

Protein modification systems as cancer biomarkers and therapeutic targets

Li Gao, Yueqin He, Kexin Wang, Qin Li, Litong Nie, Lunzhi Dai

Protein modification systems as cancer biomarkers and therapeutic targets

Li Gao^{1,‡}, Yueqin He^{1,‡}, Kexin Wang^{1,‡}, Qin Li^{1,‡}, Litong Nie², Lunzhi Dai^{1,*}

¹National Clinical Research Center for Geriatrics and Department of Laboratory Medicine, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Wuhou, Chengdu 610041, China

²Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, 6565 MD Anderson Blvd., Harris County, Houston, TX 77030, United States

*Corresponding author: Lunzhi Dai, lunzhi.dai@scu.edu.cn

[‡]Li Gao, Yueqin He, Kexin Wang, and Qin Li contributed equally to this work.

Abstract

Protein post-translational modifications (PTMs), such as acetylation, lactylation, methylation, phosphorylation, ubiquitination, and glycosylation, play central roles in regulating diverse cellular processes, including signal transduction, metabolic adaptation, chromatin organization, and proteostasis. In cancer, PTM networks are extensively rewired, with profound alterations in enzyme levels, protein modification landscapes, and crosstalk among different modification types. These changes collectively shape key cancer hallmarks, such as sustained proliferative signaling, immune evasion, and therapeutic resistance. Recent advances in proteomic technologies have enabled comprehensive mapping of PTM landscapes and their regulatory mechanisms, facilitating the identification of PTM signatures associated with tumor subtyping, disease progression, and treatment response. This review summarized biomarkers and therapeutic targets associated with dysregulated PTM regulatory pathways in cancer.

Keywords: protein modifications, cancer, biomarker, therapeutic target, precision medicine

Introduction

Cancer is increasingly recognized not merely as a consequence of genetic mutations or chromosomal instability, but as a systems-level disease driven by disruptions in multilayered regulatory networks. Although genomic and transcriptomic alterations establish the oncogenic blueprint, regulation at the proteome level ultimately executes and stabilizes malignant cellular states. Protein post-translational modifications (PTMs), including lactylation, acetylation, phosphorylation, ubiquitination, glycosylation, succinylation, crotonylation, and palmitoylation, serve as a central regulatory layer by dynamically modulating protein activity, stability, subcellular localization, and turnover [1]. Through these coordinated actions, PTMs are involved in diverse biological processes, including cell fate determination, signal transduction, metabolic adaptation, and cancer development [2, 3].

Rather than acting independently, PTMs are now recognized to function in a highly coordinated and context-dependent manner, giving rise to the concept of PTM crosstalk [4]. This refers to functional interactions between distinct modifications occurring on the same protein or across interacting proteins, enabling combinatorial and non-linear regulation of protein function. Such interactions indicate that PTMs are embedded within broader reg-

ulatory architectures that integrate enzymatic activity, substrate availability, signaling inputs, and cellular context.

On this basis, PTM regulation can be recognized as a multilayered regulatory network composed of modifying enzymes, substrates, and site-specific modifications, collectively constituting an integrated PTM system. At the site level, individual PTMs can directly reshape protein conformation and functional properties. At the protein level, co-occurring modifications collectively tune stability, interaction specificity, and subcellular localization. At the systems level, PTM enzymes and substrates form interconnected signaling networks that coordinate cellular responses across diverse biological processes.

Importantly, PTM networks are highly dynamic and extensively rewired during tumorigenesis. This rewiring is driven by dysregulation of modifying enzymes, alterations in site-specific modification landscapes, and reorganization of protein–protein interaction networks. As a result, signaling networks are remodeled, and information flow is redistributed, leading to context-dependent reprogramming of downstream cellular responses. Ultimately, these multilayered changes converge on shared oncogenic states, linking PTM alterations to clinically relevant cancer phenotypes, including uncontrolled proliferation, metabolic reprogramming, immune evasion, and therapeutic resistance [5].

Received: 9 February 2026. Revised: 29 April 2026. Accepted: 30 April 2026

© The Author(s) 2026. Published by Oxford University Press on behalf of the West China School of Medicine & West China Hospital of Sichuan University. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com

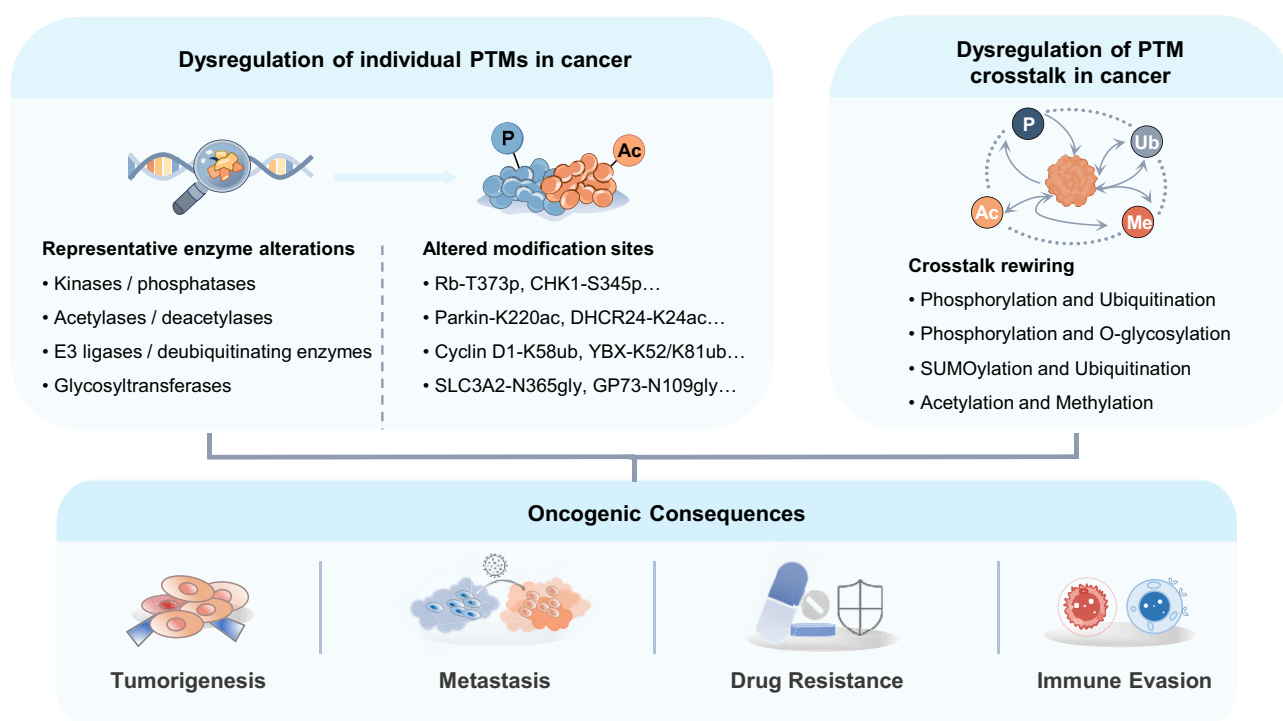


Figure 1. Dysregulated PTMs and their crosstalk in cancer. Dysregulated PTMs and their crosstalk drive tumor initiation, progression, immune escape, and treatment resistance.

Despite substantial progress in mapping individual PTMs and their associated enzymes, a systems-level understanding of PTM regulation in cancer remains incomplete. Most existing studies have focused on single modification types, individual enzymes, or discrete signaling pathways. However, these PTMs are components of integrated and multilayered regulatory systems [6–8]. To date, how distinct PTM machineries are coordinately re-programmed during tumor evolution, how multiple modification networks converge on shared cellular states, and how PTM dynamics shape clinically relevant phenotypes across cancer types are not well summarized. Moreover, although advances in PTM-centric proteomics have enabled comprehensive profiling of modifications, integrative analysis that links enzymes, PTMs, and functional outcomes is still lacking.

In this review, we have summarized the recent progress of PTMs functioning as highly interconnected regulatory networks whose dysregulation underpins fundamental aspects of cancer biology. These insights provide a foundation for discovering functional biomarkers and developing therapeutic strategies that exploit vulnerabilities in dysregulated PTM regulatory pathways.

PTM dysregulation in cancer: individual modifications and crosstalk

Aberrant PTMs are a hallmark of cancer, influencing protein activity, signaling networks, metabolism, chromatin states, and immune interactions. These alterations can occur at the level of individual PTMs or PTMs crosstalk, which further stabilizes malignant phenotypes and drives clinical heterogeneity (Fig. 1).

Dysregulation of PTMs in cancer

In cancer, PTM changes often arise from dysregulation of PTM-regulatory enzymes; however, their functional impact is exerted primarily through the modified proteins themselves [9]. The dysregulation of PTMs has a significant impact on tumorigenesis, progression, immune evasion, and therapeutic resistance.

PTM dysregulation associated with tumorigenesis and progression

Dysregulation of PTMs is a key driver of tumorigenesis and tumor metastasis acting through widespread reprogramming of cellular regulatory networks that control proliferation, survival, invasion, and other malignant phenotypes (Fig. 2A). Among these alterations, perturbations in phosphorylation system are the most prevalent. In particular, kinase-dependent rewiring of signaling pathways is a central feature of this process, as illustrated by pancreatic ductal adenocarcinoma (PDAC), in which KRAS mutations present in over 90% of cases drive resistance to KRAS inhibitors through extensive remodeling of ERK-dependent phosphorylation networks [10, 11]. Loss of tumor suppressor pathways further amplifies phosphorylation-driven signaling outputs. PTEN is frequently deficient in breast cancer (BC), which hyperactivates the PI3K–AKT axis and is associated with aggressive clinicopathological features, tumor growth, and immune evasion [12]. Beyond these canonical oncogenic pathways, phosphorylation of cytoskeletal and regulatory proteins further modulates tumor invasiveness. For example, DBN1 phosphorylation at S142 in colorectal cancer (CRC) inversely correlated with magnesium levels, driving MMP2-dependent cell migration [13]. Similarly, GSK3 α -mediated phosphorylation of THRAP3 at S248 drives migratory capacity in colon cancer (COAD) [14]. PTM heterogeneity further shapes inva-

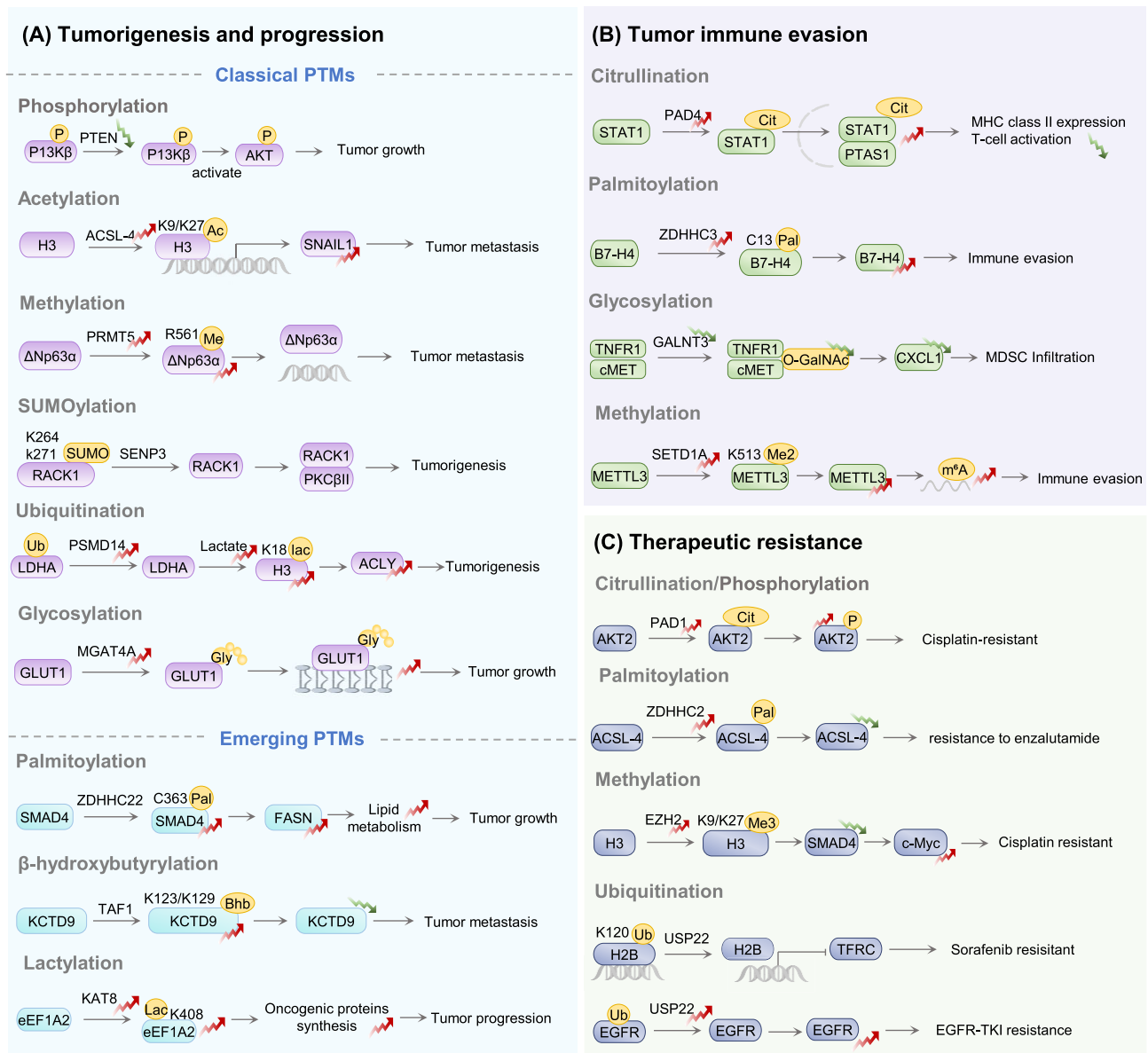


Figure 2. Examples of dysregulated PTMs in cancer. (A) Dysregulation of classical PTMs and emerging PTMs contributes to tumorigenesis and progression. (B) Dysregulation of PTMs in tumor immune evasion. (C) Dysregulation of PTMs leads to therapeutic resistance. P, phosphorylation; Ac, acetylation; Me, methylation; Ub, ubiquitination; SUMO, SUMOylation; Gly, glycosylation; Pal, palmitoylation; BHB, β-hydroxybutyrylation; Lac, lactylation; Cit, citrullination; O-GalNAc, O-GalNAcylation; Me2, demethylation; Bu, butyrylation; Mal, malonylation; Me3, trimethylation.

sive phenotypes and clinical outcomes. For instance, variations in RAI14 phosphorylation in APC-mutant CRC are associated with tumor invasiveness [15], whereas age-associated decline in CTNND1 phosphorylation at S349 disrupts cell-cell adhesion, providing a molecular basis for tumor initiation and metastasis [16].

Abnormal acetylation and methylation further reinforce malignant behavior by modulating chromatin states. Histone acetylation frequently modulates tumor suppressor genes and cell cycle dynamics [17]. In hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), HDAC3 is elevated and critical for maintaining genome integrity [18, 19]. Its loss disrupts H3K9 acetylation and trimethylation dynamics, leading to DNA damage accumulation and oncogenic transcriptional activation [20]. Similarly, elevated ACSL-4 mediates H3K9 and H3K27 hyperacetylation in the

SNAIL1 promoter and promotes epithelial-mesenchymal transition (EMT) in triple-negative breast cancer (TNBC) [21]. Parallel to these acetylation-dependent mechanisms, aberrant protein methylation further drives tumorigenesis and metastasis. PRMT5 is upregulated in advanced tongue squamous cell carcinoma and correlates with poor prognosis, where it methylates ΔNp63α at R561 to attenuate its DNA-binding capacity, and thereby promoting tumor metastasis [22]. Likewise, PRMT6 is overexpressed in BC and promotes tumor growth through dimethylation of histone H3 at R2 (H3R2me2) [23].

Moreover, dysregulation of ubiquitination and SUMOylation further drives tumor progression by alterations in oncogene transcription and cellular metabolism. Perturbation of chromatin-associated ubiquitin pathways contributes to transcriptional

deregulation, as illustrated in CRC, SMARCA3 is silenced by promoter methylation in ~40% of cases, thereby impairing the formation of the SMARCA3–SUV39H1 complex and resulting in decreased H3K23ub and H3K9me3 levels, which in turn promotes oncogene transcription [24]. Similarly, SENP3 is frequently upregulated in HCC, where it stabilizes RACK1 through deSUMOylation at K264 and K271 and promotes its interaction with PKC β II [25], thereby promoting its interaction with PKC β II and enhancing oncogenic transcription. Beyond transcriptional control, these PTMs also drive metabolic reprogramming. PTM-dependent metabolic rewiring further sustains tumor progression, exemplified by PSMD14 overexpression in prostate cancer (PCa), which deubiquitinates LDHA to elevate lactate production and upregulates ACLY to promote lipid biosynthesis, leading to poor prognosis [26, 27]. Similarly, SENP1 is upregulated in gastric cancer (GC) and associated with poor prognosis, where it drives glycolysis, cisplatin resistance, and tumorigenesis by deSUMOylating ENO1 at K256 and K394 [28].

Besides, abnormal glycosylation contributes to tumorigenesis and metastasis by coupling metabolic reprogramming with rewiring oncogenic signaling. Glycosylation-dependent metabolic adaptation is exemplified by MGAT4A upregulation in high-grade uterine endometrial carcinoma (EC), which correlates with poor prognosis; particularly in TP53-mutant EC, it promotes galectin-9-dependent signaling, stabilizes membrane GLUT1, and enhances glucose uptake [29]. FUT2 similarly supports tumor progression by activating YAP/TAZ–SREBP1-driven fatty acid reprogramming [30]. Glycosyltransferase-mediated modulation of oncogenic signaling further drives metastatic progression. In lung adenocarcinoma (LUAD), elevated GALNT6 is associated with lymph node metastasis and poor prognosis. Mechanistically, GALNT6 interacts with O-glycosylated GRP78 to activate the MEK–ERK cascade, promoting EMT and lymph node metastasis [31]. Broad protumorigenic effects have been observed across additional glycosyltransferases. Elevated C1GALT1 in bladder cancer (BLCA) promotes cell migration and proliferation by modifying target glycoproteins such as MUC16 [32], and MGAT5 overexpression in CRC, EC, and GC promotes β 1,6-GlcNAc *N*-glycan branching, reinforcing membrane dynamics and PI3K–AKT signaling to sustain an oncogenic feedback loop driving tumor growth and metastasis [33–36].

Beyond these well-characterized modifications, a growing number of recently identified PTMs have emerged as critical regulators of tumorigenesis and metastasis. These non-canonical modifications further expand the regulatory landscape of PTMs, linking protein function to diverse metabolic and signaling contexts. One illustrative example arises from lipid-associated regulation, palmitoylation of SMAD4 at C363 is elevated in PDAC, which enhances its protein stability and promotes tumor growth [37]. In parallel, metabolite-derived modifications constitute a second major regulatory axis linked to metabolic rewiring, oncogenic transcription, and protein stability. In CRC, reduced β -hydroxybutyrylation of ARG1 enhances tumorigenicity by promoting arginine metabolic reprogramming [38], whereas elevated β -hydroxybutyrylation of KCTD9 at K123/K129 in liver metastases suppresses KCTD9 protein expression, thereby driving metastatic progression [39]. Similarly, aberrant lactylation contributes to malignant adaptation. High KAT8 expression in CRC is associated with poorer survival and elevates eEF1A2 lactylation, which enhances protein synthesis to support oncogenic adaptation [40]. In HCC,

elevated lactylation of AK2 at K281 is significantly associated with poor patient prognosis by suppressing its kinase activity [41]. PD-L1 delactylation facilitates its nuclear translocation and accelerates liver cancer growth by elevating SQLE transcriptional activity [42].

Dysregulation of PTMs in tumor immune evasion

The dysregulation of PTMs not only promotes tumor growth but also facilitates immune evasion through multiple molecular mechanisms (Fig. 2B). Citrullination mediated by PAD4 in tumor-associated macrophages promotes immune escape and poor responses to immune checkpoint blockade, whereas PAD4 inhibition enhances MHC class II expression and T-cell effector functions [43]. Aberrant palmitoylation contributes to immune evasion, exemplified by upregulation of ZDHHC3 in BC, which stabilizes the immune checkpoint molecule B7-H4 via S-palmitoylation at C13 and correlates with poorer prognosis [44]. Dysregulation of protein glycosylation also reshapes immune cell infiltration. DPM1 acts as a central modulator of *N*-glycosylation in cholangiocarcinoma (CHOL), with elevated DPM1 expression linked to increased mannose-rich *N*-glycan signatures and reduced immune cell infiltration [45]. Conversely, low GALNT3 expression in LUAD is associated with poor survival by O-GalNAcylation of TNFR1 and cMET, attenuating TNFR1–NF- κ B and cMET–AKT signaling and reducing myeloid-derived suppressor cell infiltration [46]. Methylation-dependent regulation further reinforces immune evasion, as dimethylation of METTL3 at K513 is elevated in CRC and promotes tumor immune evasion by increasing its affinity for S-adenosylmethionine and enhancing m⁶A deposition on target RNAs [47].

Dysregulation of PTMs leads to therapeutic resistance

Aberrant PTM patterns are observed across multiple cancers and are associated with therapy resistance (Fig. 2C). Dysregulated citrullination and palmitoylation sustain resistant phenotypes. PAD1 is markedly upregulated in ovarian cancer (OV), particularly in CD133⁺ and cisplatin-resistant cells, where it sustains stem-like properties by promoting stemness marker expression [48]; similarly, ZDHHC2 is elevated in enzalutamide-resistant PCa and confers resistance by palmitoylating ACSL4 to regulate its stability [49]. Aberrant histone methylation drives resistance-associated transcription. EZH2 is upregulated in CRC and promotes chemotherapy resistance by activating NRP1 expression [50], and in cisplatin-resistant non-small cell lung cancer (NSCLC), upregulated EZH2 and G9a cooperatively drive resistance and malignancy via the SMAD4/ERK/c-Myc axis [51]. Additionally, altered ubiquitination dynamics reinforce survival signaling and suppress cell death. USP22 is overexpressed in HCC and LUAD. It mediates therapy resistance by deubiquitinating CDK11B and histone H2B, suppressing sorafenib-induced ferroptosis in HCC [52]; meanwhile, it stabilizes EGFR, sustaining EGFR-dependent signaling and conferring resistance to tyrosine kinase inhibitors in LUAD [53]. Metabolic and acylation-related PTMs further support adaptive resistance. SIRT5-mediated removal of malonylation from TKT at K281 facilitates metabolic adaptation under chemotherapeutic stress and promotes resistance to 5-fluorouracil [54], whereas KAT8-mediated butyrylation of HSP90 at K754 is elevated in 5-FU-resistant oesophageal squamous cell carcinoma and correlates with poor prognosis [55].

Collectively, dysregulation of PTM enzymes and modified proteins often functions as an active driver of tumorigenesis and progression, rather than merely a downstream consequence. By coordinately reshaping oncogenic signaling, metabolic adaptation, chromatin remodeling, and immune regulation, dysregulated PTM machinery endows tumor cells with enhanced survival capacity and phenotypic flexibility, thereby facilitating tumorigenesis, metastasis, immune evasion, and treatment resistance. Accordingly, PTM regulators represent not only mechanistically informative biomarkers but also attractive therapeutic vulnerabilities, as illustrated by the clinical success of kinase, HDAC, and BET inhibitors, alongside the continued emergence of novel PTM-targeted strategies.

Dysregulation of PTM crosstalk in cancer

While dysregulation of individual PTMs can initiate oncogenic events, accumulating evidence indicates that rewiring of PTM crosstalk networks is required to stabilize malignant phenotypes and sustain tumor progression. Multiple PTMs, such as phosphorylation, ubiquitination, SUMOylation, and acetylation, frequently converge on shared substrates and signaling pathways, forming highly interconnected regulatory circuits. Under physiological conditions, such crosstalk enables precise temporal and spatial control of protein function. In cancer, disruption of this coordination converts normally dynamic and reversible regulation into persistent oncogenic programs, thereby driving clinical heterogeneity, immune evasion, and therapeutic failure.

PTM crosstalk regulates oncogenic signaling and tumor suppressor networks

Aberrant PTM crosstalk exerts a dual effect in cancer, sustaining oncogenic signaling while impairing tumor suppressor pathways, even in the absence of additional genetic alterations. Phosphorylation–ubiquitination coupling within the Wnt/ β -catenin pathway exemplifies this balance in CRC, HCC, and BC (Fig. 3A). GSK3 β -mediated phosphorylation of β -catenin at S33, S37, and T41 generates a degron recognized by β -TrCP, triggering ubiquitin-dependent degradation of β -catenin [56], whereas NDR1-mediated phosphorylation at S33 and S37 enhances FBXO11-dependent turnover [57]. This tumor-suppressive axis is frequently rewired in cancer through alternative phosphorylation events, including PKA-mediated phosphorylation of β -catenin at S675, which suppresses ubiquitination without disrupting GSK3 β complex binding, and PLK1-mediated phosphorylation at S311, which promotes β -catenin association with the deubiquitinase USP2A, collectively stabilizing β -catenin and sustaining Wnt signaling [58, 59].

Beyond β -catenin, context-dependent PTM crosstalk further extends to E3 ligase networks, particularly within the TRIM family. In LUAD, TRIM25 is elevated and mediates K63-linked polyubiquitination of PTEN, impairing its membrane localization and phosphatase activity [60]. Whereas in HCC, AP5Z1 recruits TRIM21 to ubiquitinate PTEN and degradation, alongside TRIM21 further mediates K27-linked ubiquitination of AKT that counteracts K63-linked activation [61, 62]. Together, these coordinated modifications sustain PI3K-AKT-mTOR signaling and drive tumorigenesis. In addition, PTM rewiring can also restrain tumor progression in specific contexts. In temozolomide-resistant glioblastoma, phos-

phorylation of TRIM25 at S100 decreases ubiquitination of ITPKB, enhancing its stability and suppressing ROS production [63]. Integration of phosphorylation with non-canonical acylation further reinforces signaling persistence. ERK-mediated phosphorylation of GCN5 at T404 enhances GCN5-dependent lactylation of ERK1 and ERK2, weakening ERK–MEK interactions while promoting ERK dimerization and prolonged signaling [64]. Similarly, in esophageal squamous cell carcinoma, p38-mediated phosphorylation of ACSL4 at T679 increases myristoyl-CoA production, facilitating Src myristoylation and downstream ERK activation [65].

Tumor suppressor pathways are tightly controlled by PTM crosstalk, with p53 representing a central node (Fig. 3B). P300/CBP-mediated acetylation at K73 and K382 enhances p53 DNA-binding affinity, while ATM/ATR-mediated phosphorylation at S15, T18, and S20 stabilizes p53 by disrupting MDM2-mediated ubiquitination, collectively promoting transcriptional activation [66]. Disruption of this PTM network is widespread in cancer and enables functional p53 inactivation independent of TP53 mutation.

Overall, PTM crosstalk stabilizes malignant signaling states by coordinately sustaining oncogenic pathway activity and functionally dampening tumor suppressor programs, thereby contributing to heterogeneous clinical outcomes.

PTM crosstalk enforces metabolic reprogramming

Cancer cells exploit PTM crosstalk among metabolic enzymes to drive metabolic reprogramming, thereby sustaining proliferative capacity and metabolic plasticity under stress (Fig. 3C). Antagonistic modification dynamics regulate enzyme stability, ZDHHC20-mediated palmitoylation of FASN at C1471 and C1881 counteracts SNX8–TRIM28-dependent ubiquitination to prevent FASN from proteasomal degradation and promote lipogenesis, thereby accelerating hepatocarcinogenesis [67]. Likewise, coordinated phosphorylation–acetylation crosstalk similarly governs ME1 activity in CRC. PGAM5-mediated dephosphorylation of ME1 at S336 promotes ACAT1-dependent acetylation at K337, enhancing ME1 dimerization, NADPH production, and lipogenesis, whereas NEK1 and SIRT6 exert opposing effects [68]. PTM-dependent metabolic flux is further shaped by crosstalk between phosphorylation and other acylation events. Phosphorylation of SUCLA2 at S79 by p38 MAPK promotes its dissociation from GLS, which in turn enhances GLS (K311) succinylation and glutaminolysis, leading to increased antioxidant production and supporting PDAC cell survival, and being associated with advanced tumor stage and poor prognosis [69]. Similarly, JNK phosphorylates ZDHHC14 at T440 triggering its degradation, which reduces the ZDHHC14-mediated palmitoylation of ASCT2 at C39 and C48 and prevents it from lysosomal degradation, thereby promoting glutamine metabolism and NSCLC progression [70].

Collectively, PTM crosstalk converts metabolic flexibility into a malignant liability by reinforcing aggressive signaling states and sustaining anabolic metabolism.

PTM crosstalk drives chromatin remodeling in cancer

PTM crosstalk reshapes chromatin architecture by coordinating histone-modifying enzymes, thereby enforcing oncogenic transcriptional programs (Fig. 3D). Phosphorylation-dependent relocalization of chromatin regulators is exemplified by HDAC6. In

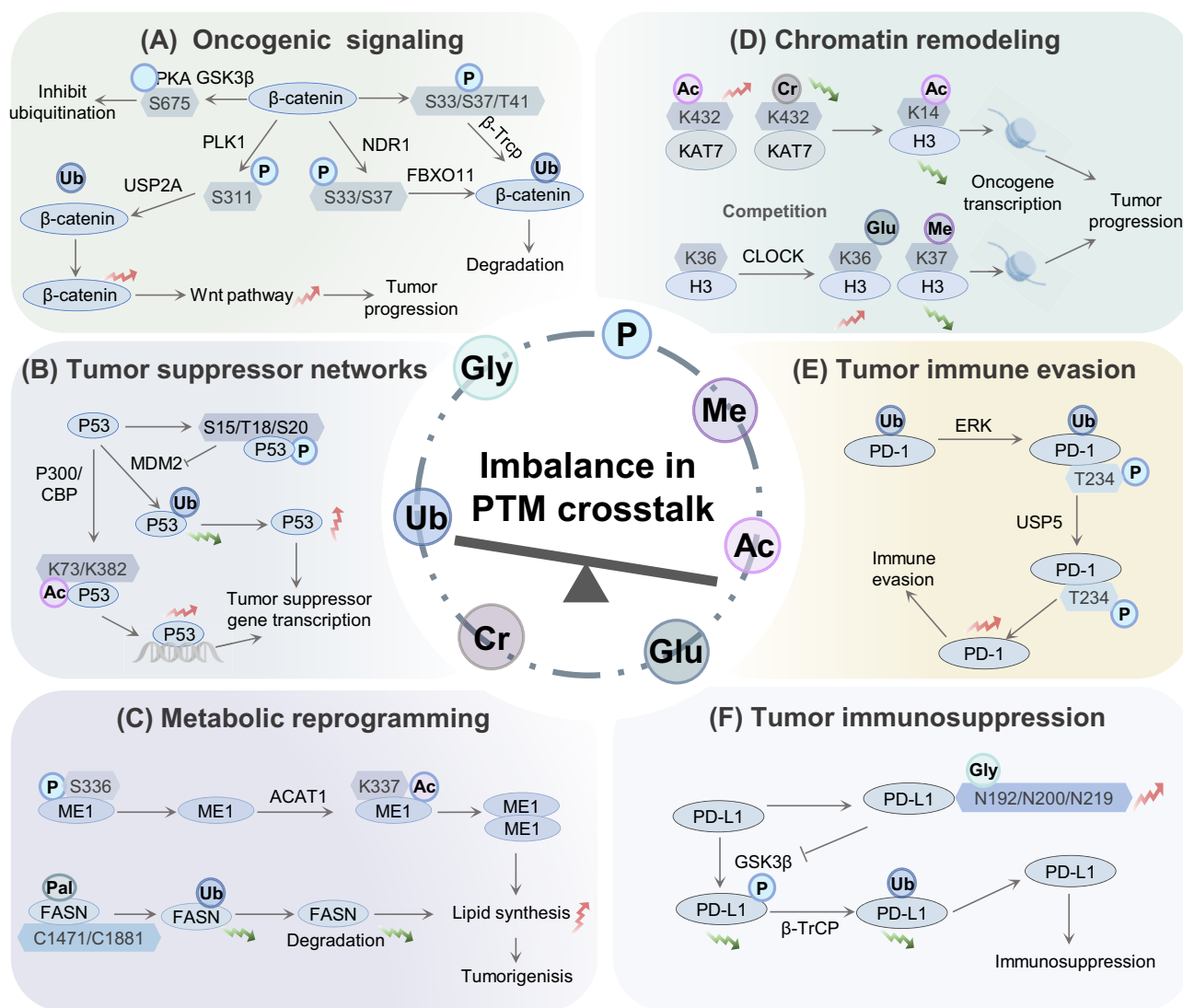


Figure 3. Aberrant PTM crosstalk in cancer. (A) PTM crosstalk regulates oncogenic signaling pathways. (B) PTM crosstalk regulates tumor suppressor networks. (C) Aberrant PTM crosstalk drives metabolic reprogramming. (D) Aberrant PTM crosstalk drives chromatin remodeling to promote oncogenic gene transcription. (E) Aberrant PTM crosstalk drives tumor immune evasion. (F) Aberrant PTM crosstalk contributes to tumor immunosuppression. P, phosphorylation; Ub, ubiquitination; Ac, acetylation; Pal, palmitoylation; Cr, crotonylation; Gly, glycosylation; Glu, glutarylation.

TNBC, phosphorylation of HDAC6 at S22 drives its nuclear translocation and phase-separated condensate formation, modulating chromatin organization and transcription to promote tumor progression [71]. Moreover, LINC00624 promotes ubiquitin-mediated HDAC6 degradation, relieving TRIM28–ZNF354C repression and enhancing pro-metastatic gene expression in HCC [72]. Competitive and cooperative PTM interactions further modulate chromatin function. In CRC, crotonylation–acetylation competition of KAT7 at K432 modulates its histone acetyltransferase activity, reducing H3K14ac at procentriole gene promoters, thereby inhibiting centriole duplication and promoting colorectal tumorigenesis [73]. Similarly, CLOCK-mediated H3K37 glutarylation is up-regulated in glioblastoma, which antagonizes SETD2-dependent H3K36me3 deposition and promotes tumorigenesis [74]. Phosphorylation–methylation–ubiquitination crosstalk further stabilizes chromatin regulators, exemplified by PKC-mediated phosphorylation of SUV39H1 at S391, which enhances PRMT1-dependent dimethylation at R378, blocking MDM2-mediated ubiquitination and increasing SUV39H1 stability, thereby promoting H3K9me3 deposition and tumor cell growth in BC [75].

Collectively, these integrated PTM networks remodel chromatin states, enabling sustained transcriptional plasticity and malignant progression.

PTM crosstalk reshapes tumor immune microenvironment

Tumor cells exploit PTM crosstalk to remodel the immune microenvironment by coordinating immune cell function, cytokine signaling, and immune checkpoint stability. Transcriptional control of immune responses is modulated by acetylation dynamics, as HDAC6-mediated deacetylation of FOXO1 at K242 promotes its nuclear localization and suppresses Th17-mediated antitumor immunity [76]. Methylation-dependent signaling further shapes immune cell recruitment. In NSCLC, aberrantly elevated NSD2-mediated dimethylation of CD147 enhances CCL5 transcription and secretion and promotes CCR5-dependent recruitment

of immunosuppressive M2-like tumor-associated macrophages [77]. In addition, checkpoint stability is reinforced through coordinated phosphorylation–ubiquitination and glycosylation networks. ERK-mediated phosphorylation of PD-1 at T234 promotes USP5-dependent deubiquitination, thereby stabilizing PD-1 and reinforcing tumor immune evasion [78], whereas N-linked glycosylation of PD-L1 at N192, N200, and N219 prevents GSK3 β -mediated phosphorylation and β -TrCP-dependent degradation, thereby sustaining PD-L1 expression and promoting immunosuppression in BC [79] (Fig. 3D–F).

Collectively, through multilayered regulatory mechanisms, tumor cells exploit PTM crosstalk to establish an immunosuppressive microenvironment that facilitates immune evasion.

Clinical implications of network-level PTM dysregulation

In summary, dysregulation of PTM crosstalk at the system level, rather than isolated modification events, underlies the stabilization of malignant phenotypes, clinical heterogeneity, and therapeutic failure. By amplifying oncogenic signaling, disabling tumor suppressor pathways, enforcing metabolic reprogramming, and reshaping chromatin and immune landscapes, aberrant PTM networks provide a mechanistic explanation for variable prognosis and treatment responses across patients. Importantly, these insights suggest that combinatorial PTM states and crosstalk signatures may outperform single PTMs as biomarkers and therapeutic targets, thereby providing a foundation for precision oncology strategies targeting PTM regulatory networks.

PTM systems as cancer biomarkers

Given the widespread dysregulation of PTMs observed in tumors, these dynamic PTMs not only reflect perturbed cellular processes but also actively modulate signaling, metabolism, chromatin regulation, and immune evasion. PTMs provide a more sensitive and real-time readout of tumor cell functional states than genomic or transcriptomic alterations. During tumor initiation and progression, they exhibit tissue-, pathway-, and stage-specific patterns, forming stable, and distinguishable molecular signatures that often precede detectable genetic changes. These dynamic modifications respond to microenvironmental cues and alterations in regulatory enzyme activity and can directly drive tumor-promoting mechanism [80]. Increasing evidence shows that tumors with similar genomic profiles can display markedly distinct functional states at the protein and PTM levels, with PTM-based profiling capturing pathway activation more accurately than genomics alone [9]. Integrative analyses across multiple PTM types further define molecular subtypes and prognostic signatures, with PTM regulatory hubs often outperforming conventional clinicopathological markers. Extending PTM profiling to circulating proteins and extracellular vesicles enables early, non-invasive cancer detection, diagnosis, and therapy guidance, such as glycosylated AFP, phosphorylated ERK, and exosomal PD-L1 [81–86]. Leveraging quantitative omics and machine learning, PTM-based models now facilitate risk stratification [87, 88], therapy response prediction [89], and prognostic assessment [90], collectively establishing PTMs as dynamic, sensitive, and functionally informative biomarkers for precision medicine.

PTM systems as diagnostic biomarkers for cancer

The dynamic nature of PTMs and their close association with malignant processes make them ideal candidates for diagnostic biomarkers. By capturing tumor-specific functional alterations, modified proteins, and their networks provide sensitive indicators for early detection, risk stratification, and therapy guidance.

In tumor cells, aberrant expression of glycosylation enzymes leads to abnormal glycosylation of membrane-bound or secreted proteins, thereby contributing to malignant transformation. Accordingly, both glycosyltransferases and their glycosylated products have attracted attention as diagnostic biomarkers. Representative clinically relevant examples include CA19-9 in PDAC, M2BPGI, and AFP-L3 in HCC, and CA125 in OV, illustrating the diagnostic value of glycosylation-related alterations across multiple tumor types [91–94]. In addition to single-marker applications, combination strategies may further improve diagnostic performance. A meta-analysis showed that the combined detection of CEA, CA125, and CA19-9 in epithelial OV achieved a pooled sensitivity of 90%, specificity of 83%, and AUC of 0.92, supporting the potential advantage of multi-marker panels over single-marker detection [95]. Other glycosylation-related markers, including PSA glycoforms in prostate cancer, HE4 in uterine corpus endometrial carcinoma (UCEC), and chromogranin A in neuroendocrine tumors (NETs), further expand the spectrum of PTM-associated diagnostic biomarkers [96–98].

Phosphorylation-related biomarkers have also shown diagnostic potential in several cancers, particularly in body fluids. A representative example is the serum phosphopeptide DpSGEGDFLA-EGGGVR, whose reduced level discriminates GC from healthy controls with high diagnostic accuracy [99]. Additional phospho-related candidates have also been reported in other malignancies, including urinary tyrosine-phosphorylated proteins (UPY-A) and GOLPH3 in bladder cancer, further supporting the potential of phosphorylation-associated markers in cancer detection [100, 101].

Beyond phosphorylation, other PTM systems have also yielded diagnostically relevant biomarkers. In the ubiquitination category, CCT3 has shown diagnostic value in AFP-negative HCC [102], suggesting its potential utility in a clinically challenging subgroup. UBE2T may also assist in the differential diagnosis of intrahepatic cholangiocarcinoma (ICC) from benign or precursor bile duct lesions [103]. In addition, methylation-related alterations are also implicated in cancer diagnosis, as illustrated by methylated SFRP2, which has been proposed as a diagnostic biomarker for GC [104].

Collectively, these findings highlight the broad diagnostic relevance of PTM systems across malignancies, as summarized in Table 1.

PTM systems as prognostic biomarkers in cancer

Beyond their diagnostic potential, dysregulated PTMs also carry significant prognostic value, reflecting tumor aggressiveness, metastatic potential, and therapeutic responsiveness.

Phosphorylation event provides site-specific prognostic information. Phosphorylation of the androgen receptor at S81 and

Table 1. PTM-based diagnostic biomarkers in cancer.

PTMs	Biomarkers	Cancers	Clinical performance
Glycosylation	CA19-9	PDAC [91]	Sensitivity: 69.1%, Specificity: 80.0%, AUC: 0.80
	M2BPGi	HCC [92]	Sensitivity: 91.7%, Specificity: 80.8%, AUC: 0.883
	AFP-L3	HCC [93, 105]	Sensitivity: 34%, Specificity: 92%, AUC: 0.755
	CA125	OV [94, 95]	Sensitivity: 77.0%, Specificity: 93.8%, AUC: 0.92
	CEA (combined with CA125 and CA19-9)	OV [95]	Sensitivity: 0.90, Specificity: 0.83, AUC: 0.92
	gly-PSA	PCa [96, 106]	Sensitivity: 81.8%, Specificity: 96.5%, AUC: 0.97
	HE4	UCEC [98]	Sensitivity: 71%, Specificity: 87%, AUC: 0.88
	Chromogranin A	NETs [97]	Sensitivity: 74.6%, Specificity: 84.7%, AUC: 0.896
Phosphorylation	DpSGEGDFLAEGGGVR	GC [99]	Sensitivity: 87.5%, Specificity: 96.7%, AUC: 0.97
	UPY-A	BC [100]	Sensitivity: 80.43%, Specificity: 78.82%, AUC: 0.92
	GOLPH3	BC [101]	Sensitivity: 83.8%, Specificity: 92.5%, AUC: 0.948
Ubiquitination	CCT3	AFP-negative HCC [102]	Sensitivity: 88.9%, Specificity: 70.5%, AUC: 0.84
	UBE2T	ICC [103]	AUC: 0.782 (vs. IHBD), 0.774 (vs. BiLIN-1/2), 0.776 (vs. BiLIN-3)
Methylation	SFRP2	GC [104]	Sensitivity: 60.9%, Specificity: 86.0%, AUC: 0.784

S213 correlates with prognosis in castration-resistant PCa and exhibits potential value for therapeutic prediction and targeted intervention [107]. Similarly, in BC and HCC, PTPN13 is considered a potential tumor suppressor, and its higher expression has been associated with favorable prognosis [108, 109].

Ubiquitination-related enzymes, particularly E3 ubiquitin ligases, are extensively involved in tumor progression and represent a rich source of prognostic biomarkers. For example, TRIM47 is a potential prognostic and metastasis-associated biomarker in head and neck squamous cell carcinoma (HNSCC) [110]. TRIM27 expression is associated with poor prognosis in renal cell carcinoma (RCC) [111]. FRMD3 represents a candidate prognostic

biomarker in BC [112]. Similarly, NEDD4L has thus been proposed as a prognostic biomarker in RCC [113]. Moreover, in acute lymphoblastic leukemia (ALL), the SCF complex subunit FBXO8 is an important prognostic biomarker and potential therapeutic target [114]. In addition to E3 ligases themselves, ubiquitination-regulated proteins and pathway components also contribute to biomarker discovery. For instance, asparagine synthetase is overexpressed in COAD and has been incorporated into ubiquitination-related prognostic signatures associated with poor outcome and altered immune landscapes [115].

Glycosylation-associated enzymes have also demonstrated prognostic relevance. Among glycosyltransferases, GalNAc-T3 is

significantly correlated with tumor differentiation status and serves as a marker of high-grade disease and poor prognosis in RCC [116]. In addition, GalNAc-T3 has also been proposed as a prognostic biomarker in early-stage GC [117]. Similarly, GLT8D1/2 expression correlates with tumor-infiltrating lymphocyte abundance and represents a potential prognostic marker in GC [118], and GalNAc-T6 is associated with favorable outcomes in PDAC [119].

HDAC6 has been reported as a potential prognostic biomarker in multiple malignancies, including LUAD, COAD, and RCC [120–122]. Beyond enzyme expression, global, and site-specific histone marks also carry important prognostic information. Decreased H3K9 acetylation together with reduced H4K20 trimethylation has been observed and correlates with increased tumor malignancy, which may serve as effective biomarkers for OV stratification and prognostic evaluation [123, 124].

Collectively, by integrating phosphorylation, glycosylation, ubiquitination, and histone modification data, PTM profiling provides a multidimensional view of tumor biology, offering both mechanistic insight and clinically actionable prognostic information. These PTM-based prognostic biomarkers across different cancer types are summarized in Table 2.

PTM systems as treatment response biomarkers for cancer

Beyond diagnosis and prognosis, PTM systems also can be used to monitor therapeutic responses. Integrated with computational modeling, PTM profiling enables stratification based on modification-specific signatures, as shown by deep learning-based citrullinated peptide analysis for disease classification and treatment prediction, underscoring its potential in precision medicine and as biomarkers for monitoring therapeutic response in oncology [146].

A growing number of phosphorylated proteins have been identified as clinically relevant biomarkers with predictive value. For instance, in NSCLC, phosphorylated SHP2 (p-SHP2) functions as a sensitive indicator of EGFR signaling activity and may help elucidate mechanisms of resistance to EGFR tyrosine kinase inhibitors [147]. Similarly, during chemotherapy or radiotherapy, the extent of eIF2 α phosphorylation reflects the induction of immunogenic cell death, a clinically relevant form of apoptosis [148]. Phosphorylation of ATM at S1981 reflects activation of the DNA damage response and can be used to predict treatment sensitivity [149].

Beyond phosphorylation, other PTM modalities also contribute to therapeutic stratification. In HCC, the hypoxia-induced E3 ligase receptor DTL is a potential prognostic and predictive biomarker for response to sorafenib [150]. In addition, in tamoxifen-resistant BC, TRIM4 serves as a prognostic and predictive biomarker [151]. Moreover, the interferon-induced ubiquitin-like protein ISG15 has emerged as a predictive biomarker for PD-1/PD-L1 immunotherapy response, supporting its application in prognostic assessment and personalized immunotherapy [152].

Importantly, protein glycosylation can also indicate therapeutic response. Enzymatic deglycosylation markedly improves the accuracy of PD-L1 detection, enabling more precise identification of TNBC patients suitable for immune checkpoint blockade. Deglycosylated PD-L1 represents a reliable predictive biomarker for immunotherapy responsiveness [153]. In PCa, alterations in the *N*-glycosylation patterns of prostate-specific antigen (PSA) signif-

icantly improve diagnostic accuracy, prognostic evaluation, and prediction of treatment response, outperforming total PSA measurements alone [106]. In addition, acetylation-related enzymes have increasingly been implicated in therapeutic resistance. Histone deacetylases HDAC1 and HDAC2 have been associated with resistance to regorafenib in acute myeloid leukemia (AML) and CRC [154, 155].

In summary, diverse PTM systems, including phosphorylation, ubiquitination, glycosylation, and acetylation, enhance biomarker accuracy while providing mechanistic insight into treatment response and resistance, underscoring their value in precision oncology. A summary of PTM-based predictive biomarkers for therapy response in cancer is provided in Table 3.

PTM systems used for cancer subtyping

Cancer is characterized by profound functional heterogeneity that is often insufficiently captured by genomic alterations alone. PTM systems provide a dynamic and pathway-resolved view of tumor states and therefore offer powerful strategies for molecular subtyping and functional stratification of cancers.

Aberrant phosphorylation events not only drive tumor progression but also exacerbate the high heterogeneity of tumor phenotypes. Accordingly, phosphorylation-mediated molecular alterations have gradually emerged as reliable tools for cancer molecular stratification, as well as important avenues for the discovery of clinically valuable biomarkers. In neuroblastoma (NB), phosphorylation networks driven by CDK5 activity have been suggested as molecular stratification. Specifically, phosphosites such as p-LARP6-T202, p-H1.5-S17, p-RBL1-s988, and p-SUV39H1-s391 collectively constitute a functional phosphoproteomic signature, serving as biomarkers that define a CDK5-dependent tumor subtype and predict therapeutic response [168]. In PCa, phosphorylated JNK at T183/Y185 (p-JNK) is associated with tumor progression and may serve as an early marker of aggressive disease [169]. Phosphorylated SMAD3 (p-SMAD3) has been identified as a predictive marker for HCC risk in patients with primary biliary cholangitis [170]. In NSCLC, EML4-ALK-positive and -negative tumors are classified into distinct molecular subtypes, and EML4-ALK fusion has been associated with resistance to EGFR tyrosine kinase inhibitors [171]. Beyond phosphorylation, global O-GlcNAcylation levels correlate positively with histologic grade in endometrial cancer (EC), and may serve as a stratification marker for advanced, poorly differentiated cases [172].

Collectively, integrating PTM-based features into molecular subtyping holds substantial promise for improving patient stratification, risk assessment, and precision therapeutic decision-making. These PTM-based biomarkers used for molecular subtyping across cancers are summarized in Table 4.

PTM systems as therapeutic targets in cancer

Accumulating evidence demonstrates that aberrant regulation of PTM systems is not merely a consequence of malignant transformation but constitutes a central driver of oncogenic signaling, transcriptional reprogramming, and proteome instability [2, 175]. Importantly, multiple components of PTM system, including writers, erasers, and readers, have proven to be pharmacologically tractable, leading to the successful development of clinically ap-

Table 2. PTM-based prognostic biomarkers in cancer.

PTMs	Biomarkers	Cancers	Clinical performance
Phosphorylation	p-AKT	HCC [125]	HR = 2.743 (95% CI = 1.132–6.534) $P = 0.031$
	PTPN13	BC [108]	HR = 0.79 (95% CI = 0.71–0.88) $P = 3e-05$
		HCC [109]	HR = 0.597 (95% CI = 0.403–0.886) $P = 0.01$
	CDK1/CDK4	CRC [126]	HR = 1.98 (95% CI = 0.91–4.28) $P = 0.079$; HR = 1.72 (95% CI = 0.78–3.81) $P = 0.18$
			HR = 0.699 (95% CI = 0.503–0.972) $P = 0.033$
	NEK2	HCC [128]	ROC = 0.960 (95% CI = 0.939–0.981) $P = 0.003$
	p-ARser81/ pARser213	PCa [107]	High expression reduced survival 5.73–2.03 years, $P = 0.000\ 297$
Ubiquitination	TRIM47	HNSCC [110]	HR = 2.044 (95% CI = 1.147–3.644), $P = 0.0153$
	FRMD3	BC [112]	HR = 0.71 (95% CI = 0.61–0.83), $P = 1.2e-05$
	NEDD4L	RCC [113]	HR = 0.44 (95% CI = 0.32–0.59), $P = 2.2e08$
	FBXO8	ALL [114]	Poor survival $P < 0.001$
	OTUB1	HCC [129]	HR = 0.214 (95% CI = 0.126–0.364), $P < 0.001$
	UBE2D1	HNSCC [130]	HR = 1.4 (95% CI = 1.08–1.83), $P = 0.012$
	RNF6	BC [131]	HR = 1.532 (95% CI = 1.121–3.642), $P = 0.026$
	TRIM27	RCC [111]	HR = 2.53 (95% CI = 1.24–5.17), $P = 0.011$
	USP33	TC [132]	HR = 2.09 (95% CI = 1.12–3.89), $P = 0.020$
	USP39	PDAC [133]	HR = 2.76 (95% CI = 1.32–5.73), $P = 0.0067$
	RNF214	HCC [134]	HR = 1.873 (95% CI = 1.084–3.235), $P = 0.024$

Table 2. Continued

PTMs	Biomarkers	Cancers	Clinical performance
Glycosylation	GalNAc-T3	RCC [116]	HR = 3.43 (95% CI = 1.13–10.38) $P = 0.03$
	GLT8D2	GC [118]	HR = 1.49 (95% CI = 1.07–2.07) $P = 0.019$
	AFP-L3	HCC [135]	RFS = 76.4% (95% CI = 61.9%–86.0%) $P < 0.001$
	HER2	BC [136]	HR = 0.94, (95% CI = 0.89–0.98) $P = 0.008$
	CEA	CRC [137]	HR = 1.343 (95% CI = 1.1–1.7) $P < 0.0001$
	GLT8D1/2	GC [138]	GLT8D1: HR = 1.97 (95% CI = 1.40–2.77) $P < 0.001$ GLT8D2: HR = 1.55 (95% CI = 1.11–2.16) $P = 0.01$
	GalNAc-T6	PDAC [119]	HR = 0.53 (95% CI = 0.31–0.92) $P = 0.024$
	CA19-9	PDAC [139, 140]	HR = 1.79 (95% CI = 1.58–2.01) $P < 0.001$
	Thyroglobulin	THCA [141]	HR = 1.85 (95% CI = 1.30–2.70) $P = 0.003$
	HDAC6	LUAD [121]	HR = 1.01 (95% CI = 1.01–1.02) $P = 1.8e-07$
Acetylation		COAD [122]	OS = 6.207 (95% CI = 1.442–26.708) $P = 0.014$
		RCC [120]	HR = 0.584 (95% CI = 0.389–0.964) $P = 0.038$
	HDAC11	LUSC [142]	HR = 2.275 (95% CI = 1.256–4.120) $P = 0.007$
	H3K9ac	BC [123]	Poor survival $P = 0.005$
	H3K56ac	CRC [143]	HR = 0.7 (95% CI = 0.47–0.94) $P = 0.02$
	H4K16ac	CRC [143]	HR = 0.7 (95% CI = 0.47–0.94) $P = 0.02$
Methylation	H4K20me3	OV [124]	HR = 2.85 (95% CI = 0.52–53.37) $P = 0.263$
	EZH2	HCC [144]	HR = 1.97 (95% CI = 1.38–2.81) $P < 0.001$
Serotonylation	TGM2	HCC [145]	Poor survival $P = 0.003$

Table 3. PTM-based predictive biomarkers for therapy response in cancer.

PTMs	Biomarkers	Cancers	Clinical performance
Phosphorylation	p-SHP2	NSCLC [147]	Low levels of SHP2 promote antitumor T-cell responses in NSCLC and overcome TKI resistance.
	p-eIF2 α	BC [148]	High expression of p-eIF2 α is linked with immunosuppression and poor response to anthracycline-based therapy.
	p-ATM	CRC [149]	p-ATM is increased in peripheral blood mononuclear cells following stereotactic body radiation therapy.
	p-GSK3 β	BC [156]	Low expression of GSK-3 β is directly associated with chemoresistance.
	p-AR	PCa [157]	p-AR positivity is associated with resistance to abiraterone or enzalutamide treatment.
	PTEN	BC [158]	Low expression of PTEN is associated with trastuzumab resistance in HER2-positive BC.
Ubiquitination	p-EGFR	NSCLC [159]	High p-EGFR expression is associated with increased sensitivity to EGFR-TKIs.
	DTL	HCC [150]	High DTL expression is related with resistance to sorafenib.
	TRIM4	BC [151]	TRIM4 enhances the sensitivity of BC cells to tamoxifen.
	ISG15	GC, LUAD [152]	Elevated ISG15 expression is associated with a better response to anti-PD-L1 therapy.
	USP14	HCC [160]	The expression of USP14 is positively correlated with lenvatinib resistance in HCC cells and tumors.
Glycosylation	USP10	NSCLC [161]	High expression of USP10 confers platinum-based chemotherapy resistance in NSCLC lacking wild-type p53.
	Gly-PD-L1	BC [153]	Deglycosylated PD-L1 shows a stronger correlation with treatment response (AUC 0.860) than non-deglycosylated PD-L1 (AUC 0.648).
	ST6Gal I	GC [162]	Elevated ST6Gal I expression correlates with trastuzumab resistance.
	CA19-9	CRC [163]	Elevated CA19-9 levels are associated with treatment failure and disease progression in CRC patients receiving chemotherapy with plus bevacizumab.
	Gly-PSA	PCa [106]	Elevated glycosylated PSA levels correlate with drug resistance in PCa.
	HE4	OV [164]	HE4 promotes resistance to adriamycin in ovarian cancer.
	hCG	TGCT [165]	The glycosylation level of hCG is positively correlated with the degree of cisplatin resistance in tenosynovial giant cell tumor (TGCT).
	CA27.29	BC [166]	A persistent increase in CA27.29 levels suggests treatment failure or disease progression.
	CA15-3	BC [167]	Reduced CA 15–3 levels are associated with favorable response and prognosis following first-line anthracycline chemotherapy.
	HDAC1	AML [154]	Higher HDAC1 expression correlates with doxorubicin resistance.
Acetylation	HDAC2	CRC [155]	Higher HDAC2 expression correlates with regorafenib resistance.

proved anticancer therapies (Fig. 4). These advances indicate that targeting PTM systems represents a viable and impactful therapeutic strategy in oncology [176, 177].

Respiratory system

NSCLC

Within respiratory malignancies, NSCLC currently provides the clearest illustration of how PTM-linked dependencies translate into practice, with a therapeutic landscape dominated by

phosphorylation-driven oncogene addiction and complemented by a smaller but expanding set of non-kinase PTM/recognition strategies. EGFR inhibition represents a cornerstone of precision treatment for EGFR-mutant NSCLC, with successive generations of EGFR tyrosine kinase inhibitors, including gefitinib, erlotinib, afatinib, and osimertinib, establishing durable, genotype-informed therapeutic paradigms [178–181]. In parallel, fusion-driven kinase addiction is exemplified by ALK-rearranged NSCLC, where a multi-generation continuum of ALK inhibitors (crizotinib, alectinib, brigatinib, ceritinib, lorlatinib, and ensartinib) has enabled sustained targeted disease control and iterative manage-

Table 4. PTM-based biomarkers for cancer molecular subtyping.

PTMs	Biomarkers	Cancers	Clinical performance
Phosphorylation	EML-ALK	NSCLC [171]	Type I: EML4-ALK+ Type II: EML4-ALK– EML4-ALK positivity was associated with resistance to EGFR tyrosine kinase inhibitors.
	STAT3/p-STAT3	OV [173]	Type I: high STAT3/p-STAT3 Type II: low STAT3/p-STAT3 High STAT3/p-STAT3 expression was correlated with poorer prognosis of OV patients.
	p-JNK	PCa [169]	Type I: high p-JNK (Gleason grades 4 or 5) Type II: low Sp-JNK (Gleason grade 3) p-JNK may serve as an early biomarker for aggressive PCa stratification.
	p-SMAD3	HCC [170]	Type I: p-SMAD3C (S423/425) Type II: p-SMAD3L (S213) pSmad3L is associated with intrahepatic metastasis, multicentric occurrence, and liver cirrhosis.
Ubiquitination	FBXW7	CRC [174]	Type I: MSI-FBXW7 ^{wt} Type II: MSI-FBXW7R465C FBXW7R465C displays worse overall survival.

Table 5. PTM-associated therapeutic targets and inhibitors in respiratory malignancies.

Cancers	Targets	Drugs/inhibitors
NSCLC	EGFR	Gefitinib [178], erlotinib [179], afatinib [180], osimertinib [181]
	ALK	Crizotinib [182], alectinib [183], brigatinib [184], ceritinib [185], lorlatinib [186], ensartinib [187]
	BRAF/MEK	Dabrafenib + trametinib [188]
	HER2	Trastuzumab (+ deruxtecan, ADC) [189], zongertinib [190]
	HDAC6	ACY-241 (+ nivolumab) [191]
	Siglec-15	NC318 (+ pembrolizumab) [192]
MPM	PAD4	GSK484 [193]
SCLC	EZH2	Tazemetostat [194]
	EZH2	Tazemetostat (+ topotecan + pembrolizumab) NCT05353439 [195, 196]
	LSD1/KDM1A	Iadademstat (+ atezolizumab or durvalumab) NCT06287775 [197]

ment of resistance [182–187]. MAPK-pathway targeting is clinically relevant in molecularly selected subsets, with combined BRAF/MEK blockade using dabrafenib plus trametinib constituting an established strategy for BRAF V600E-altered NSCLC [188].

Beyond these canonical kinase drivers, ERBB2/HER2-altered NSCLC has emerged as an additional actionable genotype. Here, clinically implemented targeting includes the HER2-directed antibody–drug conjugate trastuzumab deruxtecan, alongside next-generation HER2 inhibitors such as zongertinib, reflecting ex-

panding options for HER2-mutant NSCLC beyond traditional HER2 agents developed in BC or GC [189, 190].

Complementing kinase-centric strategies, several non-kinase PTM/recognition nodes are being evaluated predominantly in early clinical or preclinical settings. Acetylation-eraser targeting via HDAC6 inhibition has been explored using ACY-241 in combination with nivolumab, representing a clinical-stage effort to modulate tumor stress programs and immune responsiveness in NSCLC [191]. In addition, glycan-dependent immune regulation is being translated through Siglec-15 blockade: NC318,

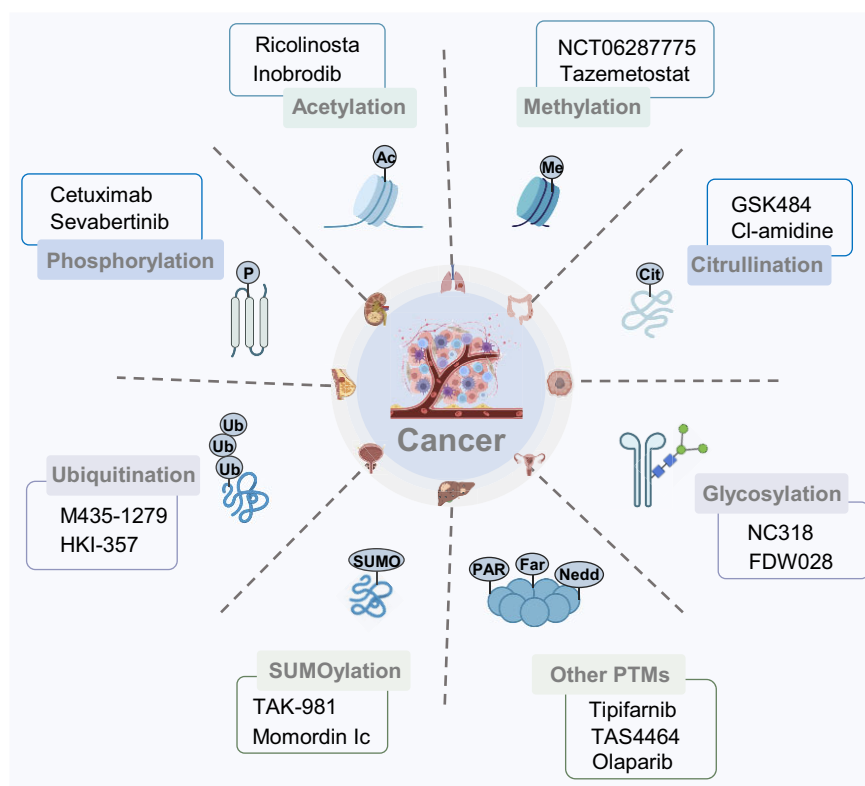


Figure 4. Targeting PTMs in cancer. Schematic overview of major PTMs in tumor-targeted therapy, highlighting the principal modification classes and their associated targeting strategies. P, phosphorylation; Ac, acetylation; Me, methylation; Ub, ubiquitination; SUMO, SUMOylation; Gly, glycosylation; Far, farnesylation; PAR, Poly(ADP-ribosyl)ation; Nedd, neddylation. The graphical components of this figure were created using BioRender (BioRender.com).

alone or in combination with pembrolizumab, exemplifies an investigational immune-directed strategy aimed at overcoming immune evasion in NSCLC [192]. Finally, citrullination-linked signaling and microenvironmental regulation have motivated PAD4 targeting; GSK484 has been used as a representative PAD4 inhibitor in NSCLC-relevant experimental systems, supporting PAD4-dependent programs as a preclinical vulnerability that may inform future combination strategies [193]. Collectively, these examples illustrate a tiered NSCLC landscape in which established kinase inhibitors dominate current clinical practice, while epigenetic, glycan-dependent immune, and citrullination-associated interventions continue to expand translational opportunities.

Malignant pleural mesothelioma and SCLC

In malignant pleural mesothelioma (MPM) and SCLC, PTM-informed strategies remain less clinically saturated than in NSCLC, but are increasingly being pursued through epigenetic and combination-oriented development. In MPM, targeting chromatin repression has gained translational traction in molecularly defined contexts such as BAP1-inactivated disease, where pharmacologic inhibition of EZH2 with tazemetostat has advanced into clinical evaluation and provides a representative example of methylation-directed intervention in a thoracic malignancy with otherwise limited targeted options [194]. Although EZH2 is also therapeutically relevant in SCLC, it is currently being explored mainly in combination regimens rather than in a molecularly selected setting, in contrast to BAP1-inactivated MPM, where EZH2

inhibition is linked to a more clearly defined disease subset. Several clinical trials are ongoing in SCLC. One approach involves EZH2 inhibition with tazemetostat in combination with topotecan and pembrolizumab (NCT05353439) [195, 196]. Another strategy targets neuroendocrine transcriptional maintenance through LSD1/KDM1A inhibition using iadademstat, combined with immune checkpoint blockade using atezolizumab or durvalumab in extensive-stage disease (NCT06287775) [197]. Together, these studies illustrate a broader therapeutic rationale that integrates epigenetic reprogramming with cytotoxic and immune-directed treatment backbones in SCLC. Representative PTM-associated therapeutic targets and inhibitors in respiratory malignancies, including NSCLC, MPM, and SCLC, are summarized in Table 5.

Hematologic system

AML

In AML, clinically actionable vulnerabilities increasingly converge on transcriptional and chromatin-dependency nodes. Among the most mature examples, disruption of KMT2A-associated transcriptional programs has translated into genotype-informed therapeutic opportunities. The menin inhibitors revumenib and ziftomenib exemplify this axis, providing a clinically tractable route to suppress KMT2A-driven leukemogenic gene expression and promote differentiation in molecularly defined AML subsets [198, 199].

In addition to the menin–KMT2A circuitry, P300/CBP has emerged as a druggable transcriptional co-activator hub in AML. The P300/CBP-directed inhibitor inobrodib represents a clini-

cally investigated strategy to attenuate acetylation-dependent enhancer function and oncogenic transcriptional maintenance in hematologic malignancies, including AML [200]. Concurrent with single-node targeting, dual-epigenetic intervention has also entered translational testing: NEO2734, a dual P300/CBP–BET inhibitor, is being investigated as a compact “writer/reader” co-targeting approach designed to more broadly collapse acetylation-coupled transcriptional programs relevant to AML pathogenesis [201].

Protein-stability control remains another exploitable layer in AML. Reactivation of p53 signaling through MDM2 inhibition has motivated combination-based regimens, as illustrated by milademetan administered with a low-dose cytarabine (LDAC) backbone and further intensified with venetoclax, reflecting a rationale to couple p53 pathway engagement with apoptotic priming in AML [202]. In addition, aberrant arginine methylation is increasingly recognized as a supporting dependency for leukemic transcription and splicing, with the PRMT5 inhibitor PRT543 advancing as a representative clinical-stage approach in AML [203]. Finally, perturbation of ubiquitin-like modification pathways offers complementary leverage over leukemic proteostasis and stress adaptation. In this context, inhibition of neddylation via the NAE inhibitor TAS4464 has been explored as a targeted strategy to impair cullin–RING ligase activity and disrupt downstream survival programs in AML models [204]. Overall, these examples illustrate how AML-directed precision strategies are expanding from mutation-centric targets toward integrated control of transcriptional regulation, epigenetic state, and protein homeostasis.

Multiple myeloma

In multiple myeloma (MM), therapeutically actionable dependencies span protein-stability control, oncogenic MAPK signaling in molecularly selected subsets, and emerging epigenetic/transcriptional vulnerabilities. The most established axis remains cereblon (CRBN) modulation, with the immunomodulatory drugs pomalidomide, lenalidomide, and thalidomide forming a foundational therapeutic class in MM [205–207]. Clinically, thalidomide was first introduced into the myeloma field because objective responses were observed in relapsed/refractory MM, demonstrating bona fide single-agent antimyeloma activity. However, in contemporary practice, thalidomide is not primarily used as monotherapy. Responses are often modest and slow to develop, and long-term single-agent use is limited by tolerability, particularly cumulative peripheral neuropathy, somnolence, constipation, and thromboembolic risk. Accordingly, in the USA, it was approved for newly diagnosed MM in combination with dexamethasone, not as monotherapy. Building on this CRBN paradigm, next-generation cereblon E3 ligase modulators (CELMoDs), such as iberdomide, further reprogram CRL4^{CRBN} substrate engagement beyond classical IMiDs and are being developed to extend activity into IMiD-refractory settings [208, 209]. Mechanistically, these agents are designed to drive deeper and more sustained depletion of key CRBN neosubstrates (e.g. IKZF1/3), thereby amplifying downstream transcriptional disruption relevant to myeloma maintenance.

In parallel, although MM is not uniformly driven by MAPK addiction, MAPK pathway targeting is clinically relevant in genomically defined subsets. Vemurafenib has shown activity in BRAF-mutant MM, and combined pathway blockade with enco-

rafenib + binimetinib provides a rational BRAF/MEK precision strategy in BRAFV600-altered myeloma [210, 211]. Beyond these targeted approaches, MEK inhibition has also been explored experimentally (e.g. PD184352) as a tool to interrogate MAPK dependence and combination potential in MM models [212].

Epigenetic and transcriptional strategies broaden the MM therapeutic landscape. Romidepsin, as an HDAC-directed agent, exemplifies acetylation-eraser targeting explored in MM [213]. More recently, direct perturbation of transcriptional co-activator machinery has been pursued via P300/CBP targeting; the P300/CBP degrader CBPD-409 represents a novel approach with preclinical activity in MM models, supporting continued exploration of co-activator dependency in myeloma [214]. Finally, methylation-linked transcriptional maintenance can be probed through combined arginine methyltransferase targeting, exemplified by PRMT1 and PRMT5 co-inhibition using GSK3368715 and EPZ015666 in MM-relevant settings [215]. Collectively, these examples illustrate how MM therapy integrates established CRBN-based disease control with increasingly genotype- and mechanism-informed strategies, while emerging epigenetic and co-activator interventions continue to expand the actionable repertoire in this malignancy.

Chronic myeloid leukemia

In chronic myeloid leukemia (CML), targeting proteostasis has been explored as a complementary vulnerability beyond canonical BCR–ABL1 kinase inhibition. In particular, inhibition of proteasome-associated deubiquitinase activity at UCHL5 and USP14 has been investigated using B-AP15 and auranofin, which disrupt 19S regulatory particle-linked deubiquitination and thereby exacerbate proteotoxic stress in leukemic cells [216, 217]. Preclinical studies in CML models, including settings relevant to tyrosine kinase inhibitor resistance, report that this deubiquitinating enzyme (DUB)-directed strategy can suppress leukemic cell survival and support the rationale for ubiquitin-proteasome system (UPS) modulation as a non-kinase therapeutic direction in CML.

Other hematologic malignancies

Outside AML, MM, and CML, HDAC blockade represents one of the most clinically mature acetylation-directed therapeutic strategies in hematologic malignancies, with demonstrated applicability across multiple lymphoma and high-risk leukemia contexts. In CTCL, HDAC inhibition is an established treatment paradigm, exemplified by vorinostat and romidepsin [218, 219]. In PTCL, HDAC-directed therapy is similarly implemented in an indication-matched manner, with belinostat and tucidinostat serving as representative agents used or evaluated in relapsed/refractory disease settings [220, 221]. In DLBCL, HDAC targeting has advanced primarily through chemo-backbone-anchored combinations, exemplified by tucidinostat plus R-CHOP, which integrates epigenetic modulation into standard immunochemotherapy regimens [222]. In ETP-ALL/LBL, an aggressive T-lineage entity, HDAC inhibition has likewise been explored in regimen-based strategies rather than monotherapy, with tucidinostat combined with pediatric-inspired chemotherapy (PIC) evaluated in newly diagnosed adult patients [223]. Overall, PTM-targeted therapies in hematologic malignancies mainly involve acetylation regulators, transcription-related factors, and proteostasis-associated enzymes. HDAC inhibition is particularly illustrative of this pattern, having achieved

Table 6. PTM-associated therapeutic targets and inhibitors in hematologic malignancies.

Cancers	Targets	Drugs/inhibitors
AML	KMT2A	Revumenib [198], ziftomenib [199]
	P300/CBP	Inobrodib [200]
	P300/CBP, BET	NEO2734 [201]
	MDM2	Milademetan (+ LDAC + venetoclax) [202]
	PRMT5	PRT543 [203]
	NAE	TAS4464 [204]
MM	CRBN	Pomalidomide [205], lenalidomide [206], thalidomide [207]
	CRL4^CRBN	Iberdomide (+ dexamethasone) [208]
	BRAF	Vemurafenib [210]
	BRAF + MEK1/2	Encorafenib + binimetinib [211]
	MEK1/2	PD184352 [212]
	HDACs	Romidepsin [213]
	P300/CBP	CBPD-409 [214]
	PRMT1 + PRMT5	EPZ015666 + GSK3368715 [215]
	UCHL5, USP14	B-AP15 [216], auranofin [217]
CML	HDACs	Vorinostat [218], romidepsin [219]
CTCL	HDACs	Belinostat [220], tucidinostat [221]
PTCL	HDACs	Tucidinostat (+ R-CHOP) [222]
DLBCL	HDACs	Tucidinostat (+ PIC) [223]
ETP-ALL	HDACs	

relatively mature clinical deployment across multiple hematologic settings, from approved single-agent use in selected T-cell lymphomas to regimen-integrated strategies in other high-risk lymphoid neoplasms. For example, vorinostat in CTCL and belinostat in relapsed/refractory PTCL both reached regulatory approval on the basis of measurable single-agent activity, with reported response rates of ~30% and 25.8% [218], respectively. By contrast, in solid tumors, HDAC inhibitors have generally shown more limited single-agent activity and are therefore more often pursued as combination partners to enhance immunotherapy or chemotherapy, as illustrated by ACY-241 plus nivolumab in NSCLC and ricolinostat/ACY-241-based combinations with paclitaxel in OV. This difference likely reflects, at least in part, the greater clinical embedding of epigenetic therapy in hematologic malignancies, whereas in solid tumors, HDAC inhibition is more often used to modulate the tumor microenvironment, immune responsiveness, or treatment sensitivity rather than to serve as a mature standalone strategy. Representative PTM-associated therapeutic targets and inhibitors in hematologic malignancies, including AML, MM, CML, CTCL, PTCL, DLBCL, and ETP-ALL, are summarized in Table 6.

Gastrointestinal and hepatobiliary system
CRC

In CRC, clinically actionable dependencies span established receptor-level targeting, genotype-defined MAPK pathway intervention, and a growing set of transcriptional, epigenetic, and protein-homeostasis vulnerabilities that are being evaluated largely in exploratory clinical or preclinical settings. At the level of receptor tyrosine kinase blockade, EGFR-directed therapy remains a cornerstone in biomarker-selected disease, exemplified by the anti-EGFR antibody cetuximab, which is clinically established in

molecularly appropriate CRC subsets and anchors multiple combination regimens in advanced disease management [224]. In parallel, BRAF-driven signaling constitutes a key precision-oncology niche in CRC. For BRAFV600E-altered metastatic CRC, the clinically established and approved strategy is combined pathway suppression, represented by encorafenib plus cetuximab, while alternative BRAF/EGFR intensification has also been clinically evaluated using vemurafenib with cetuximab and irinotecan, reflecting efforts to overcome intrinsic and adaptive feedback reactivation in this genotype-defined context [225, 226].

Beyond these mature targeted axes, several pathway-adjacent and chromatin-linked targets are expanding the translational CRC landscape. Hippo-pathway effector dependence has motivated YAP-associated inhibition using simvastatin as a representative pharmacologic approach supported primarily by preclinical CRC models [227]. Likewise, upstream signal integration through SHP2 is being clinically probed with agents such as TNO155, consistent with the broader rationale of intercepting RAS/MAPK relay and feedback signaling that sustains oncogenic growth programs [228]. Transcriptional co-activator circuitry is also being targeted through dual-node strategies, exemplified by NEO2734, a combined P300/CBP and BET inhibitor now in clinical testing that is designed to collapse acetylation-coupled transcriptional amplification relevant to CRC maintenance [229].

Protein turnover and epigenetic-state vulnerabilities further diversify actionable candidates, with most current evidence residing at the preclinical stage. The cell cycle and ubiquitin–proteasome interface has been explored via SKP2 targeting (e.g. tanshinone II) and via deubiquitinase modulation such as USP7 inhibition with P509, both reported to impair CRC cell survival programs in experimental systems [230, 231]. At the level of chromatin repression, EZH2 targeting has been investigated as a chemosensitization strategy, exemplified by tazemetostat combined with 5-FU, supporting that epigenetic intervention may reprogram therapeutic

tic responsiveness rather than act solely as a standalone cytotoxic strategy in CRC models [232]. Expanding beyond canonical signaling and chromatin targets, tumor-associated glycosylation and redox dependencies provide additional translational entry points: FUT8 inhibition with FDW028 has been reported specifically in metastatic CRC (mCRC) models, and ferroptosis-linked vulnerability has been probed via GPX4 targeting using ACE [233, 234]. Collectively, these illustrate how CRC-directed targeting is broadening from receptor and genotype-defined drivers toward diverse, mechanism-driven intervention points across signaling, transcriptional control, protein fate, and metabolic stress adaptation.

GC

In GC, actionable dependencies include both clinically established receptor-level targeting and emerging PTM-linked vulnerabilities that are currently supported mainly by preclinical evidence. Clinically, HER2 amplification defines a biomarker-selected subset in which trastuzumab combined with chemotherapy constitutes a validated therapeutic backbone and remains the most established example of targeted intervention in GC [235]. Beyond this approved axis, several PTM-associated targets have been explored predominantly at the experimental stage. In the deSUMOylation pathway, SENP1 inhibition using momordin Ic has been reported to suppress GC phenotypes and is frequently evaluated in combination with cisplatin, consistent with a chemosensitization rationale in preclinical GC models [28]. In parallel, citrullination-dependent regulation has been interrogated via PAD4 targeting, with GSK484 used as a representative PAD4 inhibitor in GC-relevant experimental settings [236]. At the level of ubiquitin conjugation, UBE2T has emerged as another candidate vulnerability, with M435-127 reported to inhibit tumor-promoting programs in GC models [237]. Collectively, these examples highlight a tiered GC landscape in which an approved HER2-directed regimen coexists with a developing set of PTM-linked targets that are often investigated in preclinical systems and, in some cases, framed explicitly around combination strategies such as cisplatin-based sensitization that may inform future mechanism-guided therapeutic expansion.

HCC

In HCC, PTM-directed targeting is expanding beyond canonical kinase inhibition toward epigenetic and metabolic dependencies that regulate lineage programs, stress adaptation, and therapeutic response, with most current evidence remaining preclinical. A recurrent theme is that PTM modulation is frequently positioned as a sensitization strategy rather than a standalone cytotoxic approach. For example, PAD4-linked citrullination has been implicated in drug-response modulation, and pharmacologic PAD4 inhibition using GSK484 has been reported to enhance the efficacy of established HCC therapies, including sorafenib and lenvatinib, supporting a combination-oriented rationale for targeting PAD4-dependent programs in HCC [238, 239].

In parallel, acetyl-CoA and lipid metabolism sustaining oncogenic transcriptional states can be targeted via ACLY, with the ACLY inhibitor EVT0185 reported to suppress HCC growth and reprogram tumor metabolic/immune features in preclinical models, positioning ACLY as a tractable metabolic cofactor node linked to acetylation-dependent regulation [240]. Additional methylation-associated chromatin dependencies have also emerged as ac-

tionable candidates. CARM1 inhibition with SGC2085 has been shown to impair tumor-promoting transcriptional programs in HCC models. Likewise, inhibition of EHMT2 (G9a) using UNC0646 or BIX-01294 supports that HCC can rely on G9a-mediated repressive chromatin states, with pharmacologic blockade disrupting growth and survival programs in experimental settings [241–243]. Expanding the repertoire of histone methyltransferase targets, SMYD3 inhibition by ZYZ384 has been reported to attenuate HCC progression, further underscoring the reliance of HCC on methylation-dependent transcriptional maintenance [244]. Finally, repression-associated chromatin remodeling can be pharmacologically perturbed through SUV39H1 targeting, with chaetocin used to validate SUV39H1-dependent vulnerabilities in HCC models [245].

Collectively, these examples define a developing PTM-targeted landscape in HCC characterized by combination-centric approaches that augment standard systemic therapies (e.g. PAD4 inhibition with sorafenib/lenvatinib), and multiple epigenetic and metabolic enzyme nodes (ACLY, CARM1, EHMT2, SMYD3, SUV39H1) that converge on chromatin state control and transcriptional plasticity. While clinical translation remains limited for many of these agents, the breadth of mechanistically distinct PTM-linked targets highlights substantial opportunity for mechanism-guided combination strategies in HCC.

PDAC

In PDAC, PTM- and proteostasis-oriented strategies are being explored primarily at the preclinical stage, reflecting the limited number of validated targeted options in this malignancy. One emerging axis involves aberrant protein citrullination mediated by PAD2, where pharmacologic inhibition using Cl-amidine and the PAD2-selective inhibitor AFM-30a has been reported to suppress PDAC-associated cellular programs in experimental models, supporting PAD2-dependent regulation as a tractable vulnerability in this context [246, 247].

Another PTM-linked entry point is palmitoylation-dependent signaling control via HHAT, with RU-SKI 43 serving as an inhibitor that suppresses hedgehog ligand maturation and impairs PDAC model growth [248]. Notably, despite the encouraging early findings reported in the mid-2010s, translation toward clinical testing has been limited. This is due in part to the widespread view that RU-SKI 43 functions primarily as a tool compound with suboptimal developability characteristics, such as poor *in vivo* stability and insufficient systemic exposure, as well as potential off-target liabilities [249].

Complementing these PTM-targeted nodes, proteostasis modulation through inhibition of proteasome-associated deubiquitinases has also been investigated. Targeting the UCHL5/USP14 axis using B-AP15 or auranofin has been reported to exacerbate proteotoxic stress and compromise PDAC cell survival programs in preclinical systems [250, 251]. Collectively, these examples delineate an emerging targeted-therapy landscape for PDAC in which citrullination, palmitoylation-linked pathways, and deubiquitinase-mediated proteostasis represent distinct but convergent PTM-based therapeutic strategies, although most studies remain at the preclinical or early clinical trial stage. Recent work has further shown that DHHCS-mediated palmitoylation of SDHB can promote T-cell exhaustion through a metabolic–epigenetic axis and that targeting this pathway may enhance the efficacy of

Table 7. PTM-associated therapeutic targets and inhibitors in gastrointestinal and hepatobiliary cancers.

Cancers	Targets	Drugs/inhibitors
CRC	EGFR	Cetuximab [224]
	BRAF	Encorafenib (+ cetuximab) [225]
		Vemurafenib (+ cetuximab + irinotecan) [226]
	YAP	Simvastatin [227]
	SHP2	TNO155 [228] 222
	P300/CBP + BET	NEO2734 [229]
	SKP2	Tanshinone IIA [230]
	USP7	P5091 [231]
	EZH2	Tazemetostat (+5-FU) [232]
	FUT8	FDW028 (ONLY mCRC) [233]
GC	GPX4	ACE [234]
	SENP1	Momordin Ic (+ cisplatin) [28]
	PAD4	GSK484 [236]
	HER2	Trastuzumab (+ chemotherapy) [235]
HCC	UBE2T	M435-1279 [237]
	PAD4	GSK484 (+ sorafenib [238]/lenvatinib [239])
	ACLY	EVT0185 [240]
	CARM1	SGC2085 [241]
	EHMT2	UNC0646 [242], BIX-01294 [243]
	SMYD3	ZYZ384 [244]
	SUV39H1	Chaetocin [245]
PDAC	PAD2	Cl-amidine [246], AFM30a [247]
	HHAT	RU-SKI 43 [248]
	UCHL5/USP14	B-AP15 [250], auranofin [251]
	Siglec-15	NC318 (+ pembrolizumab) [192]
	PAD4	GSK484 [193]

PD-1 blockade, providing an additional example of PTM-directed combination strategies in immunologically resistant PDAC [252]. Representative PTM-associated therapeutic targets and inhibitors in gastrointestinal and hepatobiliary cancers, including CRC, GC, HCC, and PDAC, are summarized in Table 7.

Gynecologic and breast cancer

BC

In BC, including TNBC, clinically actionable dependencies encompass established receptor- and pathway-level kinase targeting together with a smaller set of emerging PTM-linked vulnerabilities supported largely by preclinical evidence. At the receptor-signaling level, HER2 represents a key actionable axis in HER2-positive BC, with trastuzumab, pertuzumab, lapatinib, and neratinib forming the core of current HER2-targeted therapies [253–256]. Downstream of receptor activation, the PI3K-AKT-mTOR axis represents another therapeutic target in BC. For example, alpelisib in combination with fulvestrant targets PIK3CA-mutant, hormone receptor-positive BC [257]. Capivasertib in combination with fulvestrant inhibits AKT in selected molecular contexts [258]. Everolimus in combination with exemestane exemplifies mTORC1 inhibition as an endocrine-sensitizing therapy [259]. Beyond these mature targeted axes, multi-targeted anti-angiogenic kinase inhibitors have been explored in BC, including nintedanib combined with paclitaxel, which showed an early neoadjuvant clinical signal in HER2-negative BC [260].

At the intersection of cell-cycle regulation and ubiquitin-dependent processes, SKP2 inhibition with SMIP004 enhances the effects of radiotherapy, producing marked suppression of BC cell growth *in vitro* and *in vivo* [261]. Histone methyltransferases and demethylases further diversify actionable candidates. DOT1L inhibition with EPZ-5676 has shown preclinical activity in TNBC-relevant models [262]. In parallel, inhibition of KDM4 with Tach10 or QC6352 has been reported to suppress TNBC growth [263, 264]. Collectively, these examples illustrate a tiered landscape of targeted therapies in BC.

OV

In OV, PARP inhibitors block PARYlation and disrupt the dynamic regulation of DNA repair proteins and chromatin, thereby limiting OV growth [265]. Olaparib was the first PARP inhibitor approved in the USA for first-line maintenance monotherapy, followed by the approval of additional agents, including niraparib and rucaparib, in maintenance settings [266–268].

In addition, deacetylases and bromodomain-containing reader proteins represent therapeutic targets. For example, targeting HDAC6 with ricolinostat (ACY-1215) improves survival in preclinical models of ARID1A-mutated OV [269]. Moreover, ricolinostat or citarinostat (ACY-241) in combination with paclitaxel produces synergistic anti-tumor effects [270, 271]. Likewise, HDAC8 inhibition using PCI-34051, including combination with ACY-241, has been reported to enhance anti-tumor effects in OV models, supporting cooperative deacetylase targeting as a rational prelini-

cal strategy [272]. In addition, the bromodomain-containing protein ATAD2 has been targeted with BAY-850, which suppresses OV growth in experimental models [273].

Protein methylation system also serves as a potential therapeutic target in OV. SETD8 inhibition with UNC0379 has been shown to impair OV cell viability and tumor-associated phenotypes [274]. Histone methyltransferase DOT1L-mediated H3K79 methylation modulates oncogenic transcription. Targeting DOT1L with inhibitors such as EPZ-5676, EPZ004777, and SGC0946 has demonstrated anti-tumor activity in OV models [275]. Together, these findings highlight PTM-based therapies as an expanding therapeutic axis in OV.

EC

In EC, PTM-informed therapeutic strategies have focused on RNA splicing-associated kinases, with CLK emerging as a tractable node. The pan-CLK inhibitor SM08502 has been evaluated as a mechanistic strategy to disrupt CLK-dependent splicing programs and attenuate oncogenic transcriptional output in EC models. Importantly, SM08502 has also been investigated in a combination context, with SM08502 plus paclitaxel reported to enhance antitumor activity relative to either agent alone in preclinical EC-relevant settings, supporting a rationale for pairing splicing-pathway perturbation with cytotoxic backbone therapy in this disease [276]. Together, these findings highlight CLK inhibition as a promising translational approach to exploit RNA-processing vulnerabilities in EC. Collectively, these findings underscore the expanding therapeutic potential of PTM strategies across BC, OV, and EC. Representative PTM-associated therapeutic targets and inhibitors in gynecologic and BCs, including BC/TNBC, OV, and EC, are summarized in Table 8.

Genitourinary system

PCa

In PCa, PTM-directed targeting is emerging primarily through preclinical strategies that aim to disrupt transcription, chromatin repression, and cell-cycle-linked ubiquitin signaling programs that support progression and therapeutic resistance. One prominent axis is the transcriptional co-activator P300/CBP. Representative PROTAC degraders such as CBPD-409/CBPD-268 induce pharmacologic depletion of P300/CBP and have demonstrated antitumor activity in PCa models [278].

In addition, the ubiquitin-conjugation machinery that promotes cell proliferation has been explored. The small-molecule inhibitor HKI-357 has been reported to suppress UBE2C-dependent programs and restrain castration-resistant prostate cancer (CRPC) progression in PCa models [279]. Epigenetic repression further diversifies the landscape. EHMT2 (G9a) inhibition with BIX-01294 has been used to pharmacologically interrogate G9a-linked chromatin states in PCa model [280]. Similarly, chromatin accessibility is modulated by histone demethylases, and the KDM5 inhibitor PBIT has been shown to inhibit CRPC cell growth in preclinical studies [281].

BLCA

In BLCA, an increasing number of PTM-based therapeutic targets are being identified, and corresponding targeted agents are under development. For example, in BLCA, fibroblast growth factor

receptor (FGFR) inhibitors represent an important targeted therapeutic strategy, with erdafitinib approved for patients with locally advanced or metastatic urothelial carcinoma carrying FGFR3 alterations who have experienced disease progression after prior systemic therapy [282].

Beyond phosphorylation, methylation-based PTM systems also represent therapeutic targets in BLCA. SETD8 is a histone lysine methyltransferase that enhances oncogenic transcription. Pharmacologic inhibition with UNC0379 suppresses tumor growth and reduces cell fitness in preclinical models [283]. Likewise, KMT9 is an actionable target in muscle-invasive BC. Inhibition with KMI169 impairs tumor-promoting phenotypes in preclinical models, highlighting the potential to disrupt KMT9-driven methylation programs and suppress tumor growth [284].

RCC

In RCC, and particularly in the clear cell subtype (ccRCC), vulnerabilities associated with PTM systems and protein stability are closely integrated with the canonical von Hippel–Lindau (VHL)–hypoxia-inducible factor (HIF) oxygen-sensing pathway, representing one of the most clinically advanced paradigms of proteostasis-guided therapeutic targeting in solid tumors. Loss of VHL function in ccRCC stabilizes HIF transcriptional programs, and pharmacologic interception of this dependency has translated into clinical benefit with the HIF-2 α inhibitor belzutifan [285].

Beyond this established pathway, DUB modulation provides an additional, largely preclinical layer of intervention in RCC. USP7 has been implicated as a regulator of oncogenic stability networks in ccRCC, and the USP7 inhibitor P5091 has been reported to suppress tumor-promoting programs in RCC model systems, supporting DUB-directed perturbation of ubiquitin-dependent control as an emerging therapeutic direction [286]. Collectively, these examples highlight a tiered RCC landscape in which clinically implemented targeting of the VHL–HIF2 α axis is complemented by experimental strategies aimed at rewiring ubiquitin-mediated protein stability through DUB inhibition.

Overall, these studies highlight the therapeutic potential of targeting PTM pathways across genitourinary cancers, including PCa, BLCA, and RCC; the key PTM-associated targets and corresponding inhibitors are summarized in Table 9.

HNSCC and NB

In HNSCC, EGFR-directed therapy remains the most clinically mature targeted strategy, exemplified by the anti-EGFR antibody cetuximab, which is an approved agent and is incorporated into standard regimens in biomarker- and setting-appropriate disease contexts [287]. In parallel, chromatin-state modulation is being explored as an additional vulnerability layer: inhibition of the histone demethylase JMJD3 (KDM6B) using GSK-J1/GSK-J4 has been reported to suppress HNSCC-associated malignant phenotypes in experimental systems, supporting JMJD3-dependent epigenetic programs as a preclinical target class in this tumor type [288]. In addition, farnesylation-directed intervention has been investigated as another PTM-linked therapeutic avenue in molecularly defined HNSCC: tipifarnib, which targets the farnesyltransferase complex (FNTA/FNTB), supports protein farnesylation as a potentially actionable vulnerability in HRAS-mutant disease [289].

Table 8. PTM-associated therapeutic targets and inhibitors in gynecologic and breast cancers.

Cancers	Targets	Drugs/inhibitors
BC/TNBC	HER2	Trastuzumab [253], pertuzumab [254], lapatinib [255], neratinib [256]
	PI3K	Alpelisib (+ fulvestrant) [257]
	AKT	Capivasertib (+ fulvestrant) [258]
	mTORC1	Everolimus (+ exemestane) [259]
	TK	Nintedanib (+ paclitaxel) [260]
	SKP2	SMIP004 [261]
	DOT1L	EPZ-5676 [262]
OV	KDM4	Tach101 [263], QC6352 [264]
	HDAC6	Ricolinostat (+ paclitaxel) [270], ACY241 [277]
	HDAC8	PCI-34051 (+ ACY241) [272]
	ATAD2	BAY-850 [273]
	SETD8	UNC0379 [274]
	DOT1L	EPZ-5676, EPZ004777 and SGC0946 [275]
EC	PARP	Olaparib [266], niraparib [267], rucaparib [268]
	CLK	SM08502 (+ paclitaxel) [276]

Table 9. PTM-associated therapeutic targets and inhibitors in genitourinary cancers.

Cancers	Targets	Drugs/inhibitors
PCa	P300/CBP	CBPD-409/268 (PROTAC) [278]
	UBE2C	HKI-357 [279]
	EHMT2	BIX-01294 [280]
	KDM5	PBIT [281]
BLCA	FGFR	Erdafitinib [282]
	SETD8	UNC0379 [283]
	KMT9	KMI169 [284]
RCC	VHL	Belzutifan [285]
	USP7	P5091 [286]

Within neurodevelopmental malignancies, NB also displays tractable chromatin repression dependencies. Targeting the methyltransferase SUV39H1 with chaetocin has shown antitumor activity in preclinical NB models, consistent with reliance on H3K9 methylation-linked transcriptional repression programs in NB maintenance [290]. Collectively, these examples illustrate a tiered landscape across HNSCC and NB, in which approved EGFR blockade in HNSCC coexists with emerging, largely pre-clinical epigenetic interventions across both head and neck and neuro-oncologic tumor contexts. Representative PTM-associated therapeutic targets and inhibitors in HNSCC and NB are summarized in Table 10.

Across cancer systems, PTM-directed therapeutics now span a continuum from established, approval-anchored precision oncology to exploratory strategies that reprogram transcriptional state, chromatin architecture, and protein homeostasis. The most clinically mature landscape is observed in respiratory malignancies, particularly NSCLC, where multiple approved kinase-directed agents leverage phosphorylation-driven oncogene addiction across EGFR-, ALK-, BRAF/MEK-, and HER2-defined subsets, and are increasingly complemented by investigational non-kinase PTM/recognition nodes. More broadly, this pattern is also

Table 10. PTM-associated therapeutic targets and inhibitors in other cancers.

Cancers	Targets	Drugs/inhibitors
HNSCC	JMJD3	GSK-J1/GSK-J4 [288]
	EGFR	Cetuximab [287]
	FNTA/FNTB complex	Tipifarnib [289]
NB	SUV39H1	Chaetocin [290]

seen in molecularly defined subsets of several other solid tumors, such as BRAF V600E-altered CRC, HER2-positive GC, FGFR3-altered BLCA, and VHL-HIF2 α -dependent RCC, in which defined driver dependencies enable clinically mature, signaling-linked targeted strategies. A similarly rich, clinically actionable repertoire is evident in hematologic malignancies, where PTM-centric intervention has long been a proving ground for drugging epigenetic regulators and proteostasis circuitry, enabling both biomarker-defined therapies in AML and durable disease control in MM

alongside regimen-adapted HDAC blockade in selected lymphoid neoplasms.

By contrast, gastrointestinal/hepatobiliary, gynecologic-breast, and genitourinary cancers show a more heterogeneous pattern: a smaller number of approval-level PTM-targeted therapies are concentrated in defined molecular niches, whereas much of the current momentum lies in ongoing trials and preclinical programs that target chromatin repression, transcriptional co-activation, ubiquitin-proteasome/UBL pathways, and stress-adaptation mechanisms. This broader pattern is especially evident in tumors such as SCLC, MPM, PDAC, and parts of HCC, where clearly actionable driver-defined strategies remain limited and PTM-oriented approaches more often rely on epigenetic regulators, proteostasis pathways, and combination-based sensitization strategies rather than single-node inhibition. Notably, even in cancers with established targeted agents, such as HNSCC with cetuximab, additional PTM-directed therapies are still being pursued because single-pathway inhibition is often insufficient to produce durable responses, and resistance frequently emerges. Beyond established organ-specific examples, myristoylation represents an emerging PTM-targeted therapeutic axis. Zelenistat, an N-myristoyltransferase (NMT1/2) inhibitor, is currently in Phase I evaluation, while preclinical studies support NMT inhibition as a potential strategy in MYC/MYCN-driven tumors [291]. Overall, the cross-system view highlights two parallel trajectories: continued expansion of approved kinase-centric targeting where oncogene addiction is present, and rapid growth of PTM-informed strategies aimed at extending actionability beyond classical drivers through epigenetic, proteostatic, and immune-modulatory intervention points.

Challenges and perspectives

PTM systems constitute a major regulatory mechanism in cellular biology, and their dysregulation is increasingly recognized as a key driver of tumor initiation, progression, and therapeutic resistance. Advances in quantitative proteomics and computational analysis have substantially expanded our ability to profile PTMs, accelerating the identification of PTM-based biomarkers and therapeutic targets [292, 293]. Importantly, PTMs not only reflect oncogenic state but also actively modulate drug sensitivity and tumor-immune interactions, providing a mechanistic foundation for both biomarker development and therapeutic intervention.

Despite these advances, clinical translation remains constrained by the transient, low-stoichiometry, and context-dependent nature of many PTMs. Emerging enrichment strategies [294], spatial and low-input proteomics workflows [295–299], and targeted verification pipelines are improving analytical depth and robustness, yet scalability and standardization remain limiting factors [300, 301]. In parallel, the interpretability of PTM-centric datasets represents a major challenge, as regulatory information is encoded at the level of site-specific and context-dependent modifications rather than protein abundance [302].

Future progress will depend on integrating PTM profiling with systematic perturbation approaches and network-based computational strategies to move from descriptive maps toward mechanistic and predictive models. A key opportunity lies in the development of system-level PTM biomarkers that capture coor-

dinated activity across writers, erasers, readers, and substrates, thereby reflecting pathway state and adaptive rewiring. Viewed in this light, treating PTMs as integrated regulatory systems rather than isolated chemical marks is likely to underpin next-generation biomarkers and more durable therapeutic strategies in precision medicine.

Acknowledgements

This work was supported by Noncommunicable Chronic Diseases-National Science and Technology Major Project (grant No. 2024ZD0531100), Science and Technology Project of Sichuan Province (grant No. 2024YFFK0099), National Clinical Research Center for Geriatrics of West China Hospital (grant No. Z2024JC002), and West China Hospital 1.3.5 project for disciplines of excellence (grant No. ZYYC23013).

Author contributions

Lunzhi Dai (Conceptualization), Li Gao (Visualization, Writing – original draft, Writing – review & editing), Yueqin He (Visualization, Writing – original draft, Writing – review & editing), Kexin Wang (Visualization, Writing – original draft, Writing – review & editing), Qin Li (Visualization, Writing – original draft, Writing – review & editing), Litong Nie (Supervision).

Conflicts of interest

There is no competing interest.

References

1. Geffen Y, Anand S, Akiyama Y *et al.* Pan-cancer analysis of post-translational modifications reveals shared patterns of protein regulation. *Cell* 2023;**186**:3945–67. <https://doi.org/10.1016/j.cell.2023.07.013>
2. Zhong Q, Xiao X, Qiu Y *et al.* Protein posttranslational modifications in health and diseases: functions, regulatory mechanisms, and therapeutic implications. *MedComm* 2023;**4**:e261. <https://doi.org/10.1002/mco2.261>
3. Ling Y, Cai F, Su T *et al.* Glycosylation in kidney diseases. *Precis Clin Med* 2025;**8**:pbaf017. <https://doi.org/10.1093/pcmcdi/pbaf017>
4. Woodsmith J, Kamburov A, Stelzl U. Dual coordination of post translational modifications in human protein networks. *PLoS Comput Biol* 2013;**9**:e1002933. <https://doi.org/10.1371/journal.pcbi.1002933>
5. Li W, Li F, Zhang X *et al.* Insights into the post-translational modification and its emerging role in shaping the tumor microenvironment. *Sig Transduct Target Ther* 2021;**6**:422. <https://doi.org/10.1038/s41392-021-00825-8>
6. Bahar ME, Kim HJ, Kim DR. Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies. *Sig Transduct Target Ther* 2023;**8**:455. <https://doi.org/10.1038/s41392-023-01705-z>
7. Seeler J-S, Dejean A. SUMO and the robustness of cancer. *Nat Rev Cancer* 2017;**17**:184–97. <https://doi.org/10.1038/nrc.2016.143>

8. Tomuleasa C, Tigu A-B, Munteanu R *et al.* Therapeutic advances of targeting receptor tyrosine kinases in cancer. *Sig Transduct Target Ther* 2024;**9**:201. <https://doi.org/10.1038/s41392-024-01899-w>
9. Li Y, Porta-Pardo E, Tokheim C *et al.* Pan-cancer proteogenomics connects oncogenic drivers to functional states. *Cell* 2023;**186**:3921–44. <https://doi.org/10.1016/j.cell.2023.07.014>
10. Klomp JE, Diehl JN, Klomp JA *et al.* Determining the ERK-regulated phosphoproteome driving KRAS-mutant cancer. *Science* 2024;**384**:eadk0850. <https://doi.org/10.1126/science.adk0850>
11. Luchini C, Paolino G, Mattiolo P *et al.* KRAS wild-type pancreatic ductal adenocarcinoma: molecular pathology and therapeutic opportunities. *J Exp Clin Cancer Res* 2020;**39**:227. <https://doi.org/10.1186/s13046-020-01732-6>
12. Bergholz JS, Wang Q, Wang Q *et al.* PI3K β controls immune evasion in PTEN-deficient breast tumours. *Nature* 2023;**617**:139–46. <https://doi.org/10.1038/s41586-023-05940-w>
13. Zhang R, Hu M, Liu Y *et al.* Integrative omics uncovers low tumorous magnesium content as a driver factor of colorectal cancer. *Genomics Proteomics Bioinformatics* 2024;**22**:qzae053. <https://doi.org/10.1093/gpbjnl/qzae053>
14. Gao L, Lu Y, Chen H-N *et al.* Deciphering the clinical significance and kinase functions of gsk3 α in colon cancer by proteomics and phosphoproteomics. *Mol Cell Proteomics* 2023;**22**:100545. <https://doi.org/10.1016/j.mcpro.2023.100545>
15. Zhang R, Hu M, Chen H-N *et al.* Phenotypic heterogeneity analysis of APC-mutant colon cancer by proteomics and phosphoproteomics identifies RAI14 as a key prognostic determinant in East Asians and Westerners. *Mol Cell Proteomics* 2023;**22**:100532. <https://doi.org/10.1016/j.mcpro.2023.100532>
16. Wang X, Luo Y, He S *et al.* Age-, sex- and proximal–distal-resolved multi-omics identifies regulators of intestinal aging in non-human primates. *Nat Aging* 2024;**4**:414–33. <https://doi.org/10.1038/s43587-024-00572-9>
17. Gong Y, Zhan H, Wei N *et al.* Acetylation profiling by Iseq-Kac reveals insights into HSC aging and lineage decision. *Nat Chem Biol* 2025;**21**:1675–87. <https://doi.org/10.1038/s41589-025-01916-1>
18. Li J, Huang S, Yuan F *et al.* Prognostic and immunotherapeutic response prediction in hepatocellular carcinoma: role of non-histone acetylation/deacetylation scoring. *Discov Onc* 2025;**16**:1488. <https://doi.org/10.1007/s12672-025-03339-9>
19. Lu X, Xu S, Deng Z *et al.* Molecular mechanisms and genetic features of cholangiocarcinoma: implications for targeted therapeutic strategies. *Precis Clin Med* 2025;**8**:pbaf021. <https://doi.org/10.1093/pcmedi/pbaf021>
20. Ji H, Zhou Y, Zhuang X *et al.* HDAC3 deficiency promotes liver cancer through a defect in H3K9ac/H3K9me3 transition. *Cancer Res* 2019;**79**:3676–88. <https://doi.org/10.1158/0008-5472.CAN-18-3767>
21. Sinha A, Saini KK, Chandramouli A *et al.* ACSL4-mediated H3K9 and H3K27 hyperacetylation upregulates SNAIL to drive TNBC metastasis. *Proc Natl Acad Sci USA* 2024;**121**:e2408049121. <https://doi.org/10.1073/pnas.2408049121>
22. Fan S, W.-j. L, Qi Y *et al.* PRMT5 encourages cell migration and metastasis of tongue squamous cell carcinoma through methylating Δ Np63 α . *Cell Death Differ* 2026;**33**:465–79. <https://doi.org/10.1038/s41418-025-01575-8>
23. Wu Y, Xu X, Tong Y *et al.* Metformin impairs breast cancer growth through the inhibition of PRMT6. *Adv Sci* 2026;**13**:e08525. <https://doi.org/10.1002/advs.202508525>
24. Akano I, Hebert JM, Tiedemann RL *et al.* The SWI/SNF-related protein SMARCA3 is a histone H3K23 ubiquitin ligase that regulates H3K9me3 in cancer. *Mol Cell* 2025;**85**:2885–99. <https://doi.org/10.1016/j.molcel.2025.06.020>
25. Wang P, Qiu J, Fang Y *et al.* SENP3 inhibition suppresses hepatocellular carcinoma progression and improves the efficacy of anti-PD-1 immunotherapy. *Cell Death Differ* 2025;**32**:959–72. <https://doi.org/10.1038/s41418-024-01437-9>
26. Lu R-S, Ren L-K, Fei X-B *et al.* PSMD14-mediated LDHA deubiquitination upregulates ACLY expression via H3K18 lactylation to promote lipid synthesis and pancreatic cancer progression. *Adv Sci* 2025;**12**:e05762. <https://doi.org/10.1002/advs.202505762>
27. Loix M, Zelcer N, Bogie JFJ *et al.* The ubiquitous role of ubiquitination in lipid metabolism. *Trends Cell Biol* 2024;**34**:416–29. <https://doi.org/10.1016/j.tcb.2023.09.001>
28. Fang Y, Gu Y, Xu T *et al.* SENP1 drives glycolysis and cisplatin resistance in gastric cancer via desumoylating ENO1. *J Exp Clin Cancer Res* 2025;**44**:285. <https://doi.org/10.1186/s13046-025-03543-z>
29. Zhu Z, Sun J, Xu W *et al.* MGAT4A/galectin9-driven N-glycosylation aberration as a promoting mechanism for poor prognosis of endometrial cancer with TP53 mutation. *Adv Sci* 2024;**11**:2409764. <https://doi.org/10.1002/advs.202409764>
30. Dong C, Zhang Y, Zeng J *et al.* FUT2 promotes colorectal cancer metastasis by reprogramming fatty acid metabolism via YAP/TAZ signaling and SREBP-1. *Commun Biol* 2024;**7**:1297. <https://doi.org/10.1038/s42003-024-06993-x>
31. Song J, Liu W, Wang J *et al.* GALNT6 promotes invasion and metastasis of human lung adenocarcinoma cells through O-glycosylating chaperone protein GRP78. *Cell Death Dis* 2020;**11**:352. <https://doi.org/10.1038/s41419-020-2537-6>
32. Tan Z, Jiang Y, Liang L *et al.* Dysregulation and prometastatic function of glycosyltransferase C1GALT1 modulated by cHP1BP3/miR-1-3p axis in bladder cancer. *J Exp Clin Cancer Res* 2022;**41**:228. <https://doi.org/10.1186/s13046-022-02438-7>
33. Murata K, Miyoshi E, Kameyama M *et al.* Expression of N-acetylglucosaminyltransferase V in colorectal cancer correlates with metastasis and poor prognosis. *Clin Cancer Res* 2000;**6**:1772–7.
34. Yamamoto E, Ino K, Miyoshi E *et al.* Expression of N-acetylglucosaminyltransferase V in endometrial cancer correlates with poor prognosis. *Br J Cancer* 2007;**97**:1538–44. <https://doi.org/10.1038/sj.bjc.6604044>
35. Wang X, He H, Zhang H *et al.* Clinical and prognostic implications of β 1, 6-N-acetylglucosaminyltransferase V in patients with gastric cancer. *Cancer Sci* 2013;**104**:185–93. <https://doi.org/10.1111/cas.12049>
36. Granovsky M, Fata J, Pawling J *et al.* Suppression of tumor growth and metastasis in Mgat5-deficient mice. *Nat Med* 2000;**6**:306–12. <https://doi.org/10.1038/73163>

37. Wang Y, Zhang S, Bai J *et al.* SMAD4 palmitoylation drives a metabolic-transcriptional circuit to promote tumorigenesis and confers radiosensitivity in pancreatic cancer. *Adv Sci* 2026;**e19791**. <https://doi.org/10.1002/adv.202519791>
38. Lin C, Li Z, Zhu X *et al.* Abnormal β -hydroxybutyrylation modification of ARG1 drives reprogramming of arginine metabolism to promote the progression of colorectal cancer. *Adv Sci* 2025;**12**:e02402. <https://doi.org/10.1002/adv.202502402>
39. Su J, Zhao M, Feng W *et al.* TAF1 acetyltransferase promotes colorectal carcinoma metastasis by catalyzing β -hydroxybutyrylation of KCTD9. *Oncogene* 2026;**45**:87–103. <https://doi.org/10.1038/s41388-025-03644-1>
40. Xie B, Zhang M, Li J *et al.* KAT8-catalyzed lactylation promotes eEF1A2-mediated protein synthesis and colorectal carcinogenesis. *Proc Natl Acad Sci USA* 2024;**121**:e2314128121. <https://doi.org/10.1073/pnas.2314128121>
41. Yang Z, Yan C, Ma J *et al.* Lactylome analysis suggests lactylation-dependent mechanisms of metabolic adaptation in hepatocellular carcinoma. *Nat Metab* 2023;**5**:61–79. <https://doi.org/10.1038/s42255-022-00710-w>
42. Wang X, Li Y, Tang Y *et al.* PD-L1 delactylation-promoted nuclear translocation accelerates liver cancer growth through elevating SQLE transcription activity. *Cancer Lett* 2025;**630**:217901. <https://doi.org/10.1016/j.canlet.2025.217901>
43. Pitter MR, Kryczek I, Zhang H *et al.* PAD4 controls tumor immunity via restraining the MHC class II machinery in macrophages. *Cell Rep* 2024;**43**:113942. <https://doi.org/10.1016/j.celrep.2024.113942>
44. Yan Y, Yu J, Wang W *et al.* Palmitoylation prevents B7-H4 lysosomal degradation sustaining tumor immune evasion. *Nat Commun* 2025;**16**:4254. <https://doi.org/10.1038/s41467-025-58552-5>
45. Xia Z, Gao L, Hu M *et al.* Comparative N-glycoproteomics reveals subtype-specific N-glycosylation signatures and immune associations in cholangiocarcinoma. *Mol Cell Proteomics* 2025;**24**:101084. <https://doi.org/10.1016/j.mcpro.2025.101084>
46. Park MS, Yang AY, Lee JE *et al.* GALNT3 suppresses lung cancer by inhibiting myeloid-derived suppressor cell infiltration and angiogenesis in a TNFR and c-MET pathway-dependent manner. *Cancer Lett* 2021;**521**:294–307. <https://doi.org/10.1016/j.canlet.2021.08.015>
47. She X, Lan J, Zhang H *et al.* METTL3 methylation induces decay of endogenous retroelement transcripts to promote tumor immune evasion. *Cancer Res* 2026. <https://doi.org/10.1158/0008-5472.CAN-25-2893>
48. Xue T, Liu X, Song C *et al.* Citrullination of AKT2 catalyzed by PAD1 facilitates the maintenance of stemness characteristics of ovarian cancer stem-like cells in ovarian cancer. *Adv Sci* 2025;**12**:e01014. <https://doi.org/10.1002/adv.202501014>
49. Shao S, Li W, Hong Y *et al.* ZDHHC2-dependent palmitoylation dictates ferroptosis and castration sensitivity in prostate cancer via controlling ACSL4 degradation and lipid peroxidation. *Adv Sci* 2026;**13**:e14077. <https://doi.org/10.1002/adv.202514077>
50. Deng H, Xu Q, Zhang Q *et al.* EZH2 promotes chemoresistance in colorectal cancer by inhibiting autophagy through NRP1 suppression. *Biochem J* 2025;**482**:569–81. <https://doi.org/10.1042/BCJ20240607>
51. Zhang Q, Shi Y, Liu S *et al.* EZH2/G9a interact to mediate drug resistance in non-small-cell lung cancer by regulating the SMAD4/ERK/c-Myc signaling axis. *Cell Rep* 2024;**43**:113714. <https://doi.org/10.1016/j.celrep.2024.113714>
52. Wang X, Su Y, Lan B *et al.* USP22 promotes the proliferation and sorafenib resistance of hepatocellular carcinoma cells via its deubiquitinase activity. *Clin Transl Med* 2025;**15**:e70324. <https://doi.org/10.1002/ctm2.70324>
53. Zhang H, Han B, Lu H *et al.* USP22 promotes resistance to EGFR-TKIs by preventing ubiquitination-mediated EGFR degradation in EGFR-mutant lung adenocarcinoma. *Cancer Lett* 2018;**433**:186–98. <https://doi.org/10.1016/j.canlet.2018.07.002>
54. Wang H-L, Chen Y, Wang Y-Q *et al.* Sirtuin5 protects colorectal cancer from DNA damage by keeping nucleotide availability. *Nat Commun* 2022;**13**:6121. <https://doi.org/10.1038/s41467-022-33903-8>
55. He Y, Zheng C-C, Yang J *et al.* Lysine butyrylation of HSP90 regulated by KAT8 and HDAC11 confers chemoresistance. *Cell Discov* 2023;**9**:74. <https://doi.org/10.1038/s41421-023-00570-y>
56. Gao C, Chen G, Romero G *et al.* Induction of Gsk3 β - β -TrCP interaction is required for late phase stabilization of β -catenin in canonical Wnt signaling. *J Biol Chem* 2014;**289**:7099–108. <https://doi.org/10.1074/jbc.M113.532606>
57. Xuan Z, Chen C, Sun H *et al.* NDR1/FBXO11 promotes phosphorylation-mediated ubiquitination of β -catenin to suppress metastasis in prostate cancer. *Int J Biol Sci* 2024;**20**:4957–77. <https://doi.org/10.7150/ijbs.98907>
58. Hino S-i, Tanji C, Nakayama KI *et al.* Phosphorylation of β -catenin by cyclic AMP-dependent protein kinase stabilizes β -catenin through inhibition of its ubiquitination. *Mol Cell Biol* 2005;**25**:9063–72. <https://doi.org/10.1128/MCB.25.20.9063-9072.2005>
59. Li Y, Zhao L, Deng J *et al.* PLK1 stabilizes β -catenin to drive colorectal carcinogenesis through NFKB2-mediated transcriptional activation of USP2a and site-specific phosphorylation. *Theranostics* 2026;**16**:3488–506. <https://doi.org/10.7150/thno.122368>
60. He Y-m, Zhou X-m, Jiang S-y *et al.* TRIM25 activates AKT/mTOR by inhibiting PTEN via K63-linked polyubiquitination in non-small cell lung cancer. *Acta Pharmacol Sin* 2022;**43**:681–91. <https://doi.org/10.1038/s41401-021-00662-z>
61. Quan Z, Peng B, Hu K *et al.* AP5Z1 affects hepatocellular carcinoma growth and autophagy by regulating PTEN ubiquitination and modulating the PI3K/Akt/mTOR pathway. *J Transl Med* 2025;**23**:564. <https://doi.org/10.1186/s12967-025-06537-9>
62. Jiang Q, Song P, Zhang S *et al.* TRIM21 and OTUD6A orchestrate AKT K27-linked atypical ubiquitination to modulate cancer chemoresistance. *Nat Struct Mol Biol* 2026;**33**:84–99. <https://doi.org/10.1038/s41594-025-01697-0>
63. Yan Y, Zhou S, Chen X *et al.* Suppression of ITPKB degradation by Trim25 confers TMZ resistance in glioblastoma through ROS homeostasis. *Sig Transduct Target Ther* 2024;**9**:58. <https://doi.org/10.1038/s41392-024-01763-x>

64. Huang B, Jin M, Cui G *et al.* GCN5-ERK lactylation-phosphorylation loop amplifies lactate-driven cancer progression. *Nat Chem Biol* 2026;**22**:634–48. <https://doi.org/10.1038/s41589-025-02107-8>
65. Yuan Q, Shi Y, Wang J *et al.* p38 mediated ACSL4 phosphorylation drives stress-induced esophageal squamous cell carcinoma growth through Src myristoylation. *Nat Commun* 2025;**16**:3319. <https://doi.org/10.1038/s41467-025-58342-z>
66. Liu Y, Su Z, Tavana O *et al.* Understanding the complexity of p53 in a new era of tumor suppression. *Cancer Cell* 2024;**42**:946–67. <https://doi.org/10.1016/j.ccell.2024.04.009>
67. Mo Y, Han Y, Chen Y *et al.* ZDHHC20 mediated S-palmitoylation of fatty acid synthase (FASN) promotes hepatocarcinogenesis. *Mol Cancer* 2024;**23**:274. <https://doi.org/10.1186/s12943-024-02195-5>
68. Zhu Y, Gu L, Lin X *et al.* Dynamic regulation of ME1 phosphorylation and acetylation affects lipid metabolism and colorectal tumorigenesis. *Mol Cell* 2020;**77**:138–49. <https://doi.org/10.1016/j.molcel.2019.10.015>
69. Tong Y, Guo D, Lin S-H *et al.* SUCLA2-coupled regulation of GLS succinylation and activity counteracts oxidative stress in tumor cells. *Mol Cell* 2021;**81**:2303–16. <https://doi.org/10.1016/j.molcel.2021.04.002>
70. Chen X, Ke Z, Wei S *et al.* ASCT2 palmitoylation regulated by JNK1-ZDHHC14 axis orchestrates glutamine metabolism and NSCLC progression. *Cell Discov* 2026;**12**:13. <https://doi.org/10.1038/s41421-026-00870-z>
71. Lu B, Qiu R, Wei J *et al.* Phase separation of phospho-HDAC6 drives aberrant chromatin architecture in triple-negative breast cancer. *Nat Cancer* 2024;**5**:1622–40. <https://doi.org/10.1038/s43018-024-00816-y>
72. Li Z, Lu X, Liu Y *et al.* Gain of LINC00624 enhances liver cancer progression by disrupting the histone deacetylase 6/tripartite motif containing 28/zinc finger protein 354C corepressor complex. *Hepatology* 2021;**73**:1764–82. <https://doi.org/10.1002/hep.31530>
73. Wang M, Mu G, Qiu B *et al.* Competitive antagonism of KAT7 crotonylation against acetylation affects procentriole formation and colorectal tumorigenesis. *Nat Commun* 2025;**16**:2379. <https://doi.org/10.1038/s41467-025-57546-7>
74. Wang Y, Zhou R, Zeng X *et al.* CLOCK-catalyzed histone H3K37 glutarylation suppresses H3K36 trimethylation pathways in glioblastoma. *Sci Adv* 2026;**12**:eaea1127. <https://doi.org/10.1126/sciadv.aea1127>
75. Zhao W, Wang G, Wang P *et al.* Arginine methylation-dependent stabilization of SUV39H1 promotes breast cancer growth. *Oncogene* 2026;**45**:1220–33. <https://doi.org/10.1038/s41388-026-03712-0>
76. Qiu W, Wang B, Gao Y *et al.* Targeting histone deacetylase 6 reprograms interleukin-17-producing helper T cell pathogenicity and facilitates immunotherapies for hepatocellular carcinoma. *Hepatology* 2020;**71**:1967–87. <https://doi.org/10.1002/hep.30960>
77. Wang K, Chen X, Lin P *et al.* CD147-K148me2-driven tumor cell-macrophage crosstalk provokes NSCLC immunosuppression via the CCL5/CCR5 axis. *Adv Sci* 2024;**11**:2400611. <https://doi.org/10.1002/adv.202400611>
78. Xiao X, Shi J, He C *et al.* ERK and USP5 govern PD-1 homeostasis via deubiquitination to modulate tumor immunotherapy. *Nat Commun* 2023;**14**:2859. <https://doi.org/10.1038/s41467-023-38605-3>
79. Li C-W, Lim S-O, Xia W *et al.* Glycosylation and stabilization of programmed death ligand-1 suppresses T-cell activity. *Nat Commun* 2016;**7**:12632. <https://doi.org/10.1038/ncomms12632>
80. Zhu W, Fan C, Hou Y *et al.* Lactylation in tumor microenvironment and immunotherapy resistance: new mechanisms and challenges. *Cancer Lett* 2025;**627**:217835. <https://doi.org/10.1016/j.canlet.2025.217835>
81. Choi J, Kim GA, Han S *et al.* Longitudinal assessment of three serum biomarkers to detect very early-stage hepatocellular carcinoma. *Hepatology* 2019;**69**:1983–94. <https://doi.org/10.1002/hep.30233>
82. Zhao Y, Zhang L, Huo L *et al.* Clinical significance of fucosylated GP73 in the differential diagnosis of hepatocellular carcinoma. *Int J Biol Markers* 2018;**33**:439–46. <https://doi.org/10.1177/1724600818796646>
83. Warden DW, Ondrejka S, Lin J *et al.* Phospho-ERKTHR202/Tyr214 is overexpressed in hairy cell leukemia and is a useful diagnostic marker in bone marrow trephine sections. *Am J Surg Pathol* 2013;**37**:305–8. <https://doi.org/10.1097/PAS.0b013e3182712481>
84. Zhu L, Xu Y, Kang S *et al.* Quantification-promoted discovery of glycosylated exosomal PD-L1 as a potential tumor biomarker. *Small Methods* 2022;**6**:2200549. <https://doi.org/10.1002/smt.202200549>
85. Kaufman B, Abu-Ahmad M, Radinsky O *et al.* N-glycosylation of PD-L1 modulates the efficacy of immune checkpoint blockades targeting PD-L1 and PD-1. *Mol Cancer* 2025;**24**:140. <https://doi.org/10.1186/s12943-025-02330-w>
86. Li Y, Fu B, Wang M *et al.* Urinary extracellular vesicle N-glycomics identifies diagnostic glycosignatures for bladder cancer. *Nat Commun* 2025;**16**:2292. <https://doi.org/10.1038/s41467-025-57633-9>
87. Chen S, Li Y, Hu J *et al.* Integrating bulk RNA-seq, scRNA-seq, and spatial transcriptomics data to identify novel post-translational modification-related molecular subtypes and therapeutic responses in hepatocellular carcinoma. *Cancer Cell Int* 2025;**25**:330. <https://doi.org/10.1186/s12935-025-03964-y>
88. Liu J, Zhu X, Zha C *et al.* Succinylation heterogeneity in lung adenocarcinoma: from prognostic model to KLK6-driven tumor microenvironment remodeling. *Front Immunol* 2025;**16**:1718994. <https://doi.org/10.3389/fimmu.2025.1718994>
89. Zhang P, Wang D, Zhou G *et al.* Novel post-translational modification learning signature reveals B4GALT2 as an immune exclusion regulator in lung adenocarcinoma. *J Immunother Cancer* 2025;**13**:e010787. <https://doi.org/10.1136/jitc-2024-010787>
90. Sun Z, Yu L, Wu T *et al.* A lactylation-related gene signature predicts metastasis and prognosis in breast cancer. *Sci Rep* 2025;**15**:42171. <https://doi.org/10.1038/s41598-025-26165-z>
91. Chan A, Prassas I, Dimitromanolakis A *et al.* Validation of biomarkers that complement CA19.9 in detecting early pancreatic cancer. *Clin Cancer Res* 2014;**20**:5787–95. <https://doi.org/10.1158/1078-0432.Ccr-14-0289>

92. Mak LY, To WP, Wong DK *et al.* Serum Mac-2 binding protein glycosylation isomer level predicts hepatocellular carcinoma development in E-negative chronic hepatitis B patients. *World J Gastroenterol* 2019;**25**:1398–408. <https://doi.org/10.3748/wjg.v25.i11.1398>
93. Zhou JM, Wang T, Zhang KH. AFP-L3 for the diagnosis of early hepatocellular carcinoma: a meta-analysis. *Medicine (Baltimore)* 2021;**100**:e27673. <https://doi.org/10.1097/md.00000000000027673>
94. Funston G, Hamilton W, Abel G *et al.* The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: a population-based cohort study. *PLoS Med* 2020;**17**:e1003295. <https://doi.org/10.1371/journal.pmed.1003295>
95. Guo J, Yu J, Song X *et al.* Serum CA125, CA199 and CEA combined detection for epithelial ovarian cancer diagnosis: a meta-analysis. *Open Med* 2017;**12**:131–7. <https://doi.org/10.1515/med-2017-0020>
96. Ferrer-Batallé M, Llop E, Ramírez M *et al.* Comparative study of blood-based biomarkers, α 2,3-sialic acid PSA and PHI, for high-risk prostate cancer detection. *Int J Mol Sci* 2017;**18**:845. <https://doi.org/10.3390/ijms18040845>
97. Yang X, Yang Y, Li Z *et al.* Diagnostic value of circulating chromogranin a for neuroendocrine tumors: a systematic review and meta-analysis. *PLoS One* 2015;**10**:e0124884. <https://doi.org/10.1371/journal.pone.0124884>
98. Behrouzi R, Barr CE, Crosbie EJ. HE4 as a biomarker for endometrial cancer. *Cancers* 2021;**13**:4764. <https://doi.org/10.3390/cancers13194764>
99. Zhai G, Yang L, Luo Q *et al.* Evaluation of serum phosphopeptides as potential biomarkers of gastric cancer. *RSC Adv* 2017;**7**:21630–7. <https://doi.org/10.1039/C7RA00827A>
100. Khadjavi A, Mannu F, Destefanis P *et al.* Early diagnosis of bladder cancer through the detection of urinary tyrosine-phosphorylated proteins. *Br J Cancer* 2015;**113**:469–75. <http://doi.org/10.1038/bjc.2015.232>
101. Lu J, Zhong F, Sun B *et al.* Diagnostic utility of serum Golgi phosphoprotein 3 in bladder cancer patients. *Med Sci Monit* 2019;**25**:6736–41. <https://doi.org/10.12659/msm.915950>
102. Wang T, Zhang K-H. New blood biomarkers for the diagnosis of AFP-negative hepatocellular carcinoma. *Front Oncol* 2020;**10**:1316. <https://doi.org/10.3389/fonc.2020.01316>
103. Yu H, Wang H, Dong W *et al.* The diagnostic and prognostic value of UBE2T in intrahepatic cholangiocarcinoma. *PeerJ* 2020;**8**:e8454. <https://doi.org/10.7717/peerj.8454>
104. Miao J, Liu Y, Zhao G *et al.* Feasibility of plasma-methylated SFRP2 for early detection of gastric cancer. *Cancer Control* 2020;**27**:1073274820922559. <https://doi.org/10.1177/1073274820922559>
105. Liu A, Li Y, Shen L *et al.* Clinical utility of serum fucosylated fraction of alpha-fetoprotein in the diagnostic of hepatocellular carcinoma: a comprehensive analysis with large sample size. *Aging (Albany NY)* 2022; **14**: 2645–64. <https://doi.org/10.18632/aging.203963>
106. Chan DW, Bruzek DJ, Oesterling JE *et al.* Prostate-specific antigen as a marker for prostatic cancer: a monoclonal and a polyclonal immunoassay compared. *Clin Chem* 1987;**33**:1916–20. <https://doi.org/10.1093/clinchem/33.10.1916>
107. Mcallister MJ, McCall P, Dickson A *et al.* Androgen receptor phosphorylation at serine 81 and serine 213 in castrate-resistant prostate cancer. *Prostate Cancer Prostatic Dis* 2020;**23**:596–606. <https://doi.org/10.1038/s41391-020-0235-1>
108. Révillion F, Puech C, Rabenoelina F *et al.* Expression of the putative tumor suppressor gene PTPN13/PTPL1 is an independent prognostic marker for overall survival in breast cancer. *Int J Cancer* 2009;**124**:638–43. <https://doi.org/10.1002/ijc.23989>
109. Mcheik S, Aptekar L, Coopman P *et al.* Dual role of the PTPN13 tyrosine phosphatase in cancer. *Biomolecules* 2020;**10**:1659. <https://doi.org/10.3390/biom10121659>
110. Qin S, Chang F, Sun X *et al.* TRIM47 promotes hypopharyngeal and laryngeal cancers progression through promoting K63-linked ubiquitination of vimentin. *Cancer Sci* 2025;**116**:367–80. <https://doi.org/10.1111/cas.16397>
111. Zhang M, Yang B, Zhang L *et al.* TRIM27 is an adverse prognostic biomarker and associated with immune and molecular profiles in right-sided colon cancer. *Am J Cancer Res* 2022;**12**:4988–5003.
112. Shao W, Li J, Piao Q *et al.* FRMD3 inhibits the growth and metastasis of breast cancer through the ubiquitination-mediated degradation of vimentin and subsequent impairment of focal adhesion. *Cell Death Dis* 2023;**14**:13. <https://doi.org/10.1038/s41419-023-05552-2>
113. Qi M, Tu J, He R *et al.* NEDD4L suppresses proliferation and promotes apoptosis by ubiquitinating RAC2 expression and acts as a prognostic biomarker in clear cell renal cell carcinoma. *Int J Mol Sci* 2024;**25**:11933. <https://doi.org/10.3390/ijms252211933>
114. Xian W, Chen Y, Yu S *et al.* Ubiquitination and ALL: identifying FBXO8 as a prognostic biomarker and therapeutic target. *Front Immunol* 2025;**16**:1554231. <https://doi.org/10.3389/fimmu.2025.1554231>
115. Wang Z, Zhang W, Yin X *et al.* Multi-omics analyses were combined to construct ubiquitination-related features in colon adenocarcinoma and identify ASNS as a novel biomarker. *Front Immunol* 2024;**15**:1466286. <https://doi.org/10.3389/fimmu.2024.1466286>
116. Kitada S, Yamada S, Kuma A *et al.* Polypeptide N-acetylgalactosaminyl transferase 3 independently predicts high-grade tumours and poor prognosis in patients with renal cell carcinomas. *Br J Cancer* 2013;**109**:472–81. <https://doi.org/10.1038/bjc.2013.331>
117. Ishikawa M, Kitayama J, Nariko H *et al.* The expression pattern of UDP-N-Acetyl- α -D-galactosamine: polypeptide N-acetylgalactosaminyl transferase-3 in early gastric carcinoma. *J Surg Oncol* 2004;**86**:28–33. <https://doi.org/10.1002/jso.20042>
118. Wang H, Zheng J, Ma Q *et al.* GLT8D2 is a prognostic biomarker and regulator of immune cell infiltration in gastric cancer. *Front Immunol* 2024;**15**:1370367. <https://doi.org/10.3389/fimmu.2024.1370367>
119. Li Z, Yamada S, Inenaga S *et al.* Polypeptide N-acetylgalactosaminyltransferase 6 expression in pancreatic cancer is an independent prognostic factor indicating better overall survival. *Br J Cancer* 2011;**104**:1882–9. <https://doi.org/10.1038/bjc.2011.166>

120. Zhang Z, Cao Y, Zhao W *et al.* HDAC6 serves as a biomarker for the prognosis of patients with renal cell carcinoma. *Cance Biomark* 2017;**19**:169–75. <https://doi.org/10.3233/cbm-160298>
121. Jiang Y, Zhang J, Yu J *et al.* HDAC6 facilitates LUAD progression by inducing EMT and enhancing macrophage polarization towards the M2 phenotype. *NPJ Precis Onc* 2025;**9**:150. <https://doi.org/10.1038/s41698-025-00949-y>
122. Zeleke TZ, Pan Q, Chiuhan C *et al.* Network-based assessment of HDAC6 activity predicts preclinical and clinical responses to the HDAC6 inhibitor ricolinostat in breast cancer. *Nat Cancer* 2023;**4**:257–75. <https://doi.org/10.1038/s43018-022-00489-5>
123. Berger L, Kolben T, Meister S *et al.* Expression of H3K4me3 and H3K9ac in breast cancer. *J Cancer Res Clin Oncol* 2020;**146**:2017–27. <https://doi.org/10.1007/s00432-020-03265-z>
124. Zhen L, Gui-Lan L, Ping Y *et al.* The expression of H3K9Ac, H3K14Ac, and H4K20TriMe in epithelial ovarian tumors and the clinical significance. *Int J Gynecol Cancer* 2010;**20**:82–6. <https://doi.org/10.1111/IGC.0b013e3181ae3efa>
125. Ma Y, Chen M, Xu Z. Clinicopathological significance of AKT and phosphorylated AKT expression in hepatocellular carcinoma: a meta-analysis. *BMC Cancer* 2025;**25**:1677. <https://doi.org/10.1186/s12885-025-14948-6>
126. Guan L, Tang Y, Li G *et al.* Comprehensive analysis of role of cyclin-dependent kinases family members in colorectal cancer. *Front Oncol* 2022;**12**:921710. <https://doi.org/10.3389/fo nc.2022.921710>
127. Liu X, Li M, Chen L *et al.* High expression of SHP2 predicts a promising prognosis in colorectal cancer. *Indian J Pathol Microbiol* 2024;**67**:29–35. https://doi.org/10.4103/ijpm.ijpm_894_22
128. Li G, Zhong Y, Shen Q *et al.* NEK2 serves as a prognostic biomarker for hepatocellular carcinoma. *Int J Oncol* 2017;**50**:405–13. <https://doi.org/10.3892/ijo.2017.3837>
129. Wu Y, Mohd Sani SB, Peng K *et al.* Research progress of the Otubains subfamily in hepatocellular carcinoma. *Biomed Pharmacother* 2024;**179**:117348. <https://doi.org/10.1016/j.biopha.2024.117348>
130. Xie H, He Y, Wu Y *et al.* Silencing of UBE2D1 inhibited cell migration in gastric cancer, decreasing ubiquitination of SMAD4. *Infect Agents Cancer* 2021;**16**:63. <https://doi.org/10.1186/s13027-021-00402-2>
131. Huang Y, Zou Y, Jie Z. RNF6 promotes the migration and invasion of breast cancer by promoting the ubiquitination and degradation of MST1. *Exp Ther Med* 2022;**23**:118. <https://doi.org/10.3892/etm.2021.11041>
132. Jia M, Guo Y, Lu X. USP33 is a biomarker of disease recurrence in papillary thyroid carcinoma. *Cell Physiol Biochem* 2018;**45**:2044–53. <https://doi.org/10.1159/000488041>
133. Yuan J, Xu B, Su Y *et al.* Identification of USP39 as a prognostic and predictive biomarker for determining the response to immunotherapy in pancreatic cancer. *BMC Cancer* 2025;**25**:758. <https://doi.org/10.1186/s12885-025-14096-x>
134. Fang H, Shi X, Gao J *et al.* TMEM209 promotes hepatocellular carcinoma progression by activating the Wnt/ β -catenin signaling pathway through KPNB1 stabilization. *Cell Death Discov* 2024;**10**:438. <https://doi.org/10.1038/s41420-024-02207-9>
135. Norman JS, Li PJ, Kotwani P *et al.* AFP-L3 and DCP strongly predict early hepatocellular carcinoma recurrence after liver transplantation. *J Hepatol* 2023;**79**:1469–77. <https://doi.org/10.1016/j.jhep.2023.08.020>
136. Natali PG, Nicotra MR, Bigotti A *et al.* Expression of the p185 encoded by HER2 oncogene in normal and transformed human tissues. *Int J Cancer* 1990;**45**:457–61. <https://doi.org/10.1002/ijc.2910450314>
137. Lakemeyer L, Sander S, Wittau M *et al.* Diagnostic and prognostic value of CEA and CA19-9 in colorectal cancer. *Diseases* 2021;**9**:21. <https://doi.org/10.3390/diseases9010021>
138. Xu H, Huang K, Lin Y *et al.* Glycosyltransferase GLT8D1 and GLT8D2 serve as potential prognostic biomarkers correlated with tumor immunity in gastric cancer. *BMC Med Genomics* 2023;**16**:123. <https://doi.org/10.1186/s12920-023-01559-y>
139. Luo G, Jin K, Deng S *et al.* Roles of CA19-9 in pancreatic cancer: biomarker, predictor and promoter. *Biochim Biophys Acta Rev Cancer* 2021;**1875**:188409. <https://doi.org/10.1016/j.bbcan.2020.188409>
140. Azizian A, Rühlmann F, Krause T *et al.* CA19-9 for detecting recurrence of pancreatic cancer. *Sci Rep* 2020;**10**:1332. <https://doi.org/10.1038/s41598-020-57930-x>
141. Haugen BR, Alexander EK, Bible KC *et al.* 2015 american thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;**26**:1–133. <https://doi.org/10.1089/thy.2015.0020>
142. Li R, Wu X, Zhao P *et al.* A pan-cancer analysis identifies HDAC11 as an immunological and prognostic biomarker. *FASEB J* 2022;**36**:e22326. <https://doi.org/10.1096/fj.202101742RR>
143. Benard A, Goossens-Beumer IJ, Van Hoesel AQ *et al.* Nuclear expression of histone deacetylases and their histone modifications predicts clinical outcome in colorectal cancer. *Histopathology* 2015;**66**:270–82. <https://doi.org/10.1111/his.12534>
144. Hung SY, Lin HH, Yeh KT *et al.* Histone-modifying genes as biomarkers in hepatocellular carcinoma. *Int J Clin Exp Pathol* 2014;**7**:2496–507.
145. Dong R, Wang T, Dong W *et al.* TGM2-mediated histone serotonylation promotes HCC progression via MYC signalling pathway. *J Hepatol* 2025;**83**:105–18. <https://doi.org/10.1016/j.jhep.2024.12.038>
146. Hu M, Zhu C, Sun R *et al.* Low-input deep learning platform for citrullinated peptide identification, autoantigen discovery and rheumatoid arthritis treatment stratification. *Nat Biomed Eng* 2026. <https://doi.org/10.1038/s41551-026-01628-4>
147. Tang KH, Li S, Khodadadi-Jamayran A *et al.* Combined inhibition of SHP2 and CXCR1/2 promotes antitumor T-cell response in NSCLC. *Cancer Discov* 2022;**12**:47–61. <https://doi.org/10.1158/2159-8290.CD-21-0369>
148. Kepp O, Semeraro M, Bravo-San Pedro JM *et al.* eIF2 α phosphorylation as a biomarker of immunogenic cell death. *Semin Cancer Biol* 2015;**33**:86–92. <https://doi.org/10.1016/j.semcancer.2015.02.004>
149. Bakkenist CJ, Beumer JH, Schmitz JC. ATM serine-1981 phosphorylation is a plausible biomarker. *Cell Cycle*

- 2015;**14**:3207–8. <https://doi.org/10.1080/15384101.2015.1084205>
150. Chen ZX, Mu MY, Yang G *et al.* Hypoxia-induced DTL promotes the proliferation, metastasis, and sorafenib resistance of hepatocellular carcinoma through ubiquitin-mediated degradation of SLTM and subsequent Notch pathway activation. *Cell Death Dis* 2024;**15**:734. <https://doi.org/10.1038/s41419-024-07089-4>
151. Han D, Wang L, Long L *et al.* The E3 ligase TRIM4 facilitates SET ubiquitin-mediated degradation to enhance ER- α action in breast cancer. *Adv Sci* 2022;**9**:2201701. <https://doi.org/10.1002/adv.202201701>
152. Wei J, Zhuang Y, Jiang C *et al.* Cohort-based pan-cancer analysis and experimental studies reveal ISG15 gene as a novel biomarker for prognosis and immunotherapy efficacy prediction. *Cancer Immunol Immunother* 2025;**74**:168. <https://doi.org/10.1007/s00262-025-04026-y>
153. Lee H-H, Wang Y-N, Xia W *et al.* Removal of N-linked glycosylation enhances PD-L1 detection and predicts anti-PD-1/PD-L1 therapeutic efficacy. *Cancer Cell* 2019;**36**:168–78. <https://doi.org/10.1016/j.ccell.2019.06.008>
154. Lai Q-y, He Y-z, Peng X-w *et al.* Histone deacetylase 1 induced by neddylation inhibition contributes to drug resistance in acute myelogenous leukemia. *Cell Commun Signal* 2019;**17**:86. <https://doi.org/10.1186/s12964-019-0393-8>
155. Guan X, Liu R, Wang B *et al.* Inhibition of HDAC2 sensitises antitumour therapy by promoting NLRP3/GSDMD-mediated pyroptosis in colorectal cancer. *Clin Transl Med* 2024;**14**:e1692. <https://doi.org/10.1002/ctm2.1692>
156. Fan X, Guo D, Li S *et al.* Fusidic acid reverses chemoresistance in breast cancer via targeting DDX6 to downregulate GSK-3 β / β -catenin signaling. *Adv Sci* 2025;**12**:e04680. <https://doi.org/10.1002/adv.202504680>
157. Antonarakis ES, Lu C, Lubner B *et al.* Clinical significance of androgen receptor splice variant-7 mRNA detection in circulating tumor cells of men with metastatic castration-resistant prostate cancer treated with first- and second-line abiraterone and enzalutamide. *J Clin Oncol* 2017;**35**:2149–56. <https://doi.org/10.1200/jco.2016.70.1961>
158. Du C, Yi X, Liu W *et al.* MTDH mediates trastuzumab resistance in HER2 positive breast cancer by decreasing PTEN expression through an NF- κ B-dependent pathway. *BMC Cancer* 2014;**14**:869. <https://doi.org/10.1186/1471-2407-14-869>
159. Wang F, Wang S, Wang Z *et al.* Phosphorylated EGFR expression may predict outcome of EGFR-TKIs therapy for the advanced NSCLC patients with wild-type EGFR. *J Exp Clin Cancer Res* 2012;**31**:65. <https://doi.org/10.1186/1756-9966-31-65>
160. Xu MH, Zheng YM, Liang BG *et al.* Deubiquitination of CIB1 by USP14 promotes lenvatinib resistance via the PAK1-ERK1/2 axis in hepatocellular carcinoma. *Int J Biol Sci* 2024;**20**:3269–84. <https://doi.org/10.7150/ijbs.96031>
161. Hu C, Zhang M, Moses N *et al.* The USP10-HDAC6 axis confers cisplatin resistance in non-small cell lung cancer lacking wild-type p53. *Cell Death Dis* 2020;**11**:328. <https://doi.org/10.1038/s41419-020-2519-8>
162. Duarte HO, Rodrigues JG, Gomes C *et al.* ST6Gal1 targets the ectodomain of ErbB2 in a site-specific manner and regulates gastric cancer cell sensitivity to trastuzumab. *Oncogene* 2021;**40**:3719–33. <https://doi.org/10.1038/s41388-021-01801-w>
163. Petrioli R, Licchetta A, Roviello G *et al.* CEA and CA19.9 as early predictors of progression in advanced/metastatic colorectal cancer patients receiving oxaliplatin-based chemotherapy and bevacizumab. *Cancer Invest* 2012;**30**:65–71. <https://doi.org/10.3109/07357907.2011.629380>
164. Chang X, Ye X, Dong L *et al.* Human epididymis protein 4 (HE4) as a serum tumor biomarker in patients with ovarian carcinoma. *Int J Gynecol Cancer* 2011;**21**:852–8. <https://doi.org/10.1097/IGC.0b013e31821a3726>
165. Hires M, Jane E, Kalavaska K *et al.* Glycan signatures for the identification of cisplatin-resistant testicular cancer cell lines: specific glycoproteomics of human chorionic gonadotropin (hCG). *Cancer Med* 2022;**11**:968–82. <https://doi.org/10.1002/cam4.4515>
166. Bast RC Jr, Ravdin P, Hayes DF *et al.* 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;**19**:1865–78. <https://doi.org/10.1200/jco.2001.19.6.1865>
167. Tampellini M, Berruti A, Bitossi R *et al.* Prognostic significance of changes in CA 15-3 serum levels during chemotherapy in metastatic breast cancer patients. *Breast Cancer Res Treat* 2006;**98**:241–8. <https://doi.org/10.1007/s10549-005-9155-y>
168. Carter AM, Tan C, Pozo K *et al.* Phosphoprotein-based biomarkers as predictors for cancer therapy. *Proc Natl Acad Sci USA* 2020;**117**:18401–11. <https://doi.org/10.1073/pnas.2010103117>
169. Eickelschulte S, Kaczorowski A, Janke F *et al.* Digital spatial profiling identifies phospho-JNK as a biomarker for early risk stratification of aggressive prostate cancer. *Front Oncol* 2025;**15**:1572299. <https://doi.org/10.3389/fonc.2025.1572299>
170. Naohiro N, Katsunori Y, Rinako T *et al.* Phospho-Smad3 signaling is predictive biomarker for hepatocellular carcinoma risk assessment in primary biliary cholangitis patients. *Front Biosci (Landmark Ed)* 2021;**26**:1480–92. <https://doi.org/10.52586/5042>
171. Shaw AT, Yeap BY, Mino-Kenudson M *et al.* Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009;**27**:4247–53. <https://doi.org/10.1200/JCO.2009.22.6993>
172. Zhang N, Meng Y, Mao S *et al.* FBXO31-mediated ubiquitination of OGT maintains O-GlcNAcylation homeostasis to restrain endometrial malignancy. *Nat Commun* 2025;**16**:1274. <https://doi.org/10.1038/s41467-025-56633-z>
173. Gao S, Zhang W, Yan N *et al.* The impact of STAT3 and phospho-STAT3 expression on the prognosis and clinicopathology of ovarian cancer: a systematic review and meta-analysis. *J Ovarian Res* 2021;**14**:164. <https://doi.org/10.1186/s13048-021-00918-6>
174. Liu Y, Chen H, Bao H *et al.* Comprehensive characterization of FBXW7 mutational and clinicopathological profiles in human colorectal cancers. *Front Oncol* 2023;**13**:1154432. <https://doi.org/10.3389/fonc.2023.1154432>
175. Li D, Cai Q, Li L *et al.* Novel post-translational modifications in cancer. *Oncology* 2024;**27**:3–14. <https://doi.org/10.1515/oncologie-2024-0533>

176. Mullard A. FDA approves 100th small-molecule kinase inhibitor. *Nat Rev Drug Discov* 2025;**24**:891–5. <https://doi.org/10.1038/d41573-025-00188-7>
177. Dai W, Qiao X, Fang Y *et al*. Epigenetics-targeted drugs: current paradigms and future challenges. *Sig Transduct Target Ther* 2024;**9**:332. <https://doi.org/10.1038/s41392-024-02039-0>
178. Kazandjian D, Blumenthal GM, Yuan W *et al*. FDA approval of gefitinib for the treatment of patients with metastatic EGFR mutation-positive non-small cell lung cancer. *Clin Cancer Res* 2016;**22**:1307–12. <https://doi.org/10.1158/1078-0432.CCR-15-2266>
179. Shepherd FA, Pereira JR, Ciuleanu T *et al*. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;**353**:123–32. <https://doi.org/10.1056/NEJMoa050753>
180. Dungo RT, Keating GM. Afatinib: first global approval. *Drugs* 2013;**73**:1503–15. <https://doi.org/10.1007/s40265-013-0111-6>
181. Greig SL. Osimertinib: first global approval. *Drugs* 2016;**76**:263–73. <https://doi.org/10.1007/s40265-015-0533-4>
182. Malik SM, Maher VE, Bijwaard KE *et al*. US Food and Drug Administration approval: crizotinib for treatment of advanced or metastatic non-small cell lung cancer that is anaplastic lymphoma kinase positive. *Clin Cancer Res* 2014;**20**:2029–34. <https://doi.org/10.1158/1078-0432.CCR-13-3077>
183. Larkins E, Blumenthal GM, Chen H *et al*. FDA approval: alectinib for the treatment of metastatic, ALK-positive non-small cell lung cancer following crizotinib. *Clin Cancer Res* 2016;**22**:5171–6. <https://doi.org/10.1158/1078-0432.CCR-16-1293>
184. Markham A. Brigatinib: first global approval. *Drugs* 2017;**77**:1131–5. <https://doi.org/10.1007/s40265-017-0776-3>
185. Khozin S, Blumenthal GM, Zhang L *et al*. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. *Clin Cancer Res* 2015;**21**:2436–9. <https://doi.org/10.1158/1078-0432.CCR-14-3157>
186. Syed YY. Lorlatinib: first global approval. *Drugs* 2019;**79**:93–8. <https://doi.org/10.1007/s40265-018-1041-0>
187. Agrawal T. Efficacy and safety of ensartinib in the treatment of non-small cell lung cancer: a systematic review of clinical trials. *J Oncol Pharm Pract* 2025;10781552251387058. <https://doi.org/10.1177/10781552251387058>
188. Odogwu L, Mathieu L, Blumenthal G *et al*. FDA approval summary: dabrafenib and trametinib for the treatment of metastatic non-small cell lung cancers harboring BRAF V600E mutations. *Oncologist* 2018;**23**:740–5. <https://doi.org/10.1634/theoncologist.2017-0642>
189. Mehta GU, Vellanki PJ, Ren Y *et al*. FDA approval summary: fam-trastuzumab deruxtecan-nxki for unresectable or metastatic non-small cell lung cancer with activating HER2 mutations. *Oncologist* 2024;**29**:667–71. <https://doi.org/10.1093/oncolo/oyae151>
190. Lee A. Zongertinib: first approval. *Drugs* 2026;**86**:397–401. <https://doi.org/10.1007/s40265-025-02265-y>
191. Awad MM, Le Bruchec Y, Lu B *et al*. Selective histone deacetylase inhibitor ACY-241 (citarinostat) plus nivolumab in advanced non-small cell lung cancer: results from a phase Ib study. *Front Oncol* 2021;**11**:696512. <https://doi.org/10.3389/fonc.2021.696512>
192. Gettinger S, Goldberg S, Chiang A *et al*. MA15. 07 NC318, an anti-siglec-15 humanized mAb, alone and in combination with pembrolizumab in immunotherapy pretreated NSCLC. *J Thorac Oncol* 2023;**18**:S155. <https://doi.org/10.1016/j.jtho.2023.09.224>
193. Wu X, Chan L, Zhu D *et al*. Mitosis targeting in non-small lung cancer cells by inhibition of PAD4. *Heliyon* 2024;**10**:e27313. <https://doi.org/10.1016/j.heliyon.2024.e27313>
194. Zauderer MG, Szlosarek PW, Le Moulec S *et al*. EZH2 inhibitor tazemetostat in patients with relapsed or refractory, BAP1-inactivated malignant pleural mesothelioma: a multicentre, open-label, phase 2 study. *Lancet Oncol* 2022;**23**:758–67. [https://doi.org/10.1016/s1470-2045\(22\)00277-7](https://doi.org/10.1016/s1470-2045(22)00277-7)
195. Cao J, Chen G, Qiu L *et al*. Efficacy and safety of tazemetostat, an EZH2 inhibitor, in Chinese patients with relapsed/refractory follicular lymphoma: a multicentre, single-arm, phase 2 study. *eClinicalMedicine* 2025;**87**:103399. <https://doi.org/10.1016/j.eclinm.2025.103399>
196. Phase I Dose Escalation and Expansion Study of Tazemetostat in Combination with Topotecan and Pembrolizumab in Recurrent Small Cell Lung Cancer. *ClinicalTrials.gov* [Internet]. 2022 Apr 29 [updated 2026 Apr 13]. <https://clinicaltrials.gov/study/NCT05353439>
197. Hanrahan AJ, Chen Z, Rosen N *et al*. BRAF—a tumour-agnostic drug target with lineage-specific dependencies. *Nat Rev Clin Oncol* 2024;**21**:224–47. <https://doi.org/10.1038/s41571-023-00852-0>
198. Martínez-Gamboa DA, Kaner J. Revumenib: a new era in acute leukemia treatment. *Trends Cancer* 2025;**11**:81–3. <https://doi.org/10.1016/j.trecan.2025.01.006>
199. Wang ES, Montesinos P, Foran J *et al*. Ziftomenib in relapsed or refractory NPM1-mutated AML. *J Clin Oncol* 2025;**43**:3381–90. <https://doi.org/10.1200/JCO-25-01694>
200. Nicosia L, Spencer GJ, Brooks N *et al*. Therapeutic targeting of EP300/CBP by bromodomain inhibition in hematologic malignancies. *Cancer Cell* 2023;**41**:2136–53. <https://doi.org/10.1016/j.ccell.2023.11.001>
201. Van Gils N, Canales TM, Vermue E *et al*. The novel oral BET-CBP/p300 dual inhibitor NEO2734 is highly effective in eradicating acute myeloid leukemia blasts and stem/progenitor cells. *Hemasphere* 2021;**5**:e610. <https://doi.org/10.1097/HS.9.0000000000000610>
202. Senapati J, Muftuoglu M, Ishizawa J *et al*. A Phase I study of milademetan (DS3032b) in combination with low dose cytarabine with or without venetoclax in acute myeloid leukemia: clinical safety, efficacy, and correlative analysis. *Blood Cancer J* 2023;**13**:101. <https://doi.org/10.1038/s41408-023-00871-1>
203. Bewersdorf JP, Mi X, Lu B *et al*. Phase Ib study of PRT543, an oral protein arginine methyltransferase 5 (PRMT5) inhibitor, in patients with advanced splicing factor-mutant myeloid malignancies. *Leukemia* 2025;**39**:765–9. <https://doi.org/10.1038/s41375-025-02515-8>

204. Ochiwa H, Ailiken G, Yokoyama M *et al.* TAS4464, a NEDD8-activating enzyme inhibitor, activates both intrinsic and extrinsic apoptotic pathways via c-Myc-mediated regulation in acute myeloid leukemia. *Oncogene* 2021;**40**:1217–30. <https://doi.org/10.1038/s41388-020-01586-4>
205. Elkinson S, McCormack PL. Pomalidomide: first global approval. *Drugs* 2013;**73**:595–604. <https://doi.org/10.1007/s40265-013-0047-x>
206. Raedler LA. Revlimid (lenalidomide) now FDA approved as first-line therapy for patients with multiple myeloma. *Am Health Drug Benefits* 2016;**9**:140–3. <https://www.jhponline.com/>
207. Palumbo A, Facon T, Sonneveld P *et al.* Thalidomide for treatment of multiple myeloma: 10 years later. *Blood* 2008;**111**:3968–77. <https://doi.org/10.1182/blood-2007-10-117457>
208. Lonial S, Popat R, Hulin C *et al.* Ixerdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): a multicentre, multicohort, open-label, phase 1/2 trial. *Lancet Haematol* 2022;**9**:e822–32. [https://doi.org/10.1016/s2352-3026\(22\)00290-3](https://doi.org/10.1016/s2352-3026(22)00290-3)
209. Hartley-Brown MA, Mo CC, Nadeem O *et al.* Mezigdomide—a novel cereblon E3 ligase modulator under investigation in relapsed/refractory multiple myeloma. *Cancers* 2024;**16**:1166. <https://doi.org/10.3390/cancers16061166>
210. Raje N, Chau I, Hyman DM *et al.* Vemurafenib in patients with relapsed refractory multiple myeloma harboring BRAF (V600) mutations: a cohort of the histology-independent VEBASKET study. *JCO Precis Oncol* 2018;**2**:1. <https://doi.org/10.1200/po.18.00070>
211. Giesen N, Chatterjee M, Scheid C *et al.* A phase 2 clinical trial of combined BRAF/MEK inhibition for BRAFV600E-mutated multiple myeloma. *Blood* 2023;**141**:1685–90. <https://doi.org/10.1182/blood.2022017789>
212. Lunghi P, Giuliani N, Mazzera L *et al.* Targeting MEK/MAPK signal transduction module potentiates ATO-induced apoptosis in multiple myeloma cells through multiple signaling pathways. *Blood* 2008;**112**:2450–62. <https://doi.org/10.1182/blood-2007-10-114348>
213. Niesvizky R, Ely S, Mark T *et al.* Phase 2 trial of the histone deacetylase inhibitor romidepsin for the treatment of refractory multiple myeloma. *Cancer* 2011;**117**:336–42. <https://doi.org/10.1002/cncr.25584>
214. Corradini S, Arsalani S, Maksimos M *et al.* Investigating the therapeutic potential of the novel CBP/p300 protein degrader CBPD409 in multiple myeloma. *Blood* 2024;**144**:5828. <https://doi.org/10.1182/blood-2024-209620>
215. Nguyen HP, Liu E, Walker BA *et al.* Synergistic effects of type I PRMT1 and Type II PRMT5 inhibitors against multiple myeloma. *Blood* 2023;**142**:6593. <https://doi.org/10.1182/blood-2023-173852>
216. Jiang L, He Q, Chen X *et al.* Inhibition of proteasomal deubiquitinases USP14 and UCHL5 overcomes tyrosine kinase inhibitor resistance in chronic myeloid leukaemia. *Clin Transl Med* 2022;**12**:e1038. <https://doi.org/10.1002/ctm2.1038>
217. Chen X, Shi X, Zhao C *et al.* Anti-rheumatic agent auranofin induced apoptosis in chronic myeloid leukemia cells resistant to imatinib through both Bcr/Abl-dependent and -independent mechanisms. *Oncotarget* 2014;**5**:9118–32. <http://doi.org/10.18632/oncotarget.2361>
218. Mann BS, Johnson JR, Cohen MH *et al.* FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. *Oncologist* 2007;**12**:1247–52. <https://doi.org/10.1634/theoncologist.12-10-1247>
219. Vandermolen KM, McCulloch W, Pearce CJ *et al.* Romidepsin (Istodax, NSC 630176, FR901228, FK228, depsipeptide): a natural product recently approved for cutaneous T-cell lymphoma. *J Antibiot* 2011;**64**:525–31. <https://doi.org/10.1038/ja.2011.35>
220. Lee H-Z, Kwitkowski VE, Del Valle PL *et al.* FDA approval: belinostat for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. *Clin Cancer Res* 2015;**21**:2666–70. <https://doi.org/10.1158/1078-0432.CCR-14-3119>
221. Shi Y, Jia B, Xu W *et al.* Chidamide in relapsed or refractory peripheral T cell lymphoma: a multicenter real-world study in China. *J Hematol Oncol* 2017;**10**:69. <https://doi.org/10.1186/s13045-017-0439-6>
222. Chen X, Xie L, Zhu J *et al.* Real-world efficacy of chidamide plus R-CHOP in newly diagnosed double-expressor diffuse large B-cell lymphoma. *Ther Adv Hematol* 2024;**15**:20406207241292446. <https://doi.org/10.1177/20406207241292446>
223. Lin J, Huang Z, Cai Z *et al.* Tucidinostat plus pediatric-inspired chemotherapy for newly diagnosed adult ETP-ALL/LBL: a single-arm, phase 2 trial. *J Hematol Oncol* 2024;**17**:101. <https://doi.org/10.1186/s13045-024-01624-8>
224. Fornasier G, Francescon S, Baldo P. An update of efficacy and safety of cetuximab in metastatic colorectal cancer: a narrative review. *Adv Ther* 2018;**35**:1497–509. <https://doi.org/10.1007/s12325-018-0791-0>
225. Tabernero J, Grothey A, Van Cutsem E *et al.* Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. *J Clin Oncol* 2021;**39**:273–84. <https://doi.org/10.1200/JCO.20.02088>
226. Buzard B, Douglass L, Gustafson B *et al.* Response to osimertinib in a colorectal cancer patient with an EGFR T790M mutation: a case report. *World J Gastrointest Oncol* 2023;**15**:1829–34. <https://doi.org/10.4251/wjgo.v15.i10.1829>
227. Ni W, Mo H, Liu Y *et al.* Targeting cholesterol biosynthesis promotes anti-tumor immunity by inhibiting long non-coding RNA SNHG29-mediated YAP activation. *Mol Ther* 2021;**29**:2995–3010. <https://doi.org/10.1016/j.ymthe.2021.05.012>
228. Brana I, Shapiro G, Johnson ML *et al.* Initial results from a dose finding study of TNO155, a SHP2 inhibitor, in adults with advanced solid tumors. *J Clin Oncol* 2021;**39**:3005. http://doi.org/10.1200/JCO.2021.39.15_suppl.3005
229. Kuang C, Cai M, Risnik D *et al.* Abstract 1763: NEO2734, a novel dual bromodomain and histone acetyltransferase inhibitor, in the treatment of colorectal cancer. *Cancer Res* 2020;**80**:1763. <https://doi.org/10.1158/1538-7445.am20-1763>
230. Dong X, Li K, Wang R *et al.* Targeting Skp2 by tanshinone IIA overcomes chemoresistance in colorectal cancer. *Cell*

- Biol Toxicol* 2025;**41**:135. <https://doi.org/10.1007/s10565-025-10084-w>
231. An T, Gong Y, Li X *et al*. USP7 inhibitor P5091 inhibits Wnt signaling and colorectal tumor growth. *Biochem Pharmacol* 2017;**131**:29–39. <https://doi.org/10.1016/j.bcp.2017.02.011>
 232. Tan X, Zhang Z, Liu P *et al*. RETRACTED ARTICLE: inhibition of EZH2 enhances the therapeutic effect of 5-FU via PUMA up-regulation in colorectal cancer. *Cell Death Dis* 2020;**11**:1061. <https://doi.org/10.1038/s41419-020-03266-3>
 233. Wang M, Zhang Z, Chen M *et al*. FDW028, a novel FUT8 inhibitor, impels lysosomal proteolysis of B7-H3 via chaperone-mediated autophagy pathway and exhibits potent efficacy against metastatic colorectal cancer. *Cell Death Dis* 2023;**14**:495. <https://doi.org/10.1038/s41419-023-06027-0>
 234. Yin Y, Liang Z, Li B *et al*. Embryonic ectoderm development (EED) inhibitor APG-5918 overcomes immunomodulatory drug (IMiD) resistance as monotherapy and synergizes with IMiDs/cereblon E3 ligase modulators (CELMoDs) in preclinical models of multiple myeloma (MM). *Blood* 2025;**146**:1528. <https://doi.org/10.1182/blood-2025-1528>
 235. Bang YJ, Van Cutsem E, Feyereislova A *et al*. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *The Lancet* 2010;**376**:687–97. [https://doi.org/10.1016/s0140-6736\(10\)61121-x](https://doi.org/10.1016/s0140-6736(10)61121-x)
 236. Zhu T, Zou X, Yang C *et al*. Neutrophil extracellular traps promote gastric cancer metastasis by inducing epithelial-mesenchymal transition. *Int J Mol Med* 2021;**48**:127. <https://doi.org/10.3892/ijmm.2021.4960>
 237. Yu Z, Jiang X, Qin L *et al*. A novel UBE2T inhibitor suppresses Wnt/ β -catenin signaling hyperactivation and gastric cancer progression by blocking RACK1 ubiquitination. *Oncogene* 2021;**40**:1027–42. <https://doi.org/10.1038/s41388-020-01572-w>
 238. Huang X, Yi N, Zhu P *et al*. Sorafenib-induced macrophage extracellular traps via ARHGDI4/IL4/PADI4 axis confer drug resistance through inhibiting ferroptosis in hepatocellular carcinoma. *Biol Direct* 2024;**19**:110. <https://doi.org/10.1186/s13062-024-00560-4>
 239. Yi N, Zhang L, Huang X *et al*. Lenvatinib-activated ND-UFA4L2/IL33/PADI4 pathway induces neutrophil extracellular traps that inhibit cuproptosis in hepatocellular carcinoma. *Cell Oncol* 2025;**48**:487–504. <https://doi.org/10.1007/s13402-024-01013-w>
 240. Gautam J, Wu J, Lally JSV *et al*. ACLY inhibition promotes tumour immunity and suppresses liver cancer. *Nature* 2025;**645**:507–17. <https://doi.org/10.1038/s41586-025-09297-0>
 241. Lu J, Wu H, Zhan P *et al*. PSMD14-mediated deubiquitination of CARM1 facilitates the proliferation and metastasis of hepatocellular carcinoma by inducing the transcriptional activation of FERMT1. *Cell Death Dis* 2025;**16**:141. <https://doi.org/10.1038/s41419-025-07416-3>
 242. Gu M, Toh TB, Hooi L *et al*. Nanodiamond-mediated delivery of a G9a inhibitor for hepatocellular carcinoma therapy. *ACS Appl Mater Interfaces* 2019;**11**:45427–41. <https://doi.org/10.1021/acsami.9b16323>
 243. Namgung Y, Kim SY, Kim I. Down-regulation of survivin by BIX-01294 pretreatment overcomes resistance of hepatocellular carcinoma cells to TRAIL. *Anticancer Res* 2019;**39**:3571–8. <https://doi.org/10.21873/anticancer.13503>
 244. Ding Q, Cai J, Jin L *et al*. A novel small molecule ZYZ384 targeting SMYD3 for hepatocellular carcinoma via reducing H3K4 trimethylation of the Rac1 promoter. *MedComm* 2024;**5**:e711. <https://doi.org/10.1002/mco2.711>
 245. Chiba T, Saito T, Yuki K *et al*. Histone lysine methyltransferase SUV39H1 is a potent target for epigenetic therapy of hepatocellular carcinoma. *Int J Cancer* 2015;**136**:289–98. <https://doi.org/10.1002/ijc.28985>
 246. Uysal-Onganer P, D'alessio S, Mortoglou M *et al*. Peptidyl-arginine deiminase inhibitor application, using Cl-amidine, PAD2, PAD3 and PAD4 isozyme-specific inhibitors in pancreatic cancer cells, reveals roles for PAD2 and PAD3 in cancer invasion and modulation of extracellular vesicle signatures. *Int J Mol Sci* 2021;**22**:1396. <https://doi.org/10.3390/ijms22031396>
 247. Umemura K, Akiyama Y, Shimada S *et al*. PAD2-mediated histone citrullination drives tumor progression by enhancing cell proliferation and modifying the microenvironment in pancreatic cancer. *Mol Cancer Res* 2025;**23**:844–58. <https://doi.org/10.1158/1541-7786.Mcr-24-1095>
 248. Petrova E, Matevossian A, Resh MD. Hedgehog acyltransferase as a target in pancreatic ductal adenocarcinoma. *Oncogene* 2015;**34**:263–8. <https://doi.org/10.1038/onc.2013.575>
 249. Petrova E, Rios-Esteves J, Ouerfelli O *et al*. Inhibitors of hedgehog acyltransferase block sonic hedgehog signaling. *Nat Chem Biol* 2013;**9**:247–9. <https://doi.org/10.1038/nchembio.1184>
 250. Yang Y, Cao L, Guo Z *et al*. Deubiquitinase UCHL5 stabilizes ELK3 to potentiate cancer stemness and tumor progression in pancreatic adenocarcinoma (PAAD). *Exp Cell Res* 2022;**421**:113402. <https://doi.org/10.1016/j.yexcr.2022.113402>
 251. Rios Perez MV, Roife D, Dai B *et al*. Antineoplastic effects of auranofin in human pancreatic adenocarcinoma preclinical models. *Surg Open Sci* 2019;**1**:56–63. <https://doi.org/10.1016/j.sopen.2019.05.004>
 252. Huang F, Li C, Chen Y *et al*. Succinate dehydrogenase B palmitoylation promotes T cell exhaustion through the H3K27ac-PD1 axis in pancreatic cancer. *Cancer Lett* 2026;**642**:218277. <https://doi.org/10.1016/j.canlet.2026.218277>
 253. Wedam S, Fashoyin-Aje L, Gao X *et al*. FDA approval summary: ado-trastuzumab emtansine for the adjuvant treatment of HER2-positive early breast cancer. *Clin Cancer Res* 2020;**26**:4180–5. <https://doi.org/10.1158/1078-0432.CCR-19-3980>
 254. Blumenthal GM, Scher NS, Cortazar P *et al*. First FDA approval of dual anti-HER2 regimen: pertuzumab in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer. *Clin Cancer Res* 2013;**19**:4911–6. <https://doi.org/10.1158/1078-0432.Ccr-13-1212>
 255. Ryan Q, Ibrahim A, Cohen MH *et al*. FDA drug approval summary: lapatinib in combination with capecitabine for previously treated metastatic breast cancer that overexpresses

- HER-2. *Oncologist* 2008;**13**:1114–9. <https://doi.org/10.1634/theoncologist.2008-0816>
256. Singh H, Walker AJ, Amiri-Kordestani L *et al*. US food and drug administration approval: neratinib for the extended adjuvant treatment of early-stage HER2-positive breast cancer. *Clin Cancer Res* 2018;**24**:3486–91. <https://doi.org/10.1158/1078-0432.CCR-17-3628>
 257. Narayan P, Prowell TM, Gao JJ *et al*. FDA approval summary: alpelisib plus fulvestrant for patients with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer. *Clin Cancer Res* 2021;**27**:1842–9. <https://doi.org/10.1158/1078-0432.CCR-20-3652>
 258. Pelosci A. FDA approves capivasertib plus fulvestrant in advanced HR+, HER2–breast cancer. *Cancer Network* 2023. Retrieved from <https://www.cancernetwork.com>.
 259. Yardley DA. Adverse event management of mTOR inhibitors during treatment of hormone receptor-positive advanced breast cancer: considerations for oncologists. *Clin Breast Cancer* 2014;**14**:297–308. <https://doi.org/10.1016/j.clbc.2014.03.002>
 260. Reguera-Núñez E, Xu P, Chow A *et al*. Therapeutic impact of nintedanib with paclitaxel and/or a PD-L1 antibody in pre-clinical models of orthotopic primary or metastatic triple negative breast cancer. *J Exp Clin Cancer Res* 2019;**38**:16. <https://doi.org/10.1186/s13046-018-0999-5>
 261. Li C, Du L, Ren Y *et al*. SKP2 promotes breast cancer tumorigenesis and radiation tolerance through PDCD4 ubiquitination. *J Exp Clin Cancer Res* 2019;**38**:76. <https://doi.org/10.1186/s13046-019-1069-3>
 262. Kurani H, Razavipour SF, Harikumar KB *et al*. DOT1L is a novel cancer stem cell target for triple-negative breast cancer. *Clin Cancer Res* 2022;**28**:1948–65. <https://doi.org/10.1158/1078-0432.Ccr-21-1299>
 263. Perabo FG, Yoo S, Chandhasin C *et al*. 210P TACH101, a first-in-class KDM4 inhibitor for treatment of triple-negative breast cancer. *Ann Oncol* 2021;**32**:S450–1. <https://doi.org/10.1016/j.annonc.2021.08.492>
 264. Metzger E, Stepputtis SS, Strietz J *et al*. KDM4 inhibition targets breast cancer stem-like cells. *Cancer Res* 2017;**77**:5900–12. <https://doi.org/10.1158/0008-5472.Can-17-1754>
 265. Pignata S, Oza A, Hall G *et al*. Overall survival with maintenance olaparib in platinum-sensitive relapsed ovarian cancer by somatic or germline BRCA and homologous recombination repair mutation status. *Br J Cancer* 2025;**132**:725–32. <https://doi.org/10.1038/s41416-025-02966-x>
 266. Moore K, Colombo N, Scambia G *et al*. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018;**379**:2495–505. <https://doi.org/10.1056/NEJMoa1810858>
 267. González-Martín A, Pothuri B, Vergote I *et al*. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2019;**381**:2391–402. <https://doi.org/10.1056/NEJMoa1910962>
 268. Monk BJ, Parkinson C, Lim MC *et al*. A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45). *J Clin Oncol* 2022;**40**:3952–64. <https://doi.org/10.1200/JCO.22.01003>
 269. Bitler BG, Wu S, Park PH *et al*. ARID1A-mutated ovarian cancers depend on HDAC6 activity. *Nat Cell Biol* 2017;**19**:962–73. <https://doi.org/10.1038/ncb3582>
 270. Lee EK, Tan-Wasielewski Z, Matulonis UA *et al*. Results of an abbreviated phase Ib study of the HDAC6 inhibitor ricolinostat and paclitaxel in recurrent ovarian, fallopian tube, or primary peritoneal cancer. *Gynecol Oncol Rep* 2019;**29**:118–22. <https://doi.org/10.1016/j.gore.2019.07.010>
 271. Yoo J, Jeon YH, Lee DH *et al*. HDAC6-selective inhibitors enhance anticancer effects of paclitaxel in ovarian cancer cells. *Oncol Lett* 2021;**21**:201. <https://doi.org/10.3892/ol.2021.12462>
 272. Kim JY, Han SY, Yoo J *et al*. HDAC8-selective inhibition by PCI-34051 enhances the anticancer effects of ACY-241 in ovarian cancer cells. *Int J Mol Sci* 2022;**23**:8645. <https://doi.org/10.3390/ijms23158645>
 273. Guruviah P, Chava S, Sun CW *et al*. ATAD2 is a driver and a therapeutic target in ovarian cancer that functions by upregulating CENPE. *Cell Death Dis* 2023;**14**:456. <https://doi.org/10.1038/s41419-023-05993-9>
 274. Wada M, Kukita A, Sone K *et al*. Epigenetic modifier SETD8 as a therapeutic target for high-grade serous ovarian cancer. *Biomolecules* 2020;**10**:1686. <https://doi.org/10.3390/biom10121686>
 275. Chava S, Bugide S, Edwards YJK *et al*. Disruptor of telomeric silencing 1-like promotes ovarian cancer tumor growth by stimulating pro-tumorigenic metabolic pathways and blocking apoptosis. *Oncogenesis* 2021;**10**:48. <https://doi.org/10.1038/s41389-021-00339-6>
 276. Corr BR, Moroney MR, Woodruff E *et al*. Combination CDC-like kinase inhibition (CLK)/Dual-specificity tyrosine-regulated kinase (DYRK) and taxane therapy in CTNNB1-mutated endometrial cancer. 2023. *bioRxiv*, <https://pubmed.ncbi.nlm.nih.gov/37066339/>, 6 April 2023, preprint: not peer reviewed.
 277. Huang P, Almeciga-Pinto I, Jarpe M *et al*. Selective HDAC inhibition by ACY-241 enhances the activity of paclitaxel in solid tumor models. *Oncotarget* 2017;**8**:2694–707. <https://doi.org/10.18632/oncotarget.13738>
 278. Chen Z, Wang M, Wu D *et al*. Discovery of CBPD-409 and CBPD-268 as highly potent and orally efficacious CBP/p300 PROTAC degraders for the treatment of castration-resistant prostate cancer. *Cancer Res* 2024;**84**:4504. <https://doi.org/10.1158/1538-7445.AM2024-4504>
 279. Chen L, Zhang J, Liu W *et al*. HKI-357 inhibits castration-resistant prostate cancer by targeting UBE2C via the AKT signaling pathway. *Biochem Pharmacol* 2025;**242**:117410. <https://doi.org/10.1016/j.bcp.2025.117410>
 280. Zhang Y, Su M, Chen Y *et al*. EHMT2-mediated R-loop formation promotes the malignant progression of prostate cancer via activating Aurora B. *Clin Transl Med* 2025;**15**:e70164. <https://doi.org/10.1002/ctm2.70164>
 281. Smith T, White T, Chen Z *et al*. The KDM5 inhibitor PBIT reduces proliferation of castration-resistant prostate cancer cells via cell cycle arrest and the induction of senescence. *Exp Cell Res* 2024;**437**:113991. <https://doi.org/10.1016/j.yexcr.2024.113991>
 282. Lorient Y, Necchi A, Park Se H *et al*. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med* 2019;**381**:338–48. <https://doi.org/10.1056/NEJMoa1817323>

283. Zhang X, Chen Z, He X *et al.* SUMOylation of SETD8 promotes tumor growth by methylating and stabilizing MYC in bladder cancer. *Adv Sci* 2025;**12**:e2501734. <https://doi.org/10.1002/adv.202501734>
284. Wang S, Klein SO, Urban S *et al.* Structure-guided design of a selective inhibitor of the methyltransferase KMT9 with cellular activity. *Nat Commun* 2024;**15**:43. <https://doi.org/10.1038/s41467-023-44243-6>
285. Deeks ED. Belzutifan: first approval. *Drugs* 2021;**81**:1921–7. <https://doi.org/10.1007/s40265-021-01606-x>
286. Tu R, Ma J, Chen Y *et al.* USP7 depletion potentiates HIF2 α degradation and inhibits clear cell renal cell carcinoma progression. *Cell Death Dis* 2024;**15**:749. <https://doi.org/10.1038/s41419-024-07136-0>
287. Specenier P, Vermorken JB. Cetuximab: its unique place in head and neck cancer treatment. *Biologics* 2013;**7**:77–90. <https://doi.org/10.2147/BTT.S43628>
288. Zhang W, Cheng J, Diao P *et al.* Therapeutically targeting head and neck squamous cell carcinoma through synergistic inhibition of LSD1 and JMJD3 by TCP and GSK-J1. *Br J Cancer* 2020;**122**:528–38. <https://doi.org/10.1038/s41416-019-0680-6>
289. Ho AL, Brana I, Haddad R *et al.* Tipifarnib in head and neck squamous cell carcinoma with HRAS mutations. *J Clin Oncol* 2021;**39**:1856–64. <https://doi.org/10.1200/jco.20.02903>
290. Li M, Sun F, Wang J *et al.* SUV39H1 epigenetically modulates the MCP1-AURKA signaling axis to enhance neuroblastoma tumorigenesis. *Oncogene* 2024;**43**:3306–20. <https://doi.org/10.1038/s41388-024-03164-4>
291. Sangha R, Jamal R, Spratlin J *et al.* A first-in-human phase I trial of daily oral zelenistat, a N-myristoyltransferase inhibitor, in patients with advanced solid tumors and relapsed/refractory B-cell lymphomas. *Invest New Drugs* 2024;**42**:386–93. <https://doi.org/10.1007/s10637-024-01448-w>
292. Therachiyil L, Surendranath A, Anand A *et al.* Proteomics-driven cancer biomarkers for early detection and targeted therapy: insights from the Middle East. *J Proteome Res* 2026;**25**:21–40. <https://doi.org/10.1021/acs.jproteome.5c00949>
293. Yu J, Gui X, Zou Y *et al.* A proteogenomic analysis of cervical cancer reveals therapeutic and biological insights. *Nat Commun* 2024;**15**:10114. <https://doi.org/10.1038/s41467-024-53830-0>
294. Abelin JG, Bergstrom EJ, Rivera KD *et al.* Workflow enabling deepscale immunopeptidome, proteome, ubiquitylome, phosphoproteome, and acetylome analyses of sample-limited tissues. *Nat Commun* 2023;**14**:1851. <https://doi.org/10.1038/s41467-023-37547-0>
295. Hu B, He R, Pang K *et al.* High-resolution spatially resolved proteomics of complex tissues based on microfluidics and transfer learning. *Cell* 2025;**188**:734–48. <https://doi.org/10.1016/j.cell.2024.12.023>
296. Makhmut A, Qin D, Fritzsche S *et al.* A framework for ultra-low-input spatial tissue proteomics. *Cell Syst* 2023;**14**:1002–14. <https://doi.org/10.1016/j.cels.2023.10.003>
297. Mund A, Coscia F, Kriston A *et al.* Deep visual proteomics defines single-cell identity and heterogeneity. *Nat Biotechnol* 2022;**40**:1231–40. <https://doi.org/10.1038/s41587-022-01302-5>
298. Keren L, Bosse M, Thompson S *et al.* MIBI-TOF: a multiplexed imaging platform relates cellular phenotypes and tissue structure. *Sci Adv* 2019;**5**:eaax5851. <https://doi.org/10.1126/sciadv.aax5851>
299. Xiao X, Hu M, Gao L *et al.* Low-input redoxomics facilitates global identification of metabolic regulators of oxidative stress in the gut. *Sig Transduct Target Ther* 2025;**10**:8. <https://doi.org/10.1038/s41392-024-02094-7>
300. Abbatiello SE, Schilling B, Mani D *et al.* Large-scale interlaboratory study to develop, analytically validate and apply highly multiplexed, quantitative peptide assays to measure cancer-relevant proteins in plasma. *Mol Cell Proteomics* 2015;**14**:2357–74. <https://doi.org/10.1074/mcp.M114.047050>
301. Kennedy JJ, Abbatiello SE, Kim K *et al.* Demonstrating the feasibility of large-scale development of standardized assays to quantify human proteins. *Nat Methods* 2014;**11**:149–55. <https://doi.org/10.1038/NMETH.2763>
302. Babur Ö, Luna A, Korkut A *et al.* Causal interactions from proteomic profiles: molecular data meet pathway knowledge. *Patterns* 2021;**2**:100257. <https://doi.org/10.1016/j.patt.2021.100257>

Received: 9 February 2026. Revised: 29 April 2026. Accepted: 30 April 2026

© The Author(s) 2026. Published by Oxford University Press on behalf of the West China School of Medicine & West China Hospital of Sichuan University. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site-for further information please contact journals.permissions@oup.com