilefs*14). This frameshift mutation is caused by the deletion of two nucleotides (TC) at positions 994–995 in the *TP53* cDNA. This alteration results in a change from cysteine to isoleucine at amino acid 332, followed by a premature stop codon 14 amino acids downstream (p.Cys332Ilefs*14). Although this mutation primarily leads to a loss of transcriptional activity, it retains residual antiproliferative effects and can induce cellular senescence [25]. (4) Splice-site mutations in the *TP53* gene are genetic changes that occur at the junctions between exons and introns, disrupting the normal splicing process of mRNA. When these mutations occur in *TP53*, they can lead to abnormal splicing, resulting in the production of non-functional or truncated p53 proteins. This disruption compromises the protein's essential role as a tumor suppressor. Examples of *TP53* splice-site mutations: (a) *TP53* c.375 + 1G > A: This somatic splice mutation affects a splice donor site in intron 3 (or the + 1 position of intron 4) of the *TP53* gene. It leads to a truncated protein that lacks essential coding sequences, including the DNA-binding and oligomerization domains, rendering it non-functional. This mutation is associated with various cancers, such as high-grade serous ovarian cancer, breast cancer, and bladder cancer [26]. (b) *TP53* c.560-1G > C (IVS05-1G > C) is a pathogenic splice-site mutation involving a G to C substitution just before coding exon 5, at the acceptor splice site of intron 4. This change disrupts RNA splicing, typically resulting in a loss of protein function. It has been associated with Li-Fraumeni Syndrome and rhabdomyosarcoma [27]. (5) Deletions and large genomic rearrangements of *TP53* gene are significant alterations that compromise the p53 protein. Unlike point mutations, which modify specific nucleotides, deletions remove entire DNA segments, while large rearrangements involve complex structural changes, such as inversions or translocations. These substantial changes are frequently seen in human cancers and are often linked to more aggressive disease forms. (a) Deletion of chromosome 17p. This is a well-known example of a *TP53* gene alteration located on the short arm of chromosome 17 (17p13.1), including chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), glioblastoma, and colorectal cancer. It often leads to the loss of one *TP53* allele and usually a point mutation in the other, resulting in the complete inactivation of the p53 protein [28, 29].

(b) Large deletions encompassing the entire *TP53* gene in Li-Fraumeni Syndrome (LFS). These large deletions increase the high cancer risk associated with LFS patients and are linked to more aggressive cancer characteristics [30, 31]. (c) Recurrent genomic rearrangements in intron 1 of *TP53* in osteosarcoma. Beyond simple deletions, complex genomic rearrangements, specifically recurrent rearrangements within intron 1 of the *TP53* gene, have been identified as a mechanism of *TP53* inactivation in osteosarcoma. These rearrangements can occur somatically in sporadic cases or as germline events leading to LFS. Whole-genome sequencing has revealed that these structural variations are particular to osteosarcoma [32]. Table 1 summarizes major *TP53* mutation classes and representative, clinically relevant hotspot mutations discussed in the text and is not intended to provide an exhaustive catalog of all *TP53* variants.

Structural disruption and loss of DNA binding

The central DNA-binding domain (residues 100–300) is essential for p53's transcriptional activity. Mutations in this domain can be categorized into two major types: **(1) Conformational (structural) mutants.** Unlike contact mutants that affect DNA-binding residues, conformational mutants affect the structural integrity and stability of p53, especially in its DNA-binding domain (DBD) [33, 34]. Even a single amino acid change can cause significant misfolding, hindering its ability to bind to target DNA sequences effectively. p53 R175H exhibits dominant-negative effects over wild-type p53 by forming mixed tetramers that inactivate functional proteins, thereby promoting tumor progression. Its presence is often associated with poor prognosis and resistance to conventional therapies [16, 35, 36]. (**2**) **Contact mutants of p53**. R248Q and R273H are notable contact mutants of the p53 tumor suppressor protein that impair its ability to bind to DNA response elements. As a well-documented gain-of-function (GOF) mutation, R248Q not only loses tumor suppressor activity but also promotes tumor progression, metastasis, and drug resistance. Its GOF activities may alter gene expression related to cell proliferation and survival, and modify metabolic pathways [20, 37–40]. R273H is a well-characterized GOF mutant that promotes cancer progression and modifies cellular metabolism to support tumor growth. It is associated with aggressive tumor

Table 1 TP53 mutation classes with representative hotspot mutations and therapeutic implications

Mutation Class	Representative Hotspot Mutations	Structural / Biochemical Impact	DNE / GOF Tendency	Typical Cancers	Therapeutic Implications
Contact	R248Q/W, R273H/C, R282W	Loss of sequence-specific DNA binding	Strong DNE; context-dependent GOF	Colon, Lung, H&N	Variable reactivation; checkpoint targeting [20, 37-43]
Conformational	R175H, Y220C	Zinc coordination loss / crevice formation	Frequent GOF; aggregation-prone	Breast, Ovary, Sarcoma	Zinc metallochaperones; stabilizers [16, 155, 243]
Truncating	Nonsense, frameshift	Null or severely truncated protein	Minimal DNE / GOF	Multiple	Treated as p53-null; exploit DDR [22-25]
Splice / Isoform	Δ40p53, Δ133p53	Altered domains / regulation	Context-dependent	Variable	Prognostic nuance [26, 27, 61]
LOH / Deletion	WT allele loss	Increased mutant dosage	Amplified GOF	Aggressive tumors	Biomarker of poor outcome [28-32]

characteristics, increased metastatic potential, and resistance to standard cancer therapies [20, 41–43].

Dominant-negative *TP53* mutations and their role in human disease

p53 functions as a tetrameric transcription factor, with oligomerization required for DNA binding and gene activation [44–47]. This structural requirement underlies the biological significance of dominant-negative (DN) mutations, in which a defective p53 protein interferes with the function of the wild-type allele. Such effects are particularly consequential for tumor suppressors like *TP53*, where DN inhibition can severely compromise pathway activity even in heterozygous settings [12, 48–50]. Dominant-negative p53 proteins reduce the effective pool of functional p53 [36], accelerate tumorigenesis [41, 51], and may facilitate the emergence of gain-of-function (GOF) phenotypes [52–54]. Therefore, therapeutic strategies aimed at restoring p53 activity must account for both loss of wild-type function and active inhibition by mutant p53.

Mechanistically, dominant-negative suppression arises primarily through hetero-oligomerization, whereby mutant p53 subunits incorporate into mixed tetramers, thereby disrupting their stability and DNA-binding capacity. Notably, the C-terminal oligomerization domain of p53 is itself sufficient to exert dominant-negative effects, emphasizing the importance of tetramer integrity in p53 regulation [55]. Experimental studies have shown that expression of C-terminal p53 fragments containing the oligomerization domain can inhibit wild-type p53 function, highlighting the relevance of mutations or alterations affecting this region [56–58].

Consistent with these mechanistic principles, *TP53* is the most commonly mutated gene in human cancer, with missense mutations accounting for approximately 70–75% of all alterations [4, 59]. Many of these missense variants encode full-length proteins that oligomerize and therefore exhibit dominant-negative activity [48, 60]. Dominant-negative mutations are highly enriched at recurrent hotspot residues within the DNA-binding domain, including R175, G245, R248, R249, R273, and R282 [4, 59], and are prevalent across a broad spectrum of malignancies, including breast, colorectal, lung, ovarian, head and neck cancers, glioblastoma, and hematological malignancies [4]. In addition to missense mutations, dominant-negative suppression of p53 can also arise from specific p53 isoforms generated by alternative splicing or translation. Isoforms such as Δ40p53 and Δ133p53 retain the oligomerization domain but lack full transactivation potential, enabling them to form mixed tetramers with full-length p53 and attenuate its transcriptional activity [61].

Structurally, dominant-negative *TP53* mutations can be broadly categorized into two classes: (i) Conformational mutants (e.g., R175H, G245S, R282W), which destabilize the p53 core domain and impair proper folding; and (ii) DNA-contact mutants (e.g., R248Q/W, R273H), which retain overall structural integrity but directly disrupt sequence-specific DNA binding [62]. Despite distinct molecular defects, both classes preserve oligomerization capacity and efficiently inhibit wild-type p53 through formation of inactive mixed tetramers [48, 62].

Clinically, dominant-negative *TP53* mutations are associated with early tumor development, aggressive disease progression, poor prognosis, and resistance to chemotherapy and radiotherapy [4, 63]. In breast and colorectal cancers, patients harboring dominant-negative *TP53* mutations exhibit worse clinical outcomes than those with *TP53*-null

tumors, suggesting that dominant-negative interference may be more deleterious than complete loss of p53 function [63]. The pathological impact of dominant-negative *TP53* mutations is further underscored in Li–Fraumeni syndrome, where germline missense mutations frequently encode dominant-negative p53 proteins, conferring exceptionally high lifetime cancer risk and early-onset malignancies, including sarcomas, breast cancers, brain tumors, and leukemias [64].

Together, dominant-negative *TP53* mutations represent a distinct and clinically significant class of p53 alterations, defined by active suppression of residual wild-type p53 rather than passive loss of function. Their prevalence across cancer types and association with adverse clinical outcomes underscore the importance of therapeutic approaches that either counteract dominant-negative inhibition, reactivate wild-type p53, or selectively eliminate mutant p53 [63].

Gain-of-Function (GOF) activities of p53 mutations

GOF activities of p53 mutations refer to a phenomenon where mutant p53 proteins not only lose their original tumor suppressor functions but also acquire novel, oncogenic properties that actively promote cancer development and progression. This concept significantly expands our understanding of *TP53*'s role in cancer beyond simply being a "loss-of-function" tumor suppressor. These GOF properties contribute directly to the malignant phenotype, often by mechanisms independent of their normal DNA-binding and transcriptional functions [56, 64–66].

GOF activities in p53 mutations are significant for several reasons: (1) Enhanced malignancy. GOF mutant p53 proteins can lead to more aggressive tumors, increased growth rates, and greater resistance to cell death. (2) Therapeutic challenge. Simply restoring wild-type p53 function may not be sufficient, as the mutant protein's oncogenic activities can continue promoting tumor growth. Therapies must target both the reactivation of wild-type p53 and the inhibition of GOF functions. (3) Prognostic indicator. Specific GOF p53 mutations are often associated with more aggressive tumors, greater metastatic potential, and poorer patient outcomes. (4) Novel therapeutic targets. Research is ongoing into strategies that target mutant p53 proteins or their downstream effects as potential therapies.

In addition to loss of tumor suppressive activity, many missense p53 mutants acquire GOF properties that actively promote tumor progression. A well-established GOF mechanism involves aberrant interactions between mutant p53 and the p53 family members p63 and p73. Multiple studies have shown that mutant p53 proteins bind and sequester p63 and p73, thereby inhibiting their transcriptional programs governing apoptosis, differentiation, and genomic stability [67–69]. This dominant-negative interference contributes to enhanced invasion, metastasis, and chemoresistance across multiple cancer types and is widely regarded as a core component of mutant p53 GOF biology. The regulation of p63 and p73 isoforms is complex, involving intricate control by E3 ligases and molecular chaperones such as Hsp70, which dictate their stability and activity [70]. Furthermore, our work has shown that p63 itself is a key regulator of microRNA processing through its interaction with Ago2, linking this tumor suppressor family directly to post-transcriptional gene regulation [71]. The sequestration of these family members by mutant p53 disrupts these critical functions. Mutant p53 has the ability to change the transcription of genes that are not typically associated with wild-type p53 targets.

This may involve binding to new DNA sequences, interacting with other transcription factors such as NF-Y and SP1, or recruiting enzymes that modify chromatin. These actions can activate oncogenic pathways or suppress tumor-suppressive pathways [72]. Some GOF mutants have been demonstrated to reprogram cellular metabolism, enhancing glycolysis and glutaminolysis, which are critical for the rapid proliferation of cancer cells [73–75]. Mutant p53 contributes to increased genomic instability, leading to additional mutations and chromosomal rearrangements that drive tumor evolution [76–78]. GOF mutants can enhance cell migration, invasion, and metastatic spread by upregulating genes associated with epithelial-mesenchymal transition (EMT), angiogenesis, and extracellular matrix remodeling [79–81]. Many common "hotspot" missense mutations in *TP53* are known to exhibit significant GOF, such as p53 R175H [41], p53 R248Q [82], and p53 R273H [83]. The p53R175H mutation is frequently classified as dominant-negative because it interferes with wild-type p53 function by hetero-oligomerization. However, extensive experimental evidence has also demonstrated that p53R175H exhibits gain-of-function properties, including activation of oncogenic transcriptional programs and promotion of invasion and metastasis in p53-null or mutant contexts [83, 84]. Thus, R175H is widely regarded as a mutation with dual dominant-negative and gain-of-function activities, depending on cellular context and p53 allelic status.

Importantly, these GOF effects are context-dependent, varying across cancer types and mutation hotspots. The concept of mutant p53 as an "oncoprotein" has changed our understanding of *TP53*; it is not just a "loss-of-function" gene but also a contributor to cancer aggressiveness. As illustrated in Fig. 3, dominant-negative and gain-of-function mutant p53 activities reshape transcriptional programs, chromatin states, and downstream signaling pathways, creating vulnerabilities that can be targeted for therapeutic intervention.

The E3 ligase network: a complex web of p53 regulators beyond MDM2

Mdm2 (MDM2 or Hdm2 in humans) is a key negative regulator of the p53 protein [85, 86]. Loss of Mdm2 in mice results in an embryonic-lethal phenotype. However, this early

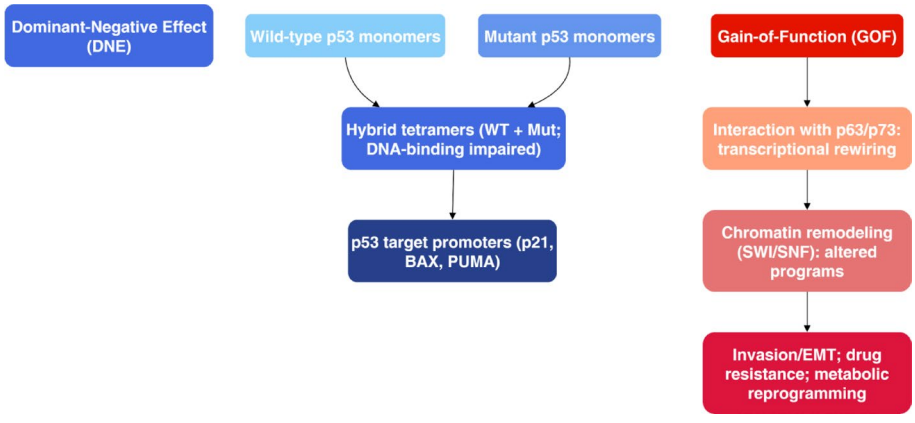


Fig. 3 Dominant-negative and gain-of-function mechanisms of mutant p53. Mutant p53 proteins impede wild-type p53 function through two main mechanisms: (1) Dominant-negative effect (DNE): Hybrid tetramers formed by wild-type and mutant p53 reduce DNA-binding ability, leading to decreased transcription of target genes like p21, BAX, and PUMA. (2) Gain-of-Function (GOF): Mutant p53 gains new oncogenic traits through interactions with p63 and p73, resulting in transcriptional changes, chromatin remodeling (via SWI/SNF complexes), and activation of processes that promote invasion, epithelial–mesenchymal transition (EMT), drug resistance, and metabolic reprogramming

embryonic lethality in Mdm2-null mice is rescued by deleting the p53 gene, indicating the importance of Mdm2's negative regulatory function on p53 during development [87, 88]. MDM2 mediates mono- or multiple ubiquitination of p53 [89], but only polyubiquitin chains are efficiently recognized by the proteasome [8]. MDM4, also known as MDMX, is a close homolog of MDM2 and a crucial regulator of the tumor suppressor protein p53 [90]. Although MDM4 lacks intrinsic E3 ligase activity, it forms heterodimers with MDM2, which stabilizes MDM2 and enhances its E3 ligase function toward p53 [91]. Genetic studies have shown that Mdm4 deletion results in p53-dependent embryonic lethality, highlighting its essential role in regulating p53 activity during development [92, 93]. In contrast to the MDM2/MDM4 complex, Pirh2 is a p53-inducible E3 ligase that ubiquitinates p53 mainly as part of a negative feedback loop. While Pirh2 contributes to p53 turnover, it does not mimic the effects of Mdm2 or Mdm4 loss in vivo and appears to play a more context-dependent or stress-responsive role [94]. We provide evidence that Pirh2 is a critical negative regulator of p53 and represents a new pathway for maintaining p53. Additionally, Pirh2 regulates other p53 family members, such as p73, and its stability and activity can be modulated by the E3 ligase AIP4 [95, 96]. Currently, Pirh2 is not considered a clinically targetable E3 ligase, and no selective small-molecule inhibitors of Pirh2 have been reported. Unlike MDM2, Pirh2 lacks a well-defined ligandable pocket analogous to the p53-binding cleft of MDM2, and its catalytic RING domain presents substantial challenges for selective pharmacologic inhibition.

Genetic studies further distinguish Pirh2 from MDM2/MDM4. Pirh2 knockout mice are viable and do not display embryonic lethality, in contrast to the p53-dependent lethality observed in Mdm2- or Mdm4-null animals [97]. Pirh2-deficient mice exhibit relatively mild phenotypes, including altered p53 responses under specific stress conditions, supporting the view that Pirh2 functions as a context-dependent or auxiliary regulator of p53, rather than a dominant, non-redundant suppressor [97]. Together, these observations suggest that while Pirh2 contributes to fine-tuning p53 signaling, it is currently less attractive as a therapeutic target than the MDM2/MDM4 axis. Therefore, MDM2, with the support of MDM4, serves as the primary, non-redundant E3 ligase responsible for maintaining p53 suppression and facilitating its proteasome-mediated degradation. Furthermore, UBE4B is essential and required for MDM2-mediated p53 polyubiquitination and degradation [8]. UBE4B mediates not only p53 polyubiquitination and degradation, but also inhibits p53-dependent transactivation and apoptosis.

Clinical associations of p53 mutations

The associations of *TP53* mutations in clinical settings are crucial because they act as significant prognostic and predictive biomarkers across various human cancers. Mutations in *p53* predict the likely course and outcome of disease for a patient, regardless of treatment [98–100]. Specific p53 mutations can predict how patients will respond to particular therapies, such as chemotherapy, radiation, targeted agents, and immunotherapy. This allows for more personalized and effective treatment strategies [101, 102]. Identifying individuals with *p53* mutations can help determine who might benefit from more aggressive treatment approaches or closer surveillance [103, 104]. Mutations in p53 guide the development of new drugs that specifically target cells with mutant p53 or aim to restore wild-type p53 function [34, 105].

Mutations in *TP53* gene are present in nearly all human cancers, but they vary in prevalence and clinical significance across different cancer types. For example, in breast cancer, mutations in *p53* gene are frequently associated with triple-negative breast cancer subtypes. The presence of mutant p53 is connected to a worse prognosis for patients [106, 107]. *TP53* is the most frequently mutated gene in NSCLC, found in about 50% of adenocarcinomas and over 80% of squamous cell carcinomas [108–110]. *TP53* mutations are frequently observed in colorectal cancer, especially in later stages and specific molecular subtypes. Their presence typically correlates with a poorer prognosis [111–113]. Mutations in *TP53* gene play a significant role in the resistance to therapy and the recurrence of glioblastoma [114–116]. High-grade serous carcinoma in ovarian cancer shows *TP53* mutations in over 95% of cases, underscoring its critical role [117–119]. Li-Fraumeni Syndrome is associated with germline mutations in the *TP53* gene, which significantly increase the risk of various cancers, including sarcomas, breast cancer, and brain tumors. This underscores the vital role of functional p53 in tumor suppression [120, 121].

These examples demonstrate the diverse effects of p53 mutations — from sporadic somatic events that influence tumor evolution to inherited mutations that contribute to cancer predisposition syndromes. These mechanistic insights provide essential context for understanding how *TP53* mutations influence therapeutic response, as discussed in the following sections.

A weakened shield: impact of p53 mutations on cancer therapy

Unlike prior reviews that focused on mechanistic aspects of p53 dysfunction, this section emphasizes recent translational and clinical evidence linking *TP53* status to therapeutic response. Loss or mutation of p53 profoundly alters tumor responses to therapy. Wild-type p53 coordinates cell cycle arrest, DNA repair, and apoptosis in response to therapeutic stress, whereas TP53 mutations disable these safeguards, allowing cancer cells to survive and adapt under treatment pressure. Clinically, *TP53* mutations are associated with therapy resistance, disease progression, and poor patient outcomes across many tumor types.

TP53 mutations and response to genotoxic and targeted therapies

TP53 status plays a crucial role in determining tumor sensitivity to chemotherapy and radiotherapy [5, 122]. Tumors that retain wild-type p53 typically respond better to DNA-damaging agents due to p53-dependent mechanisms, such as cell cycle arrest and apoptosis. In contrast, tumors with *TP53* mutations often show either intrinsic or acquired resistance to these treatments [123, 124]. Similarly, the effectiveness of several targeted therapies is influenced by p53 status, particularly those targeting DNA damage response pathways or angiogenic signaling. Instead of providing an exhaustive review of these well-established relationships, we summarize overarching therapeutic strategy categories influenced by TP53 mutations (Table 2) rather than disease-specific clinical outcome data.

TP53 mutations and immunotherapy responses

Emerging evidence shows that *TP53* mutations can significantly influence responses to immunotherapy, highlighting their growing clinical importance [125–127]. Mutant p53

Table 2 Established therapeutic strategies influenced by TP53 mutation status

Strategy	Modality	Example agents/approaches	Development stage	Key considerations
Reactivation	Small molecules	APR-246, ZMC1, PC14586	Phase II/III and preclinical	Mutation-dependent efficacy; combinations often needed [153, 157, 243]
Degradation	Chaperone/HDAC disruption	17-AAG/ganetespib; Panobinostat	Early clinical / combination	Broad effects; toxicity windows matter [160-165]
	PROTACs	p53-targeting degraders	Preclinical	Potentially selective for mutant p53 forms [166]
Bypass	Apoptosis induction	BH3 mimetics (venetoclax/navitoclax)	Approved/clinical	p53-independent killing of primed tumors [209-211]
Exploit	Checkpoint inhibition	WEE1 (adavosertib), CHK1/ATR inhibitors	Clinical	Most effective in p53-deficient contexts under replication stress. [174-179]
Immune	Neoantigen targeting	Mutant p53 vaccines/TCRs	Early clinical trials	Patient-specific design; HLA constraints [127]

affects tumor immunogenicity through various mechanisms, including altered apoptosis, changes in the tumor microenvironment, and modulation of immune checkpoint pathways [127–129]. While *TP53*-driven genomic instability can increase neoantigen burden and enhance responsiveness to immune checkpoint inhibitors in certain contexts [130], mutant p53 can also promote immunosuppressive signaling and immune evasion [128, 129]. Notably, recent studies in non-small cell lung cancer indicate that *TP53* mutations can have varying effects on immunotherapy outcomes, depending on co-occurring oncogenic alterations. This underscores the context-dependent nature of these interactions [125, 126].

Prognostic and translational implications of *TP53* mutations

TP53 mutations remain among the strongest prognostic biomarkers in oncology, consistently associated with poor survival and reduced treatment efficacy [4, 131, 132]. In addition to their prognostic significance, translational studies and clinical trials increasingly consider *TP53* status to stratify patients and guide therapeutic development [4, 133]. Recent trials in solid tumors and hematologic malignancies highlight both the limitations of *TP53* as a predictive biomarker for standard therapies and its growing relevance for emerging p53-directed strategies [35, 134]. Basket trials targeting specific *TP53* mutations, such as Y220C-selective reactivators, exemplify a shift toward mutation-informed trial design and precision oncology approaches [135–137]. These findings position *TP53* mutations as both mechanistic drivers and clinically actionable biomarkers for prognosis and therapeutic response.

Restoring the guardian: strategies to target mutant p53

Given the high occurrence of *TP53* mutations in cancer and their significant effect on treatment responses, restoring or reactivating p53 function has become a key objective in translational oncology. Unlike other tumor suppressors, mutant p53 is often stably expressed and accumulates in cancer cells. This presents both a challenge and an opportunity: it is a challenge because conventional therapies can fail when p53 is absent; however, it also presents an opportunity because the protein is present, can be targeted with drugs, and is associated with vulnerabilities specific to cancer. Researchers have developed multiple strategies to restore wild-type p53 function, eliminate mutant protein, or target downstream pathways. These approaches are changing how clinicians and researchers perceive mutant p53—not just as a loss of function but as a potential therapeutic target.

Gene therapy approaches

One of the earliest strategies to restore p53 activity was gene therapy, which aimed to reintroduce wild-type *TP53* into tumor cells. (1) Viral vector delivery. Adenoviral constructs encoding the wild-type p53 protein, such as Gendicine in China [139] and Advexin in the U.S [140]., were developed in the 1990s and 2000s. Gendicine, the world's first approved gene therapy, was approved in 2003 for the treatment of HNSCC [138–140]. Clinical results revealed improved responses to radiotherapy and better survival rates. Nonetheless, challenges such as limited transduction efficiency, immune responses, and transient expression have hampered its broader application. Some engineered adenoviruses selectively replicate in p53-deficient cells (e.g., ONYX-015) [141]. ONYX-015 (dl1520) was an early, extensively studied oncolytic adenovirus that lacked the E1B-55 K gene and was designed to replicate selectively in p53-deficient cancer cells. It showed some activity in HNSCC and other tumors [142]. (2) Next-generation approaches. Recent advances in nanoparticle delivery [143] and CRISPR/*Cas9* editing [144, 145] are reigniting interest in *p53* gene therapy. CRISPR-based strategies enable direct correction of hotspot mutations, although challenges related to specificity and delivery remain. Gene therapy has demonstrated that reactivating p53 pathways is both feasible and therapeutically relevant.

Reactivation of wild-type p53 via MDM2 inhibition

In tumors retaining wild-type *TP53*, pharmacologic inhibition of MDM2 represents a direct strategy to restore p53 tumor suppressor activity. Small-molecule MDM2 inhibitors, including Nutlin-3, RG7112, and the clinical-grade inhibitor navtemadlin (KRT-232), disrupt the p53–MDM2 interaction, preventing p53 ubiquitination and degradation [146–150]. This leads to p53 stabilization and activation of transcriptional programs governing cell cycle arrest and apoptosis. Navtemadlin (KRT-232) is an oral MDM2 inhibitor that reactivates p53 in *TP53* wild-type myelofibrosis cells. In the Phase III BOREAS study (NCT03662126), navtemadlin monotherapy demonstrated significant efficacy compared to the best available therapy in JAK-inhibitor relapsed or refractory myelofibrosis, improving spleen volume, symptom burden, and biomarkers of disease modification [146, 147]. However, p53 turnover is regulated by a network of E3 ligases, including Pirh2 [94] and UBE4B [8], highlighting the complexity of sustaining p53 activation and the challenges associated with targeting this pathway long-term.

More recently, we have shown that the SWIB/MDM2 motif of UBE4B is critical for activating the p53 pathway, highlighting the intricate protein-protein interactions that fine-tune p53 stability [6]. This complexity underscores why targeting the central p53-MDM2 interaction remains an attractive, albeit challenging, therapeutic strategy. Nutlins were among the first potent and selective small-molecule MDM2 inhibitors [148, 149]. Nutlins are designed to bind to MDM2, thereby blocking its interaction with p53. This inhibition prevents p53 degradation, leading to its accumulation and activation of tumor suppressor functions, such as cell cycle arrest and apoptosis, in cancer cells with wild-type p53 [148, 149, 151, 152]. A more advanced MDM2 inhibitor, Idasanutlin (RG7388), has undergone testing in clinical trials, especially for acute myeloid leukemia (AML) with wild-type p53 [153].

Targeting mutant p53 for degradation

Targeting mutant p53 has long been seen as a primary goal in cancer therapy. Historically, it seemed challenging due to p53's role as a transcription factor and the diverse mutations in the *TP53* gene. However, advancements in p53 biology and drug discovery are making it increasingly feasible to target mutant p53 therapeutically.

Diverse strategies are being developed to target mutant p53, ranging from restoring its wild-type function to promoting its degradation or inhibiting its oncogenic activities.

(1) Reactivation/Restoration of wild-type-like conformation. Many common missense mutations in p53, especially those that affect its conformation, result in misfolding and destabilization, particularly in the DNA-binding domain. This approach uses small molecules that bind to the mutant p53 protein, thereby facilitating its refolding into a functional conformation similar to that of the wild-type protein. Once properly folded, the p53 protein can bind to DNA and activate its target genes. For example, (a) APR-246 (eprenetapopt). This prodrug is converted to methylene quinuclidinone (MQ), which binds to mutant p53 and targets cysteine residues, thereby restoring its function. It has shown promising results in clinical trials for *TP53*-mutated MDS and AML [154]. (b) PC14586 (rezatapopt). A highly specific small molecule designed to reactivate the *TP53* Y220C mutant. It binds to a specific pocket created by the Y220C mutation, stabilizing the protein and restoring its wild-type function. It has shown early clinical activity in solid tumor basket trials [155]. (c) COTI-2 is a small molecule demonstrating efficacy in preclinical models and early clinical trials for *TP53*-mutated cancers, believed to reactivate mutant p53 [156]. (d) p53 requires zinc for proper folding. Compounds such as zinc metallochaperones (e.g., ZMC1) restore zinc coordination to misfolded mutants, rescuing DNA-binding function [157]. Preclinical models show strong antitumor effects, especially in R175H mutants.

(2) Degradation of mutant p53. This strategy aims to eliminate the harmful mutant p53 protein found in cancer cells. Mutant p53 often accumulates to high levels due to its increased stability and resistance to degradation. Approaches include: **(a) HSP90 inhibitors**: Heat shock protein 90 (HSP90) is a molecular chaperone that assists in the proper folding and stability of numerous client proteins, including many that are oncogenic. HSP90 often stabilizes misfolded mutant p53. Inhibiting HSP90 can lead to the degradation of mutant p53 [158, 159]. Ganetespib, an HSP90 inhibitor, has been shown in preclinical studies to inhibit HSP90, thereby decreasing mutant p53 levels in various cancer cell lines and restoring sensitivity to apoptosis [160, 161]. **(b) HDAC inhibitors.**

Histone deacetylase (HDAC) inhibitors are a class of drugs that block the activity of HDAC enzymes, which are involved in removing acetyl groups from histones and other proteins. This leads to increased acetylation, primarily affecting chromatin structure and gene expression. However, HDAC inhibitors can also affect the stability and degradation of non-histone proteins, including p53. Some studies suggest that HDAC inhibitors can induce the acetylation of mutant p53, which may target it for degradation or alter the expression of chaperones and proteasomal components involved in the turnover of mutant p53. Their effect on mutant p53 is often indirect and context-dependent [162, 163]. Vorinostat (SAHA), Panobinostat, and Romidepsin are FDA-approved HDAC inhibitors. While their primary action is on chromatin, they have been observed to modulate the stability of mutant p53 in some cancer models [164–166]. **(c) Proteolysis-targeting chimeras** (PROTACs) are groundbreaking bifunctional small molecules designed to induce the targeted degradation of specific proteins [167]. A PROTAC molecule typically consists of three parts: a ligand that binds to the target protein (e.g., mutant p53), a ligand that binds to an E3 ubiquitin ligase, and a linker connecting the two. By bringing mutant p53 into close proximity with an E3 ligase, the PROTAC forces the ubiquitination of mutant p53, marking it for rapid and efficient degradation by the proteasome. This offers high specificity and the potential for catalytic degradation (a single PROTAC molecule can induce the degradation of multiple target proteins). While a clinically approved PROTAC specifically targeting mutant p53 is still in development, this technology represents one of the most exciting avenues. Proof-of-concept studies are underway, demonstrating the feasibility of designing PROTACs to degrade mutant p53 isoforms. The challenge lies in finding suitable "binder" molecules that can selectively engage different mutant p53 conformations [167]. **(d) Autophagy modulators.** Autophagy ("self-eating") is a lysosomal degradation pathway responsible for clearing damaged organelles, protein aggregates, and other cellular components. Mutant p53 proteins, especially those that misfold and aggregate, can sometimes be cleared through the autophagy-lysosome pathway. However, the role of autophagy in mutant p53 degradation is complex and context-dependent. Autophagy inducers, such as resveratrol and rapamycin, have been explored in preclinical studies for their potential to reduce mutant p53 levels [168, 169]. Conversely, autophagy inhibitors such as chloroquine and hydroxychloroquine are being tested in cancer therapies, but their effects on mutant p53 degradation can vary significantly [170, 171]. **(e) Targeting p53 phosphorylation-dependent degradation**. The stability of p53 is tightly regulated by post-translational modifications, including phosphorylation, which occurs in response to cellular stress. While phosphorylation at key sites, such as Serine 15, is known to stabilize wild-type p53, our research has uncovered a paradoxical mechanism in which the E3 ligase UBE4B specifically targets p53 phosphorylated at Serines 15 and 392 for degradation [172]. This suggests that in certain contexts, phosphorylation can flag p53 for destruction. More recently, we have shown that phosphorylation of UBE4B itself is a key regulatory switch. DNA damage induces UBE4B phosphorylation, which in turn prevents its degradation of p53, leading to p53 accumulation and an enhanced cellular response to damage [173]. Understanding this dynamic interplay between phosphorylation and ubiquitination opens new therapeutic avenues, in which modulating the activity of kinases or ligases could be used to control the fate of both wild-type and mutant p53. Importantly, degradation-based strategies are most applicable to TP53 missense "hotspot" mutants that exhibit increased

protein stability and accumulation in tumors, including R175H, R248Q/W, R273H, and R282W. These conformational and DNA-contact mutants evade efficient MDM2-mediated turnover and become highly dependent on molecular chaperones such as HSP90, thereby sustaining their oncogenic gain-of-function activities. In contrast, truncating mutations and many nonsense or frameshift variants typically produce unstable or absent p53 protein and are therefore less likely to benefit from degradation approaches.

(3) Inhibition of GOF activities. Rather than restoring wild-type p53 function, an alternative strategy aims to inhibit the oncogenic GOF activities of mutant p53. A prominent approach focuses on disrupting aberrant protein–protein interactions formed by mutant p53, particularly those involving p63 and p73. Blocking mutant p53–p63/p73 interactions has been shown to restore p63/p73 tumor suppressor functions and suppress invasion, metastasis, and survival signaling. Peptides and small molecules designed to disrupt these interactions selectively represent a promising, albeit still largely preclinical, strategy to counteract mutant p53 GOF activities [41, 174].

Targeted degradation is appealing because it bypasses the challenge of restoring wild-type function and instead removes the oncogenic protein altogether. The therapeutic strategies aimed at targeting mutant p53 are illustrated in Fig. 4.

Exploiting synthetic lethality and vulnerabilities in p53-mutant tumors

The primary advantage of this approach lies in its ability to target a compensatory pathway that p53-mutant cancer cells depend on while sparing normal cells with functional p53. This concept of synthetic lethality provides a means to eliminate cancer cells with minimal toxicity to healthy tissues.

Significant advancements have been made in this field, particularly in the areas of cell cycle checkpoint inhibitors and DNA damage repair inhibitors. **(1) Cell cycle checkpoint inhibitors.** Wild-type p53 is crucial for the G1/S and G2/M cell cycle checkpoints, which pause cell division in response to DNA damage for repair. When p53 is mutated or lost, cancer cells rely on alternative checkpoints, such as the G2/M checkpoint regulated by CHK1/2 and WEE1. Inhibiting these compensatory checkpoints forces p53-deficient cells into mitosis with unrepaired DNA, leading to cell death or mitotic catastrophe. In contrast, normal cells with functional p53 can still activate the G1/S checkpoint and tolerate damage, providing a potential therapeutic advantage. For example, **(a) CHK1/CHK2 inhibitors** (e.g., Adavosertib/MK-1775, Prexasertib). These agents inhibit the activity of checkpoint kinases 1 and 2 (CHK1/2), which are activated by ATR/ATM in response to DNA damage. In cells with *TP53* mutations, blocking CHK1/2 results in extensive DNA damage and cell death. Adavosertib has demonstrated significant clinical activity in *TP53*-mutated ovarian cancer, NSCLC, and other solid tumors, often in combination with chemotherapy, providing strong evidence of synthetic lethality. It has progressed to late-stage clinical trials [175–178]. **(b) WEE1 inhibitors** (e.g., Adarotene). WEE1 kinase is another critical regulator of the G2/M checkpoint. Inhibiting WEE1 in p53-mutant cells results in premature entry into mitosis with unrepaired DNA, leading to cell death [179, 180]. **(2) DNA damage repair (DDR) inhibitors.** p53 plays a crucial role in the DNA damage response by regulating genes involved in various repair pathways. Its loss can increase cells' reliance on specific alternative repair mechanisms. Inhibiting these compensatory pathways can lead to synthetic lethality. For example, by PARP inhibitors. **(a) PARP inhibitors.** PARP

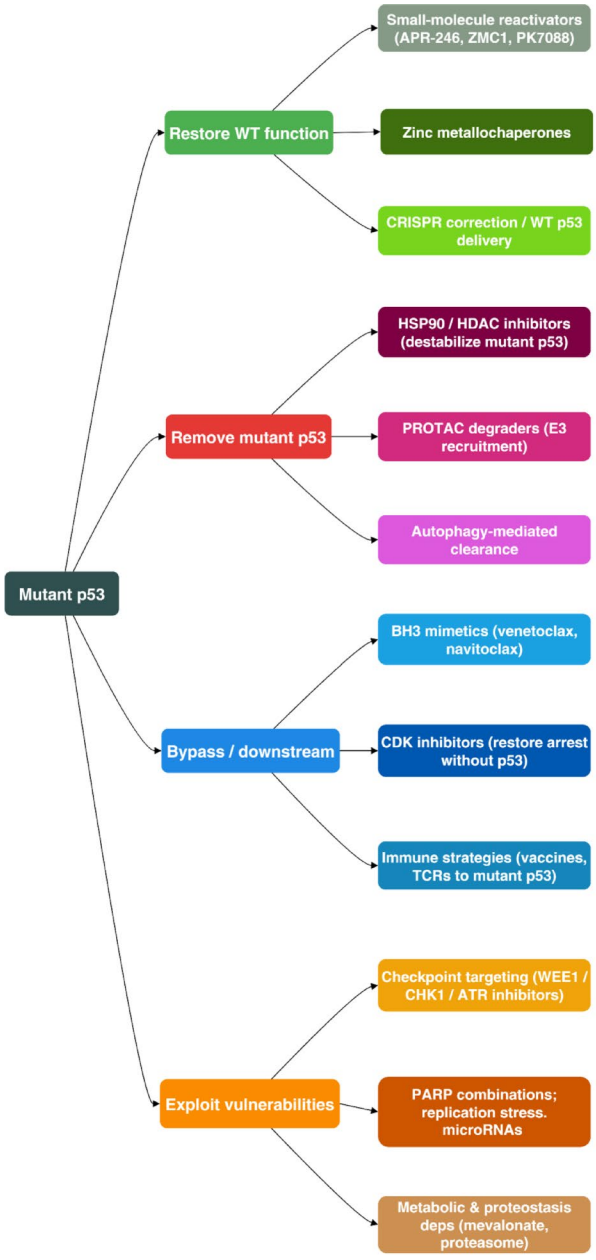


Fig. 4 Therapeutic strategies targeting mutant p53. Strategies for targeting mutant p53 can be grouped into three main areas: (1) Restoration: This includes small-molecule reactivators like APR-246 and eprenetapopt, zinc metallochaperones, and CRISPR-based delivery of wild-type p53. (2) Removal: This approach focuses on destabilizing mutant p53 using HSP90 or HDAC inhibitors, PROTAC degraders, and autophagy-mediated clearance. (3) Bypassing and Exploiting Vulnerabilities: Strategies in this category target downstream dependencies or exploit synthetic lethal interactions, including BCL-2/BCL-xL inhibitors, CDK inhibitors, immune strategies, checkpoint kinase inhibitors, PARP combinations, and metabolic or proteasome targeting. These approaches highlight both direct and indirect methods to counteract oncogenesis driven by mutant p53

inhibitors are well-known for their synthetic lethality in the presence of BRCA mutations, which are defects in the homologous recombination repair pathway. However, there is an increasing understanding of how these inhibitors interact with p53 status. In certain situations, mutations in *TP53* gene—especially those that result in a complete loss of p53 function—can cause cells to rely more on PARP-mediated DNA repair. This

reliance makes them more sensitive to PARP inhibitors. The concept of synthetic lethality in this context can be complex and varies depending on specific circumstances [7, 181–183]. **(b) ATR inhibitors.** ATR kinase is activated in response to replication stress and single-strand DNA breaks, coordinating subsequent repair processes. Mutations in the *TP53* gene can alter a cell's dependence on ATR, leading to synthetic lethality when ATR inhibitors are used in specific contexts, particularly when combined with agents that induce replication stress [184–186]. **(3) Metabolic vulnerabilities.** Mutant p53 has the ability to alter cellular metabolism to promote rapid growth and survival of cells. On the other hand, the loss of wild-type p53 can lead to metabolic weaknesses that can be targeted. Cells that lack p53 may become increasingly reliant on specific metabolic pathways to generate energy or maintain redox balance, for example, **(a) Glutaminolysis inhibition.** Some studies indicate that p53-deficient cells may rely more on glutaminolysis, a metabolic pathway that converts glutamine into essential metabolites, for growth and survival. Thus, inhibiting glutaminase (GLS) could be synthetically lethal [74, 187, 188]. **(b) Serine/Glycine biosynthesis inhibition.** p53 can regulate pathways for serine and glycine synthesis. In its absence, targeting these pathways could be synthetically lethal [189]. **(4) Proteotoxic stress.** Mutant p53 proteins often misfold and accumulate, which places a significant burden on the cell's protein quality control systems, including chaperones and the proteasome. By further inhibiting these quality control systems, we can exploit this existing "proteotoxic stress" and push p53-mutant cells beyond their tolerance threshold, ultimately leading to cell death. **(a) Proteasome inhibitors** (e.g., Bortezomib, Carfilzomib). These drugs block the proteasome, a major protein degradation complex. While used in multiple myeloma, in other contexts, they could exacerbate proteotoxic stress in p53-mutant cells with high levels of misfolded proteins [190–192]. **(b) HSP90 inhibitors**: As mentioned previously, HSP90 inhibition leads to the degradation of mutant p53 by unmasking it for proteasomal degradation, which is a form of inducing proteotoxic stress on the cell. **(5) Targeting regulatory pathways as a synthetic vulnerability**. The loss of p53 function forces cancer cells to become dependent on alternative survival pathways, creating synthetic vulnerabilities. This extends to the regulatory machinery that normally controls p53. For instance, the p53/UBE4B pathway, which our lab has characterized, can be targeted to exploit this dependency. We have shown that microRNA-1301 suppresses tumor cell migration and invasion by directly targeting the p53/UBE4B pathway, demonstrating a natural regulatory mechanism that can be mimicked therapeutically [193]. Such strategies, which aim to manipulate p53 regulators, represent a novel form of synthetic lethality by pushing a deregulated system toward collapse.

Significant progress has been made in utilizing synthetic lethality for p53-mutant tumors, particularly with cell cycle checkpoint inhibitors, such as CHK1 inhibitors like Adavosertib. Clinical data demonstrate its effectiveness, particularly with DNA-damaging agents in p53-mutated cancers, such as ovarian cancer. While areas such as metabolic vulnerabilities and proteotoxic stress are promising in preclinical research, they are still lagging behind in clinical application compared to checkpoint inhibitors. The success of these strategies continues to inspire the search for new treatments. A summary of selected clinical evidence linking *TP53* status to outcome is provided in Table 3.

Table 3 Selected clinical evidence linking TP53 status to outcome (illustrative)

Disease	Therapy focus	TP53 status considered	Key finding
High-grade serous ovarian cancer	Platinum chemotherapy	Mutant prevalent	High relapse; chemoresistance common [26, 118- 120]
AML/MDS	APR-246 + azacitidine	Mutant	Stratified responses; mixed phase III trial outcomes [154, 155]
HNSCC	Radiotherapy	Mutant vs. WT	Mutant predicts poorer local control [63, 122]
NSCLC	Chemotherapy ± EGFR inhibitors	Mutant	Worse outcomes associated with TP53 mutation [125, 226, 227]
Basket trials (MDM2 inhibitors)	MDM2 blockade	WT required	Benefit limited to WT TP53 tumors [135-137, 155]

Targeting downstream pathways of p53

The downstream pathways of p53 are an essential strategy in cancer therapy for tumors with *TP53* mutations [2, 194]. Rather than restoring mutant p53 function, this approach focuses on the consequences of p53 dysfunction [195]. It aims to exploit vulnerabilities arising from the absence of wild-type p53 or the oncogenic activities of mutant p53 by targeting genes and proteins that are abnormally regulated [196, 197]. As illustrated in Fig. 3, dominant-negative and gain-of-function mutant p53 activities rewire transcriptional programs and signaling pathways, providing the mechanistic basis for targeting downstream apoptotic, cell cycle, immune, and angiogenic pathways [198–200].

(1) Apoptotic pathways. Wild-type p53 is a powerful inducer of apoptosis, primarily by increasing the levels of pro-apoptotic BCL-2 family members, such as PUMA, NOXA, and BAX, while inhibiting anti-apoptotic proteins [201–204]. When p53 is mutated, cells lose this essential trigger for apoptosis, allowing survival despite damage or stress [205].

To restore programmed cell death, strategies include direct activation of pro-apoptotic pathways or inhibition of anti-apoptotic proteins [206]. **(a) BH3 mimetics (e.g., Venetoclax)** inhibit anti-apoptotic BCL-2 family members and release pro-apoptotic proteins, triggering apoptosis independently of p53 [207, 208]. Venetoclax is effective in leukemias such as CLL, where *TP53* mutations are a major risk factor [209–211]. **(b) TRAIL receptor agonists** activate extrinsic apoptotic signaling and can bypass upstream defects, including p53 loss [212–214].

(2) Cell cycle regulators. Wild-type p53 induces cell cycle arrest primarily through transcriptional activation of *CDKN1A/p21* [215, 216]. Loss of this checkpoint in p53-mutant cells promotes unchecked proliferation and genomic instability [217, 218]. CDK4/6 inhibitors block G1 progression and can induce arrest or senescence in p53-deficient contexts [219, 220]. While most effective in HR+/HER2 – breast cancer, altered cell-cycle dependencies in *TP53*-mutant tumors are under investigation [221, 222].

(3) Immune modulation. Mutant p53 influences the tumor microenvironment by increasing genomic instability and neoantigen load, while also promoting immunosuppression via PD-L1 upregulation and recruitment of myeloid-derived suppressor cells [223–225]. Immune checkpoint inhibitors (ICIs) may be effective in *TP53*-mutated tumors with high tumor mutational burden, such as NSCLC [125, 226, 227]. However, specific GOF p53 mutants can also drive immune evasion, suggesting the need for combination strategies [228–230].

(4) Angiogenesis inhibitors. Wild-type p53 suppresses angiogenesis by inducing anti-angiogenic factors such as thrombospondin-1 and repressing VEGF [231–233]. In contrast, GOF p53 mutants can promote angiogenesis and metastasis [231, 234, 235]. VEGF/VEGFR inhibitors, including bevacizumab and multi-kinase inhibitors, may therefore be particularly relevant in tumors where mutant p53 drives angiogenic signaling [236–238].

By understanding the specific downstream effects of p53 dysfunction across tumor types, researchers and clinicians can strategically leverage existing targeted therapies or develop new ones to treat p53-mutant cancers effectively. This approach often serves as the foundation for personalized and combination therapies. The key pathways targeted by p53 and the corresponding therapeutic strategies are summarized in Table 4.

The future of p53-targeted cancer therapy

Few molecules in cancer biology have garnered as much attention as p53. Originally identified as a viral oncoprotein-binding partner, p53 has since been recognized as the most frequently mutated tumor suppressor gene. This has positioned it at the center of decades of research. However, despite extensive efforts, there is currently no universally effective therapy that directly targets p53 in clinical practice. The future of p53-targeted therapy will depend on integrating insights from structural biology, drug development, and clinical oncology with the precision tools of modern medicine.

Personalized medicine and p53 mutational status

Personalized medicine, also known as precision medicine, is an approach to patient care that customizes medical decisions, treatments, practices, or products for each individual based on their predicted response or risk of disease [4, 131]. In oncology, this often involves using the unique molecular profile of a tumor, including the mutational status of the *TP53* gene, to guide treatment choices [239]. *TP53* is the most commonly mutated gene in human cancer [131, 240], making it a key factor in developing personalized medicine strategies.

Understanding the p53 status of a tumor is essential for clinicians because it allows them to stratify risk and prognosis. TP53 mutations are often associated with more aggressive disease, higher rates of recurrence, and decreased overall survival in various types of cancer, including chronic lymphocytic leukemia (CLL), breast cancer, and glioblastoma [63, 132, 196, 241]. Therefore, identifying these mutations is crucial

Table 4 Key p53 target pathways and associated therapeutic strategies

Function	Representative p53 target genes	Therapeutic leverage
Cell-cycle arrest	CDKN1A (p21)	CDK inhibitors show synergy with p53 loss or mutation [215, 216].
DNA repair	GADD45, DDB2, XPC	PARP, ATR, and CHK1 inhibitors in combination therapies [175-186].
Apoptosis	BAX, PUMA, NOXA, FAS	BH3 mimetics; death receptor agonists [198, 201-204].
Senescence	PAI-1, IGFBP3	Senolytics are explored in specific contexts [30, 219, 220].
Metabolism	TIGAR, SCO2, GLS2	Metabolic inhibitors (e.g., targeting OXPHOS or glycolysis) [73-75].
Angiogenesis	TSP1, repression of VEGFA	Anti-VEGF synergy varies with p53 status [236-238].
Immune modulation	STING axis components, MHC Class I regulators	Immune checkpoint blockade; therapeutic vaccines [127].

for assessing risk, and it may warrant more intensive monitoring or a more aggressive initial treatment approach [242]. The presence or absence of functional p53 can significantly influence a tumor's response to therapy [149], including: (a) Chemotherapy and radiotherapy. Many conventional DNA-damaging agents rely on wild-type p53 to induce apoptosis [241, 242]. Consequently, *TP53*-mutated tumors often exhibit resistance to chemotherapy and radiation, necessitating alternative therapeutic strategies. (b) Targeted agents. In tumors retaining wild-type p53 but exhibiting p53 inactivation due to MDM2 overexpression, MDM2 inhibitors represent a rational, personalized approach [148, 149]. In contrast, tumors harboring specific *TP53* missense mutations (e.g., Y220C) may benefit from mutation-specific reactivators, such as PC14586 [136, 243]. (c) Immunotherapy. In some tumor contexts, particularly non–small cell lung cancer, *TP53* mutations correlate with higher tumor mutational burden and improved responses to immune checkpoint inhibitors [223, 225, 244], thereby informing patient selection for immunotherapy. (d) Synthetic lethality. Targeting synthetic lethal interactions in p53-deficient cells, such as inhibition of CHK1/CHK2 or other DNA damage response components, exploits vulnerabilities that arise specifically from loss of p53 function [245–247]. In addition, patients with defined *TP53* mutations are frequently selected for enrollment in clinical trials evaluating novel p53-directed therapies, including mutant p53 reactivators, degraders, and PROTAC-based approaches [154, 167]. Future clinical practice will likely incorporate routine *TP53* sequencing as a biomarker for therapy selection [126]. Customized therapeutic strategies—such as mutation-specific reactivation or targeted degradation—may be matched to individual patient genotypes [126, 167]. In addition, p53 status may inform the design of rational combination therapies, including immune checkpoint blockade or metabolic modulation, to exploit p53-dependent vulnerabilities [35].

Challenges and limitations in targeting p53

Despite the significant potential of targeting p53 in therapies and incorporating TP53 status into personalized medicine, considerable challenges remain [248].

(1) The wide range of TP53 alterations, from missense mutations that affect DNA binding to null mutations, complicates the development of universal therapies. This diversity often requires the creation of mutation-specific drugs, such as structure-correctors for the Y220C mutation, along with precise biomarker-driven patient stratification [11, 62].

(2) The biological effects of p53 mutations can differ significantly depending on the tissue type and genetic background, a phenomenon known as "context dependence." A treatment that works well in one tissue type may be ineffective in another due to overlapping signaling pathways or different downstream effectors. This variability makes it challenging to predict therapeutic responses [195].

(3) Small molecules, gene therapy vectors, and nanoparticle-based delivery systems face challenges related to stability, selectivity, and off-target toxicity. For example, viral vectors often induce immunogenicity, while small molecules targeting protein-protein interactions (like MDM2 inhibitors) have been hampered by dose-limiting hematological toxicities [249, 250].

(4) As with many targeted therapies, tumors can acquire compensatory or bypass mechanisms that diminish the durability of p53-directed treatments. Mechanisms

include the upregulation of downstream anti-apoptotic factors (e.g., MCL-1) or the emergence of secondary mutations that prevent drug binding [251].

(5) Many p53-targeting agents have historically been evaluated in late-stage, heavily pretreated patients with complex genomic landscapes. This approach may underestimate the true therapeutic potential of these drugs, suggesting that earlier intervention strategies or specific combination settings are required to reveal meaningful clinical benefit [35, 248]. Addressing these challenges will require continued innovation in drug design, improved biomarker integration, and more efficient clinical trial frameworks [35].

Ongoing research and novel therapies

Despite these challenges, the future of personalized medicine based on *TP53* mutational status remains promising and will likely require a multifaceted approach [250].

(1) Efforts are ongoing to develop more potent, selective, and orally bioavailable compounds that reactivate specific mutant p53 conformations (e.g., PC14586 for the Y220C mutation) or induce degradation of mutant p53 through PROTAC-based strategies [167, 252]. Clinical progress with agents such as APR-246 (eprenetapopt) and the specific Y220C reactivator has validated these concepts, showing promise in early-phase trials [154, 155].

(2) Combining p53-targeting agents with chemotherapy, radiotherapy, targeted therapies, or immunotherapy may enhance efficacy and overcome resistance. For instance, restoring p53 function can sensitize tumors to immune checkpoint blockade by remodeling the tumor microenvironment [253, 254].

(3) CRISPR-based gene editing technologies offer the potential for precise correction of *TP53* mutations. While preclinical models have demonstrated feasibility, challenges related to delivery efficiency, off-target effects, and safety remain substantial obstacles to clinical translation [255, 256].

(4) Identifying and clinically translating synthetic lethal interactions in p53-mutant cancers—such as targeting the G2/M checkpoint via WEE1 or CHK1 inhibitors—represents a major therapeutic opportunity [257, 258].

(5) Artificial intelligence and deep learning tools, such as AlphaFold, are increasingly used to predict the 3D structures of specific p53 mutants, identify novel druggable pockets, and guide rational drug design [259, 260].

(6) Routine, cost-effective genomic profiling will facilitate precise identification of *TP53* mutation types and co-mutations, enabling more informed, personalized treatment decisions [261, 262]. Figure 5 illustrates a precision medicine framework targeting p53 in cancer therapy.

Conclusion and future perspectives

The tumor suppressor p53 remains one of the most critical guardians of genomic stability, and its frequent mutation across cancers underscores its central role in tumorigenesis [3, 239]. Mutant p53 not only disables canonical tumor-suppressive pathways but also exerts dominant-negative and gain-of-function effects that promote cancer progression and therapeutic resistance [51, 196]. These alterations complicate responses to conventional therapies while shaping sensitivity to emerging targeted and immunotherapeutic approaches [128, 263].

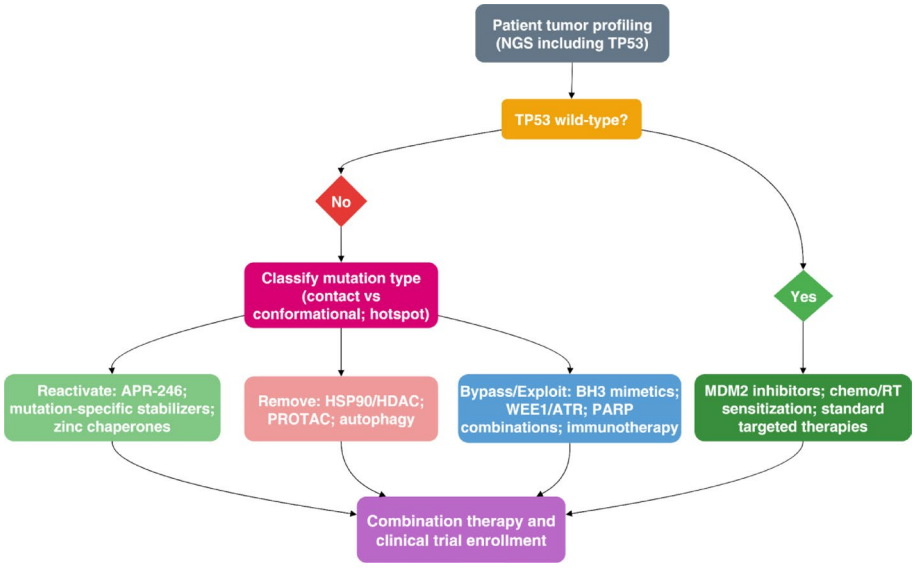


Fig. 5 Precision medicine framework for targeting p53 in cancer. Patient tumor profiling, particularly next-generation sequencing (NGS) of the *TP53* gene, is essential for shaping treatment strategies. For wild-type *TP53*, therapies focus on enhancing p53 function by using MDM2 inhibitors or combining them with chemotherapy and targeted therapies. If *TP53* is mutated, treatment depends on the type of mutation. Options include: (1) Reactivation with small molecules (like APR-246) and stabilizers. (2) Removal through HSP90/HDAC inhibition or PROTAC degraders. (3) Exploiting vulnerabilities using BH3 mimetics, checkpoint inhibitors, or immunotherapy. These approaches ultimately aim to combine therapies and encourage participation in clinical trials to improve patient outcomes

p53 mutations offer opportunities for therapeutic innovation, including gene therapy, small-molecule reactivation, targeted degradation, and strategies based on synthetic lethality [35, 195, 258]. The rapid evolution of technologies such as CRISPR editing, PROTACs, and precision drug design suggests that effective p53-targeted therapies may soon become clinically feasible [167, 250, 264].

Ultimately, successful p53-targeted therapy will depend not only on targeting the mutant protein itself but also on understanding the broader regulatory networks governing p53 stability and function. The ubiquitin–proteasome system represents a critical hub of vulnerability, and modulating key E3 ligases or stress-response pathways offers a promising—albeit complex—therapeutic window [265–267]. This systems-level view of the p53 pathway provides fertile ground for continued therapeutic innovation.

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