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REVIEW

Drugging non-canonical kinases in cancer therapeutics: Molecular targets, underlying mechanisms and small-molecule inhibitors

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Abstract Non-canonical kinases (NCKs) are emerging as druggable targets in oncology, yet a comprehensive map linking their molecular mechanisms and targeting strategies to small-molecule modulators is lacking. Based on the hallmarks of cancer, we explain how NCKs buffer replication stress to preserve genome integrity, reprogram metabolic and stress pathways, coordinate angiogenesis and invasion, and support durable remodeling of the immune-tumor microenvironment. We review preclinical progress from hit identification to lead optimization, highlighting exploitable ATP-site and allosteric pockets, targeted protein degradation, and rational dual-node designs, all supported by structural insights and phenotypic discovery. Early clinical signals from mTOR, ATR, and DNA-PKcs inhibitors, along with late-preclinical programs targeting eEF2K, TBK1, FAM20C, TRPM7, and WNKs, reveal context-dependent NCK vulnerabilities. With further exploration of NCK functions and structures, additional targeted drugs are likely to be developed, potentially transforming non-canonical kinase biology into durable precision oncology.

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1. Introduction

Protein kinases are key components in cellular signaling networks, regulating proliferation, survival, metabolism, and stress responses. Small-molecule inhibitors of protein kinases have established a paradigm in cancer therapy[1,2]. However, the human kinome includes a variety of underexplored non-canonical kinases (NCKs) beyond traditional eukaryotic protein kinases (ePKs), such as classical atypical protein kinases (aPKs)—enzymes that differ from the ePK catalytic domain in sequence or structure but still retain kinase activity—as well as a subset of ePKs that maintain a protein-kinase-like (PKL) fold yet harbor non-canonical active-site motifs or regulatory elements, such as with-No-Lysine [K] kinases (WNKs), haploid germ cell-specific nuclear protein kinase (HASPIN), maternal embryonic leucine zipper kinase (MELK), selected cyclin-dependent kinases (CDKs). In this review, we use the term "canonical kinases" to denote classical Hanks-type ePKs with a bilobal PKL fold and conserved VAIK/HRD/DFG motifs that populate archetypal signaling cascades such as receptor tyrosine kinase−rat sarcom−rapidly accelerated fibrosarcoma−mitogen-activated protein kinase kinase−extracellular signal-regulated kinase (RTK−RAS−RAF−MEK−ERK) and phosphoinositide 3-kinase−protein kinase B−mechanistic target of rapamycin (PI3K−AKT−mTOR). By contrast, we define NCKs as kinases or kinase-like proteins that deviate from this blueprint at the level of catalytic architecture, conserved motifs, or core regulatory elements, forming a structurally distinct yet therapeutically relevant subset of the kinome[3].

From the perspective of tumor biology hallmarks, NCKs are closely linked to multiple malignant phenotypes. Regarding genomic instability and replication stress, phosphatidylinositol 3-kinase-related kinases (PIKKs) family, such as ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3-related (ATR), DNA-dependent protein kinase catalytic subunit (DNA-PKcs), and suppressor with morphological effect on genitalia 1 (SMG1), detect damage and coordinate checkpoints and repair; for sustained proliferation, TATA-box binding protein-associated factor 1 (TAF1), transformation/transcription domain-associated protein (TRRAP) and right open reading frame kinase (RIOKs) ensure transcription and ribosome flux, while HASPIN/MELK maintain mitotic speed and accuracy; in metabolic reprogramming, mTOR, pyruvate dehydrogenase kinases (PDHKs), aarF domain-containing kinase 3/4 (ADCK3/4), eukaryotic elongation factor 2 kinase (eEF2K), and WNKs collectively reshape energy and ion homeostasis; concerning anti-apoptosis, TANK-binding kinase 1 (TBK1), RIOK1, p53-related protein kinase (PRPK), and bromodomain-containing protein 4 (BRD4) either activate nuclear factor kappa B (NF-κB) upstream or suppress tumor protein p53 surveillance downstream; meanwhile, the alpha-protein kinase 1-TRAF-interacting protein with forkhead-associated domain (ALPK1−TIFA) axis, TBK1, family with sequence similarity 20C (FAM20C), transient receptor potential melastatin 7 (TRPM7), and atypical protein kinase C (aPKC) isoforms propel the inflammatory, angiogenic, invasive, and metastatic continuum. This network-based division of labor explains how NCKs enable tumors with selective adaptability and pathway redundancy.

NCKs have long been considered "difficult to drug" targets because their domains and catalytic mechanisms differ from those of the classic kinase family, which complicates ATP competitive inhibition. In recent years, structural biology analysis, expansion of chemical probe libraries, and the development of allosteric and covalent inhibition strategies have opened new pathways for unconventional targeting approaches, including allosteric regulation, fragment ligation or merging, covalent anchoring, substrate competition, and conformational stabilization[4]. Small molecules targeting NCKs have transitioned from tool compounds to pharmaceutical exploration, demonstrating three potential advantages: first, their unique active site and allosteric cavity offer space for high selectivity and reduce the off-target risk associated with traditional ATP-competitive inhibition; second, NCKs are crucial nodes in tumor-dependent pathways such as replication stress, protein biosynthesis burden, immune escape, and metabolic reprogramming. Inhibition of NCKs can often create "synthetic lethal" tumor-selective effects; third, tumor-dependent pathways may use NCK as a bypass. Tumors resistant to ePK inhibitors frequently reroute signal transduction through NCK, highlighting the potential of combination therapy[5,6].

The clinical development of NCK-targeted agents is accelerating, especially PIKK inhibitors. Camonsertib (an ATR inhibitor) shows synthetic lethality signals in homologous recombination (HR)-deficient and *ATM*-deficient settings. AZD0156 (an ATM inhibitor), when combined with radiotherapy and poly ADP-ribose polymerase (PARP) inhibitors, is being evaluated across multiple cancer indications. Peposertib (a DNA-PK inhibitor) has entered numerous clinical trials as a radiosensitizer. Furthermore, mTOR inhibitors have expanded beyond allosteric agents (such as rapalogs, including rapamycin) to ATP-competitive inhibitors for combination therapies targeting refractory tumors[7]. Beyond these, a series of emerging NCKs has led to breakthroughs in druggability: structural studies have uncovered the small-molecule binding pocket and activation mechanism of ALPK1; the crystal structure of the inhibitor-RIOK2 complex provides a basis for optimization; and chemical tool molecules targeting ADCKs are emerging, advancing functional and pharmacological research (Fig. 1).

In summary, targeting NCKs provides opportunities to overcome inhibitor resistance and pathway redundancy, while enabling strategies against tumor-specific hallmarks. This review synthesizes current knowledge on non-canonical kinases, aligns their functions with oncogenic hallmarks, and evaluates translational opportunities, aiming to establish NCKs as the next generation of targets for precision oncology[8].

2. Background and drug-discovery landscape

2.1. Definitions and taxonomy

The unusual characteristics of NCKs are primarily linked to (i) the absence or modification of typical Hanks-type sequence motifs within the catalytic domain and/or clear divergence from the canonical bilobal PKL fold. In addition, many NCKs display (ii) unconventional modes of activation and regulation; (iii) atypical substrate ranges or subcellular localization, which further distinguish them from classical ePKs. In a few cases, kinase-like proteins that have lost key catalytic residues but retain a PKL-related scaffold serve as scaffolds rather than bona fide catalytic NCKs within NCK-centric signaling modules. In this review, we therefore use "NCKs" to denote atypical non-PKL families (PIKK, α-kinases, Fam20, PDHK, ADCK, RIO) together with a subset of PKL-fold ePKs (*e.g.*, WNKs, HASPIN, MELK, selected CDKs) that harbor such non-canonical structural or catalytic features,

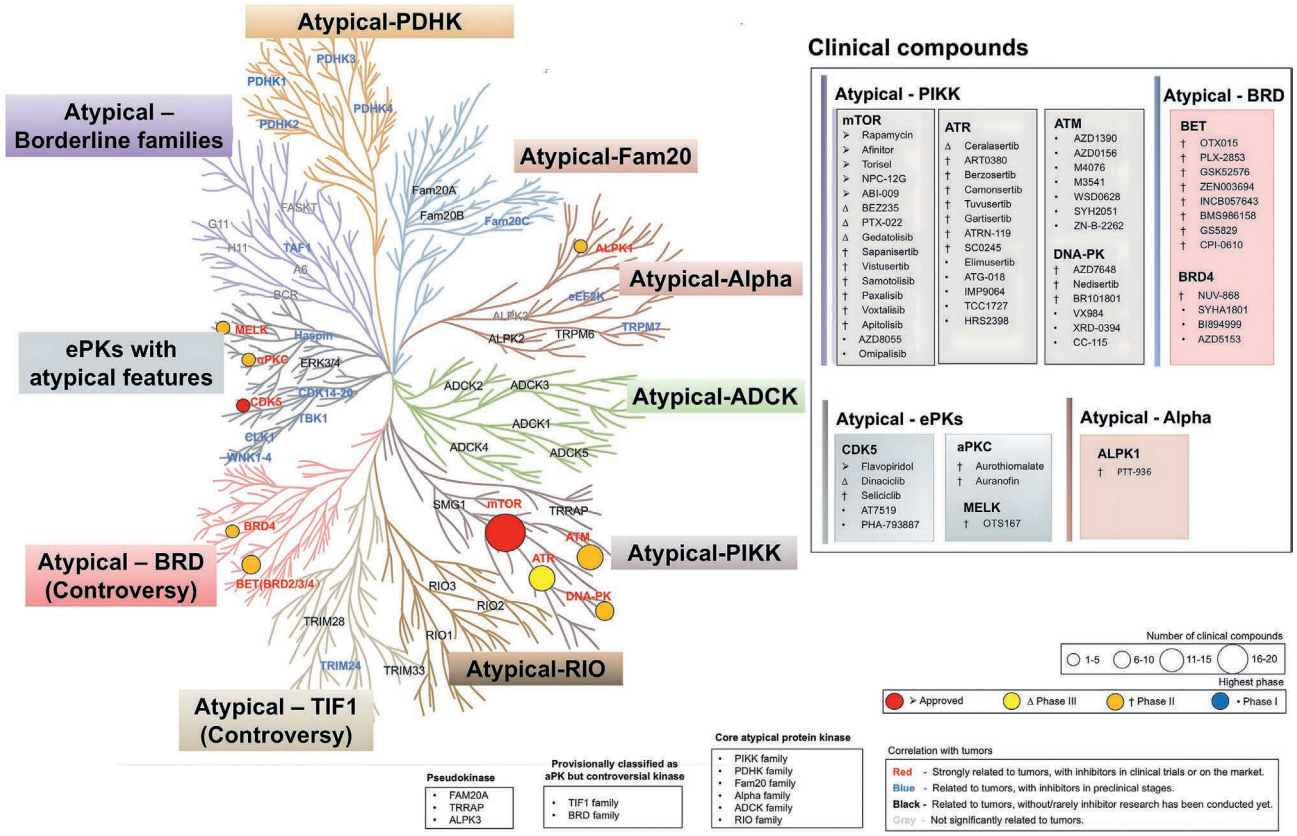

Figure 1 An overview of the NCKs tree and its clinical drug progress. The figure illustrates the phylogenetic classification tree of non-canonical kinases (NCKs) and their correlation with tumors, as well as the current progress of clinical drug candidates for each target. On the left is a target tree based on kinase structure and phylogenetic relationships, dividing NCKs into multiple families. Each node represents a target protein, and its color and size indicate its relevance to the tumor and the clinical stage of the existing drug, respectively. The block diagram on the right summarizes the current representative drugs targeting various NCK targets and their clinical stages.

rather than to encompass any kinase with non-canonical biological functions broadly.

The core aPKs are divided into six families: PIKK, PDHK/BCKDK, Alpha, ADCK, RIO, and Fam20. Structurally, these kinases can be categorized into two related groups. The first includes atypical kinases (non-PKL) that either lack the canonical bilobal protein-kinase-like core or exhibit significant tertiary-structure differences[9]. Examples include the PIKK family, such as ATM, ATR, DNA-PK, mTOR, SMG1, and -TRRAP, which feature extensive HEAT/HEAT-like α-solenoid scaffolds flanking atypical catalytic modules[10]; The α-kinases, such as TRPM6/7, ALPK1-3, and eEF2K, have a distinctive catalytic architecture and recognize noncanonical substrate contexts[11]; the secretory-pathway kinase FAM20C, has a fold different from cytosolic ePKs and phosphorylates luminal or secreted proteins[12]. The second category includes PKL-fold kinases that maintain a conserved catalytic core but differ from typical ePK behavior in regulation, activation, or substrate preference. Notable families include ADCK (ADCK1−5), RIO (RIOK1−3), and PDHKs[13−15].

Several ePKs also show structurally or catalytically unusual features, including TBK1, WNK1−4, HASPIN, PRPK, MELK and selected CDKs such as CDK5 and CDK14−20, which retain a PKL catalytic core but harbor non-canonical active-site configurations or regulatory modules and are therefore discussed here as PKL-fold NCKs[16]. In addition, although early reports suggested that members of the tripartite motif-containing protein (TIF1) and bromodomain-containing protein (BRD) families might possess atypical kinase activity, structural and biochemical studies have redefined them as epigenetic readers and scaffolding proteins rather than bona fide kinases[17−19]. Crystallographic and biochemical studies show that the C-terminal plant homeodomain-bromodomain (PHD-BRD) module of TIF1 proteins, exemplified by tripartite motif-containing 24 (TRIM24), forms a compact structural unit in which the PHD finger recognizes histone lysine methylation states. In contrast, the bromodomain adopts a conserved α-helical fold that binds acetyl-lysine residues[20−22]. Sequence-alignment and domain-mapping analyses demonstrate that TIF1 family members completely lack canonical kinase motifs, instead harboring RING, B-box, coiled-coil, and PHD-BRD modules that mediate protein-protein and chromatin interactions[23,24]. Rather than acting as enzymes, TIF1 proteins function as platforms within chromatin-associated complexes that recruit, or themselves serve as substrates for, classical kinases such as DNA-PKcs and ATM[25]. These observations indicate that the previously reported phosphorylation or "kinase-like" activity is most likely attributable to co-purified kinase partners rather than intrinsic TIF1 catalysis[26,27]. Similarly, several studies mapped the putative kinase activity of BRD4 to a central BD2-B-BID region (approximately residues 351−598) rather than to any domain with a recognizable ePK-like fold. Within this segment, a cluster of basic residues and predicted α-helices can bind ATP and support low-level phosphate transfer *in vitro*, leading to the proposal that

BRD4 harbors an "intrinsic atypical kinase domain[28]. Structurally, this BD2-B-BID segment contains helical bundles and basic patches that create an ATP-binding surface and support autophosphorylation and phosphorylation of Pol II CTD, myelocytomatosis oncogene (MYC), and TATA-box binding protein associated factor 7 (TAF7) in biochemical assays, which resembles the behavior of a protein kinase. However, high-resolution analyses have not identified a canonical bilobal kinase fold or conserved HRD/DFG motifs in this region. In other words, BRD4 can transiently bind ATP and catalyze phosphate transfer. Still, it does so without a recognizable ePK-like catalytic architecture[29] Importantly, the BET (BRD2/3/4/BRDT)-directed small molecules discussed in this review—both inhibitors and proteolysis-targeting chimera (PROTAC) degraders—do not target this putative BD2-B-BID kinase region. Instead, they bind to the acetyl-lysine-recognition pockets of BD1/BD2 or use these bromodomains as warheads to drive ubiquitin-dependent degradation of BRD2/3/4, thereby modulating their reader/scaffold functions rather than directly inhibiting an intrinsic kinase active site (Fig. 2).

2.2. *Drug-discovery landscape*

Kinase signaling lies at the core of oncogenic networks, and the clinical success of imatinib, erlotinib, and vemurafenib has established kinases as tractable drug targets[30]. However, most approved therapies still target canonical tyrosine or serine-threonine kinases, leaving NCKs comparatively underexplored. The structural idiosyncrasies of NCKs—including divergent sequence motifs, noncanonical folds, and scaffold-mediated regulation—are increasingly recognized as alternative molecular entry points for next-generation therapeutics[31].

Further progress in structural biology has inspired drug discovery[32]. The long-range allostery of the PIKK family has been directly observed through high-resolution structures. The near-atomic-resolution structure of the full-length human ATR-ATRIP complex uncovers new allosteric binding sites on ATR, providing a vital foundation for the structural design of precision anticancer therapies[33]. Cryo-electron microscopy of mammalian target of rapamycin complex 1 (mTORC1) revealed its membrane-contact-dependent catalytic geometric rearrangement, suggesting that interventions at these membrane-anchoring interfaces may regulate mTORC1 activity, providing a new target for drug and synthetic biology[34].

Furthermore, the ATP grooves in some NCKs are either shallow, narrow, and highly polar, or blocked by peripheral structures with variable conformations, or even contain local secondary structures that differ significantly from those of typical kinases. As a result, it is challenging to develop high-affinity compounds using common chemical scaffolds that target ATP-binding pockets. However, the "grooves" unique to this family of proteins are directly linked to the conformational switch, offering a new approach for drug design.

For example, ALPK1 has been confirmed to use NDP-Heptose (ADP-heptose) as an allosteric ligand, and the first selective small molecules have emerged[35]. Recently, structure-guided screening/lead series and cell activity probes have emerged that target the interaction grooves of ADCK3 lipids/quinone cofactors[36]. There are positions in the active region of WNK that can bind to the Cl^-/water molecule network. After binding, the inactivated conformation will be locked[37]. The gate (gated cavity) of the TRPM7 channel can be selectively stabilized in a closed state by small molecules[38]. These pockets have rigorous requirements for charge, hydrophobicity, and shape. Some need strong anion/cation interaction (Cl^-/Mg^{2+} sites), some require long strip-shaped hydrophobic channels (lipid phase channels), and some need multi-point hydrogen bonds of sugar ligands. Hence, it naturally leads to high cross Kino'me selectivity.

Pseudo-kinase scaffolds led by FAM20A, which are catalytically inactive but structurally stable, have clear protein-protein interaction (PPI) interfaces and are more suitable for PROTACs or molecular gels (targeting "function" rather than "activity"), thus turning a traditionally "undruggable" class into one amenable to chemical silencing[39–42]. Early TRRAP degraders have elicited synthetic-lethal phenotypes in cell-based and murine models[41,42].

Despite these advantages, NCKs face several obstacles: (i) atypical pockets limit the effectiveness of high-throughput ATP-site screens; (ii) many kinases display low basal activity, complicating biochemical assay readouts; and (iii) lineage-specific homologs can narrow the therapeutic window. Potential solutions are advancing rapidly. Cryo-electron microscopy structures and AlphaFold predictions now guide fragment screens toward cryptic pockets, and reversible-covalent chemotypes are used to lock irregular geometries in place[43–45].

In summary, the private cavities, selectivity determinants, and degrader-friendly scaffolds inherent to NCK architecture are redefining the limits of kinase pharmacology. Continued focus on structurally identifiable pockets, custom allosteric grooves, and surfaces suitable for targeted degradation is set to turn these ideas into a steady pipeline of first-in-class therapeutics.

3. Non-canonical kinases across cancer hallmarks

NCKs are increasingly recognized as nodes within an interconnected network that interacts with multiple cancer hallmarks—including genomic instability, proliferative signaling, metabolic reprogramming, resistance to cell death, inflammation, angiogenesis, invasion, and metastasis[46]. As nodal regulators across these pathways, NCKs are thought to confer the plasticity required for tumor initiation, adaptation, survival, and dissemination.

3.1. *Genomic instability & mutation*

Genomic instability is widely regarded as initiating tumorigenesis. In normal cells, NCKs help maintain genomic integrity, but in tumors they are repeatedly co-opted to balance DNA repair with proliferation, thereby creating selectable—and therapeutically targetable—dependencies.

At the apex of DNA damage sensing, the PIKK family—ATM, ATR, DNA-PKcs, and SMG1—constitutes the core of the DNA damage response (DDR. Upon detection of double-strand breaks, ATM undergoes autophosphorylation and initiates a cascade in which tumor protein p53, Checkpoint kinase 2 (CHK2), and H2A histone family member X (H2AX) are phosphorylated, enforcing G1/S arrest and coordinating HR and non-homologous end joining (NHEJ)[47,48]. ATR is activated primarily by single-stranded DNA at stalled replication forks, leading to checkpoint kinase 1 (CHK1) and replication protein A (RPA) phosphorylation and the establishment of intra-S checkpoints that stabilize replication under stress[48]. DNA-PKcs, recruited to DNA ends *via* Ku heterodimer (Ku70/80), phosphorylates X-ray repair cross-complementing protein 4 (XRCC4) and DNA cross-link repair 1C (Artemis) to

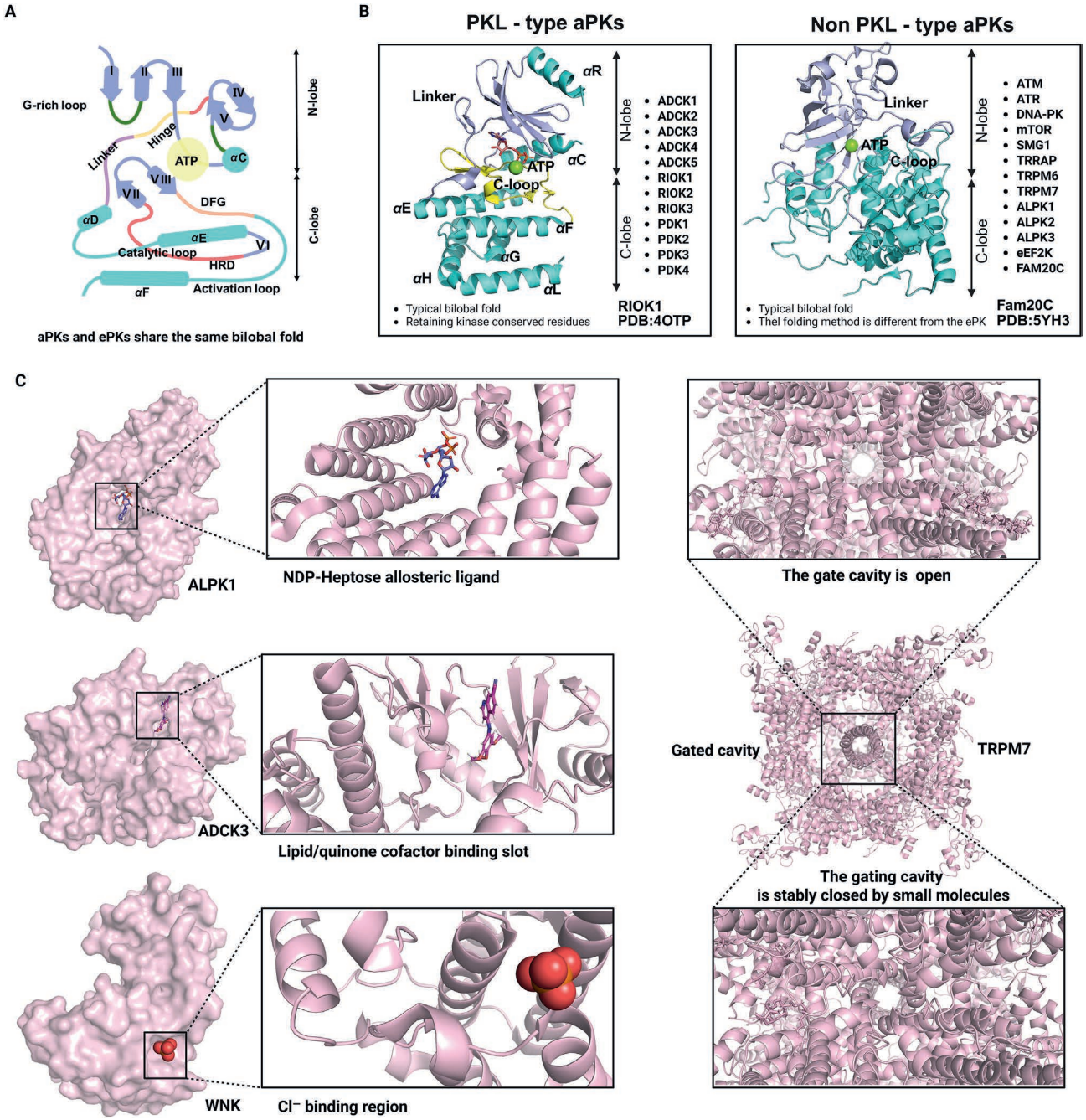

Figure 2 Structural Pharmacology of NCKs. (A) Schematic representation of the two-lobe fold (N-lobe and C-lobe) shared by typical serine/threonine/tyrosine kinases (ePKs) and some atypical protein kinases (aPKs): it contains key structural elements such as G-rich loop, αC, catalytic loop (HRD), DFG, and activation loop to locate ATP and catalytic sites. (B) A two-category structural framework for aPKs. Left: protein-kinase-like (PKL)-type aPKs retain a bileaf fold and conserved sites near ePK (as shown for right open reading frame kinase 1 (RIOK1); PDB: 4OTP). Right: Non-PKL-type aPKs have different folds and connection regions from ePK (taking Fam20C as an example; PDB: 5YH3). (C) A co-crystal/complex pocket view of representative NCKs showing structural features directly related to the druggable site (pink is the protein surface; ligands and key elements are highlighted as sticks or spheres). The left column is: the NDP-Heptose allosteric pocket of alpha-kinase 1 (ALPK1); the lipid/quinone-like cofactor binding groove of ADCK3/COQ8A; and the Cl^- binding region of WNK. Right column: The gated cavity of transient receptor potential melastatin 7 (TRPM7), comparing the open state with the closed state stabilized by small molecule inhibitors.

complete NHEJ and to enable V(D)J recombination in lymphoid cells [49]. SMG1 integrates mRNA surveillance with checkpoint control by phosphorylating UPF1 during nonsense-mediated decay and by modifying p53[50,51]. Collectively, this axis detects lesions, pauses cell-cycle progression, and executes accurate end joining; yet in cancer, it is often recalibrated to permit "repair-while-replicating," a state that underlies the synthetic-lethal efficacy of PIKK-targeted therapies.

Mitotic fidelity is safeguarded by HASPIN, an atypical Ser/Thr kinase that accumulates in late S/G2 and is activated by CDK1 and

Polo-like kinase 1 (PLK1) at mitotic entry[52−55]. By phosphorylating histone H3 at Thr3, HASPIN creates a centromeric docking site for the chromosomal passenger complex (CPC), thereby positioning Aurora B, correcting erroneous kinetochore-microtubule attachments, and sustaining the spindle-assembly checkpoint[54,55]. Genetic or pharmacologic inhibition of Aurora B displaces Aurora B, provokes chromosome segregation errors, and culminates in aneuploidy or mitotic cell death[56]. HASPIN is frequently overexpressed in aggressive tumors, including pancreatic and hepatocellular carcinomas, and the HASPIN inhibitor CHR-6494 synergizes with taxanes to trigger catastrophic mitosis in preclinical models[57,58]. HASPIN thus shifts the balance between speed and fidelity: when upregulated, it enables high-throughput division without overtly lengthening the cell cycle; when inhibited, error correction collapses.

Between damage sensing and repair, chromatin is rapidly restructured. TRRAP, a catalytically inactive non-canonical kinase, scaffolds transformation/transcription domain-associated protein (SAGA) and tat-interactive protein (Tip60) to promote histone H4 acetylation at breaks, licensing ATM/ATR signaling and facilitating nucleosome eviction[59−62]. Beyond DNA repair, TRRAP anchors MYC and adenovirus E2 promoter-binding factor (E2F) at target promoters, amplifying growth-associated transcriptional programs that are recurrently upregulated in cancer, and genomic amplification of TRRAP correlates with poor outcomes in pediatric solid tumors[61]. In parallel, TRIM24, tripartite motif-containing 28 (TRIM28), and tripartite motif-containing 33 (TRIM33) constitute a complementary switch: TRIM28 is phosphorylated at Ser824 by ATM or DNA-PKcs immediately after DNA damage, relieving kruppel-associated box (KRAB)-mediated silencing and permitting local transcription of repair genes, whereas TRIM24 and TRIM33 act as ligand-dependent co-activators of estrogen receptor and transforming growth factor beta (TGF-β)/mothers against decapentaplegic homologs (SMAD) pathways, driving oncogenic outputs when overexpressed[63]. Together, these factors open a transient "repair window" while sustaining pro-growth transcription, thereby explaining how tumors maintain biosynthetic throughput under genotoxic stress.

PRPK adds translational and telomeric layers to checkpoint control. As the catalytic subunit of the endopeptidase-like kinase chromatin-associated/kinase, endopeptidase and other proteins of small size (EKC/KEOPS) complex, PRPK catalyzes installation of the universal N^6-threonylcarbamoyladenosine (t^6A) modification on tRNAs, safeguarding translational fidelity and ribosomal processivity[64]; the same complex contributes to telomere length regulation, positioning PRPK at the intersection of proteostasis and chromosome-end maintenance[65]. PRPK has also been reported to phosphorylate p53 at Ser15, thereby modulating the amplitude of the p53 damage response[66]. In aggressive tumors, *PRPK* overexpression has been associated with lowered p53 activation thresholds and sustained proliferation under genotoxic stress. In contrast, genetic or pharmacologic inhibition resensitizes cells to DNA-damaging therapy and suppresses tumor growth in myeloma models[66]. The developmental essentiality revealed by germline loss-of-function (Galloway−Mowat syndrome) underscores that PRPK is not ancillary; rather, it couples accurate protein synthesis and telomere integrity to checkpoint regulation[67].

These factors redefine the cellular balance between speed and fidelity. ATM and ATR expand checkpoint buffering to afford repair time; TRRAP and the TRIM proteins maintain permissive chromatin and keep growth programs primed during this window; PRPK modulates p53 output while safeguarding the proteome and telomeres; and HASPIN preserves high-throughput chromosome segregation. Synthetic-lethal combinations—such as inhibition of ATR or DNA-PKcs with PARP inhibitors or radiotherapy—impair upstream repair capacity in replication-stressed tumors, whereas concurrent blockade of ATR and HASPIN is expected to collapse checkpoint signaling and error correction. Finally, PRPK antagonism or disruption of TRRAP-dependent acetyltransferase docking may restore p53 activity and convert DNA-damaging regimens from cytostatic to cytotoxic.

3.2. Sustained proliferative signaling

To sustain unchecked division, cancer cells mobilize a set of NCKs—including mTOR, -TAF1, TRRAP, RIOK1−3, HASPIN, MELK, and CDK5.

First, an mTOR-centered metabolic program sustains proliferative signaling. mTOR orchestrates tumor anabolism through two structurally and functionally distinct complexes[68]. Hyperactivation of the PI3K−AKT−mTOR axis—present in approximately 30% of human cancers—drives metabolic reprogramming: mTORC1 upregulates glycolytic enzymes and glucose uptake, thereby promoting the Warburg effect[65,69], expands translational capacity; and simultaneously suppresses autophagy, removing catabolic restraint on growth[70]. These metabolic outputs couple directly to cell-cycle entry, establishing mTOR as a master proliferative rheostat.

TAF1, the largest subunit of the transcription factor IID (TFIID) transcription initiation complex, couples promoter clearance to cell−cycle progression through its intrinsic serine/threonine kinase activity. TAF1 phosphorylates RAP74 (a TFIIF subunit), thereby facilitating RNA polymerase II elongation; it also phosphorylates p53 at Thr55, marking it for degradation and lowering the G1 checkpoint threshold[71−73]. TAF1 additionally phosphorylates histone H2B at selected promoters, reinforcing transcriptional activation of growth-related genes. Cancer genomes frequently exhibit *TAF1* copy-number gains or overexpression, linking heightened TAF1 activity to amplified MYC/E2F programs and unrestrained S-phase entry. These features position TAF1 as a transcriptional "gate valve" whose inhibition may restore p53 activity and resensitize tumors to cell-cycle-targeted therapy. In addition, the atypical scaffold kinase TRRAP amplifies proliferative transcriptional programs by anchoring MYC and E2F to their target promoters, in part by recruiting histone acetyltransferase complexes such as SAGA and Tip60[59,60]. This coordinated engagement unlocks growth-promoting gene expression while enabling cancer cells to evade checkpoint control. The RIO kinase family provides an indispensable throughput valve between transcriptional upshift and protein synthesis. RIOK1−3 ensure that ribosome supply keeps pace with the anabolic demands imposed by mTOR- and TAF1-driven activity[74,75].

The successful execution of the G2/M program is mediated by two kinases positioned at complementary nodes of mitotic control. As outlined, HASPIN becomes fully activated through phosphorylation by CDK1 and PLK1 during early mitosis. In parallel, MELK phosphorylates forkhead box protein M1 (FOXM1), thereby amplifying a G2/M transcriptional program that drives spindle assembly and chromosome congression[76,77]. MELK is overexpressed in basal-like breast cancers, lung cancers, and glioblastomas, and its inhibition—alone or in combination with DNA-damaging agents—can induce synthetic lethality while

sparing most normal tissues[76−81]. Collectively, HASPIN secures chromosomal fidelity, whereas MELK drives the mitotic transcriptional surge. Additionally, nuclear CDK5 phosphorylates and inactivates $p21^{Cip1/Waf1}$, thereby relieving the G1 restraint[76,77]. Similarly, ERK3/4/5 has been implicated in the G1−S transition and invasion.

Together, these seven kinase modules delineate a proliferative cascade in cancer cells. Nutrient and growth factor availability is first sensed by mTOR, committing the cell to an anabolic state; MYC/E2F-driven transcription is then enabled by TAF1 and further amplified by TRRAP. RIOK1−2 expand ribosome output, closing the gap between transcriptional demand and translational capacity, whereas HASPIN and MELK coordinate chromosome segregation and the G2/M transcriptional surge to complete mitosis. CDK5 and ERK3/4/5 also contribute as auxiliary regulators of this process.

3.3. *Reprogramming cellular metabolism*

Cancer cells extensively reprogram metabolic pathways to sustain rapid proliferation and adapt to stress. This rewiring is orchestrated by a defined set of kinases—including mTOR, PDHKs, ADCK3, eEF2K, WNK, ALPKs, and TBK1.

As noted above, hyperactive mTORC1/2 signaling converts growth-factor and nutrient cues into an anabolic program. Complementing this nutrient-sensing hub, the E1α subunit of the pyruvate dehydrogenase complex is phosphorylated by PDHK1-4, diverting pyruvate away from the tricarboxylic acid (TCA) cycle and favoring aerobic glycolysis[82,83]. PDHK1 and PDHK3 are frequently overexpressed, reinforcing the Warburg phenotype, whereas PDHK4 is induced under nutrient scarcity to conserve glucose[84]. Pharmacologic inhibition of PDHKs forces pyruvate oxidation, increases oxidative stress, impairs tumor growth, and acts synergistically with mTOR blockade in preclinical models[85,86]. Collectively, mTOR and PDHKs establish a two-tiered metabolic system in which extracellular nutrient availability is sensed and intracellular carbon flux is rerouted, committing cancer cells to anabolism.

ADCK1−5 safeguard mitochondrial metabolism and limit oxidative stress in tumors by regulating coenzyme Q (CoQ) biosynthesis. ADCK3 and ADCK4 are essential for multiple steps in the CoQ pathway; their loss causes primary CoQ deficiency, impairs oxidative phosphorylation (OXPHOS), and increases reactive oxygen species (ROS) generation[87−89]. ADCK2 insufficiency likewise reduces CoQ levels and provokes OXPHOS dysfunction and muscle atrophy[90].

To balance biosynthetic demand with limited resources, cancer cells exploit eEF2K. This Ca^{2+}/calmodulin-dependent kinase phosphorylates eEF2 at Thr56, transiently arresting ribosomal translocation and curbing ATP-intensive protein synthesis[91]. eEF2K activity is induced by energy-stress signals such as AMPK activation and cytosolic Ca^{2+}, but is suppressed by nutrient sufficiency *via* mTOR-ribosomal protein S6 kinase (S6K) feedback, thereby enabling dynamic tuning of translational output[91,92]. Under hypoxia, glucose deprivation, or radiotherapy, tumor cells become dependent on eEF2K to conserve energy, limit oxidative damage, and maintain viability[93]. Conversely, genetic or pharmacologic inhibition of eEF2K removes this metabolic brake, leading to ATP depletion and heightened sensitivity to nutrient scarcity and chemoradiation in multiple cancer models[94]. Thus, eEF2K functions as an adaptable throttle that couples intracellular energy status to translational flux and represents a therapeutic node for undermining tumor resilience under metabolic stress.

Maintaining intracellular ionic strength and cell volume is metabolically costly, and tumors frequently delegate this task to the WNK kinase family. Hyperosmotic shrinkage is sensed by WNK1 and WNK4, which activate the downstream TE20/SPS1-related proline-alanine-rich protein kinase (SPAK) and oxidative stress-responsive kinase 1 (OSR1); in turn, the Na^+-K^+-$2Cl^-$ (NKCC) and Na^+-Cl^- (NCC) cotransporters are stimulated to restore K^+/Cl^- balance and cell volume[95−98]. Systemic electrolyte homeostasis is disrupted, and Gordon's syndrome arises from loss-of-function mutations in WNK1 or WNK4, underscoring the physiological importance of these genes[99]. Accordingly, WNK1−4 are thought to furnish tumor cells with a rapid means of stabilizing ion-dependent enzyme activity and sustaining metabolic output in fluctuating microenvironments. In addition, ALPK1 couples pathogen-derived signals to pro-tumorigenic inflammation and metabolic adaptation[100−103]. Diverse innate-immune inputs—cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING)-, retinoic acid-inducible gene I (RIG-I), and Toll-like receptors (TLRs)—are integrated by TBK1 with cellular energy pathways, thereby providing tumors with an adaptable bioenergetic framework that supports growth in hostile microenvironments.

In summary, nutrient and growth factor signals are first converted by mTOR and the PDHKs into a glycolytic, anabolic program, whereas ADCK3/4 maintains mitochondrial electron transport to sustain ATP production and restrain oxidative stress. eEF2K then functions as an adaptive throttle, transiently suppressing translation when energy becomes limiting. Osmotic and ionic fluctuations are transduced by WNK kinases into signals that stabilize enzyme activity and cell volume, thereby buffering metabolic flux against changes in the microenvironment. Microbial or inflammatory cues are linked by ALPK1 and TBK1 to NF-κB activation and glucose uptake, thereby aligning innate immune signaling with bioenergetic rewiring. By coordinating nutrient sensing, mitochondrial function, translational economy, ion homeostasis, and inflammatory adaptation, this atypical-kinase network confers the metabolic plasticity required for sustained growth in hostile niches.

3.4. *Enabling replicative immortality*

Replicative immortality requires continuous protein synthesis, error-free chromosome segregation, and mitotic resilience under stress; these demands are enabled by NCKs—particularly RIOKs, HASPIN, and MELK.

Replicative immortality depends on the continuous availability of functional ribosomes, thereby sustaining biosynthetic output across successive cell cycles. RIOK1−3 drives the final maturation of 40S ribosomal subunits, coupling ribosome availability to cell-cycle progression. Inhibition or depletion of RIOK1/2 disrupts pre-40S export, triggers nucleolar stress, and activates a p53-dependent checkpoint that arrests cells in early G1[74,75,104−106]. Conversely, *RIOK1/2* overexpression—frequently observed in aggressive tumors—suppresses this checkpoint, preserves translational capacity, and enables unchecked proliferation despite oncogenic stress[107]. Although RIOK3 is less critical for ribosome biogenesis under homeostatic conditions, it supports tumor adaptation through its roles in innate immune signaling and cytoskeletal remodeling[108,109]. Together, RIOK kinases constitute a key node within the atypical-kinase network, insulating cancer

cells from ribosomal insufficiency and enforcing the biosynthetic continuity required for limitless replication.

To sustain limitless divisions, tumor cells must prevent the gradual accumulation of chromosome-segregation errors that would otherwise trigger senescence or death. By ensuring chromosomal fidelity without lengthening the cell−cycle duration, HASPIN functions as an essential "license to divide" for immortal tumor lineages and presents a tractable vulnerability for mitosis-targeted therapy[58,110]. MELK confers the mitotic resilience characteristic of embryonic and stem-cell populations. Under physiological conditions, MELK supports asymmetric division of progenitor cells, underscoring its role in sustaining high-frequency mitosis under developmental or genotoxic pressure[78]. By maintaining FOXM1-driven mitotic gene expression and buffering DNA damage, MELK acts as a stem-like engine that enables replicative immortality across diverse malignancies.

Collectively, RIOK1−3, HASPIN, and MELK establish a three-tiered safeguard that underwrites replicative immortality. RIOK kinases prevent nucleolar-stress checkpoints by synchronizing 40S maturation with G1−S progression, thereby sustaining the ribosomal throughput that fuels continuous protein synthesis. HASPIN secures chromosomal fidelity by phosphorylating centromeric H3 at Thr3, positioning Aurora B for error correction and averting aneuploidy without lengthening the cell cycle. MELK amplifies FOXM1-dependent G2/M transcription and buffers against DNA damage, endowing tumor cells with a stem-like capacity to divide rapidly under genotoxic pressure. By sequentially removing biosynthetic, karyotypic, and checkpoint constraints, this atypical-kinase triad provides the mechanistic foundation for limitless self-renewal.

3.5. *Resisting cell death*

TBK1 amplifies NF-κB signaling; RIOK1, together with SMG1 and PRPK, suppresses p53 surveillance; and BRD4 sustains pro-survival transcription, thereby enabling tumor cells to withstand both intrinsic stress and therapeutic assault. Together, these factors assemble a stratified anti-apoptotic network.

Canonically, TBK1 is a central non-canonical IκB kinase (IKK)-family kinase that couples pattern-recognition receptor (PRR) signaling to type I interferon and inflammatory cytokine production in innate immunity, upon sensing viral or self-derived nucleic acids, receptors such as RIG-I and melanoma differentiation-associated gene 5 (MDA5), toll like receptor 3/4 (TLR3/4), and the DNA sensor cGAS signal through the adaptors mitochondrial antiviral-signaling protein (MAVS), TIR-containing adaptor molecule-1 (TRIF), and stimulator of interferon genes (STING), respectively, to recruit and activate TBK1 within higher-order signalosomes[111,112]. Activated TBK1 phosphorylates interferon regulatory factor 3 (IRF3) and interferon regulatory factor 7 (IRF7) on their C-terminal serine clusters, driving their dimerization and nuclear translocation, and cooperates with the canonical IKK complex to enhance NF-κB activation, thereby inducing a broad antiviral and pro-inflammatory transcriptional program[113]. This canonical pattern-recognition receptor (PRR)-TBK1-IRF3/7 module forms the core of antiviral innate immune activation and provides the physiological backdrop for its tumor-specific functions[114]. Tumor cells, however, repurpose this innate immune circuitry: instead of merely mounting antiviral responses, TBK1 becomes a constitutive survival hub that amplifies NF-κB signaling and suppresses extrinsic cell-death pathways. TBK1 constitutes the first line of defense against programmed cell death by constitutively activating NF-κB and directly suppressing receptor-interacting serine/threonine kinase 1 (RIPK1)-dependent apoptosis and necroptosis. In Kirsten rat sarcoma viral oncogene *(KRAS)*-mutant lung tumors and MYC-driven acute myeloid leukemia (AML), oncogenic signaling hard-wires TBK1 activity, sustaining expression of anti-apoptotic NF-κB targets and rendering cancer cells critically dependent on the kinase for survival[115]. Genetic ablation or pharmacologic inhibition of TBK1 dismantles this checkpoint, unleashing TNFα-triggered death pathways and producing pronounced tumor regression—an effect abrogated by concomitant RIPK1 inactivation[115]. TBK1 further promotes therapeutic resilience: phosphorylation of Argonaute 2 (AGO2) at Ser417 reprograms microRNA output, upregulates oncogenic miRs, and enables epidermal growth factor receptor (*EGFR*)-mutant non-small cell lung cancers to evade gefitinib—a resistance overcome by combined TBK1 and EGFR blockade[116]. Thus, TBK1 functions as a central survival hub—interdicting extrinsic death signals, rewiring gene regulation, and insulating tumors from targeted therapies—and offers an attractive target for pro-apoptotic combination strategies.

A second anti-death layer is built by systematically attenuating the p53 pathway. *RIOK1* overexpression—frequently observed in treatment-refractory cancers—recruits an E3-ligase complex, accelerating p53 degradation and thereby blunting p53-dependent apoptosis while permitting continued proliferation after DNA damage[104−106]. Although classically regarded as a DNA-damage kinase, SMG1 diverts its activity toward nonsense-mediated mRNA decay, limiting the accumulation of stress-induced p53 transcripts and effectively lowering the apoptotic threshold[50,51]. PRPK-mediated phosphorylation of p53 at Ser15 promotes murine double minute 2 (MDM2)-dependent turnover, diminishing both transcriptional activation and mitochondrial death signaling[117]. Collectively, these non-canonical kinases dismantle p53 surveillance at the levels of protein stability, mRNA quality control, and post-translational modification, thereby insulating tumor cells from genotoxic therapies and underscoring the rationale for combinatorial p53-reactivation strategies.

BRD4 is a non-catalytic regulator closely linked to atypical-kinase networks that sustains cell survival by activating anti-apoptotic and therapy-resistance genes. Operating at the interface of chromatin engagement and RNA polymerase II activation, BRD4 supports expression of MYC, BCL-2, and DNA-repair programs that enable tumor cells to evade cell death[118]. In triple-negative breast cancer and diffuse large B-cell lymphoma, BRD4 upregulates the ferroptosis suppressor ferroptosis suppressor protein 1 (FSP1), promoting ferroptosis resistance; combined bromodomain and extraterminal (BET) inhibition and ferroptosis induction yield synergistic cytotoxicity[119,120]. In ovarian and colorectal cancers, BRD4 bromodomain inhibitors arrest cells in G0/G1 and induce apoptosis, particularly in combination with chemotherapeutics[121].

Collectively, TBK1, RIOK1, SMG1, PRPK, and BRD4 assemble a multilayered defense that shields cancer cells from intrinsic and therapy-induced death. Upstream, TBK1 constitutively activates NF-κB and blocks RIPK1-mediated apoptosis. RIOK1, supported by SMG1 and PRPK, disables the p53 checkpoint at the levels of protein turnover, mRNA surveillance, and stress-site phosphorylation, thereby uncoupling DNA damage from apoptotic execution. Downstream, BRD4 sustains transcriptional addiction to MYC, BCL-2, and DNA-repair programs. By interlocking signal blockade, checkpoint suppression, and pro-survival transcription, NCKs create a robust apoptosis-resistant state.

3.6. Tumor-promoting inflammation and inducing angiogenesis

Sustained NF-κB-centric inflammatory signaling—driven intrinsically by TBK1 and extrinsically by the microbiota sensor ALPK1—reprograms the tumor microenvironment into a cytokine-rich, immunosuppressive niche, thereby fostering angiogenesis, immune evasion, and therapeutic resistance.

Within tumor cells, TBK1 functions as an inflammation-angiogenesis linchpin. Upon activation, TBK1 triggers NF-κB and IRF3 signaling, upregulating interleukin-6/10/1β (IL-6/10/1β) and vascular endothelial growth factor (VEGF); this cytokine suite recruits M2-polarized macrophages, promotes helper T cell 17 (Th17) polarization, and stimulates endothelial sprouting, collectively providing vascular support and an immunosuppressive stroma[115]. In parallel, TBK1 phosphorylates AKT, enhancing glycolytic flux and lactate export; the resulting acidic, hypoxic milieu further biases myeloid cells toward pro-angiogenic phenotypes while excluding effector T lymphocytes[116]. TBK1 also induces programmed death-ligand 1 (PD-L1) expression, establishing a feed-forward circuit of immune evasion and angiogenesis that is especially prominent in "cold" *KRAS*-mutant carcinomas[122].

In gastrointestinal tumors enriched for *Fusobacterium nucleatum* or other Gram-negative microbes, the α-kinase ALPK1 senses the bacterial metabolite ADP-heptose. The kinase then autophosphorylates, recruits, and phosphorylates the adaptor TIFA, triggering a potent NF-κB surge[101,102,123]. This signaling wave elevates IL-6, IL-8, and reactive oxygen species, which in turn attract neutrophils and tumor-associated macrophages, activate hypoxia-inducible factor 1-alpha (HIF-1α), and stimulate endothelial sprouting[123,124]. Concurrently, it fosters chemoresistance, while sustained myeloid infiltration perpetuates a positive feedback loop of angiogenic VEGF and matrix-remodeling enzymes[125]. Gain-of-function *ALPK1* mutations or chronic bacterial exposure remodel the tumor microenvironment into an inflammation-driven vascular niche that supports rapid growth and immune evasion[100,126]. Preclinical silencing of ALPK1—or depletion of ADP-heptose-producing microbiota—dampens cytokine output, normalizes the vasculature, and resensitizes colorectal and gastric cancer models to chemotherapy, identifying the alpha-kinase 1—TRAF-interacting protein with FHA domain axis (ALPK1—TIFA axis) as a tractable link among dysbiosis, inflammation, and tumor angiogenesis.

Together, TBK1 and ALPK1 form a two-pronged inflammatory engine that couples cytokine release to neovascularization. Oncogenic signaling or cytosolic DNA locks TBK1 into an NF-κB/IRF3 circuit that elevates IL-6, IL-10, and VEGF, acidifies the microenvironment, and upregulates PD-L1, thereby fostering angiogenesis and T-cell exclusion. At mucosal sites, microbiota-derived ADP-heptose activates the ALPK1-TIFA axis, driving IL-8, ROS, and HIF-1α outputs that recruit pro-angiogenic myeloid cells, intensify vessel sprouting, and accelerate DNA damage and therapy resistance.

3.7. Activating invasion and metastasis

NCKs orchestrate successive stages of the metastatic cascade by destabilizing epithelial polarity, retuning the extracellular matrix, reprogramming cytoskeletal dynamics, and activating pro-inflammatory circuits, thereby enabling cancer cell dissemination.

The partitioning-defective (PAR) usually enforces epithelial integrity *via* the aPKC polarity complex; however, atypical PKC isoforms are frequently co-opted by tumor cells to trigger epithelial-mesenchymal transition (EMT). PKCι, often amplified at chromosome 3q26, disrupts apical-basal polarity and engages ras-related C3 botulinum toxin substrate 1 (RAC1), integrin, and AKT signaling, thereby initiating motility[127—129]. In *KRAS*-mutant lung cancer, co-amplification of *PRKCI* and SRY-box transcription factor 2 (SOX2) drives a stem-like invasive state, whereas genetic ablation of PKCι *in vivo* blocks tumor initiation and metastasis[130]. In esophageal squamous carcinoma, PKCι sustains S-phase kinase-associated protein 2 (SKP2)—AKT activation, coupling survival to migration; in lung adenocarcinoma, PKCι forms a feed-forward loop with Yes-associated protein (YAP), accelerating proliferation and invasion[131—134]. Although PKCζ was once regarded as a polarity safeguard, breast-cancer studies reveal a pro-metastatic PKCζ—NF-κB—p65 axis; constitutively active NF-κB rescues invasiveness in PKCζ-depleted cells, confirming its driver role[128,135]. Small-molecule inhibition of PKCι arrests EMT and suppresses metastatic spread in preclinical models[136], highlighting atypical PKCs as tractable polarity "off switches" situated at the apex of the metastatic cascade.

Additionally, more than one hundred secreted or extracellular matrix proteins are phosphorylated by FAM20C—the principal "Golgi casein kinase"—thereby remodeling the tumor secretome to favor invasion and the formation of metastatic niches[137,138]. High FAM20C expression correlates with enhanced migration and distant spread in breast, prostate, and glioma models; mechanistically, the kinase activates osteopontin (OPN), insulin-like growth factor-binding proteins (IGFBPs), and fibrillin, loosening cell-matrix adhesion and recruiting pro-metastatic stromal cells[137,138]. Myeloid-derived FAM20C suppresses osteolysis *via* osteopontin phosphorylation, whereas tumor-intrinsic FAM20C phosphorylates bone morphogenetic protein 4 (BMP4), stimulating osteoclast differentiation and promoting bone metastasis[139]. Pharmacologic inhibition (*e.g.*, FL-1607 or compound **3r**) or RNAi-mediated knockdown attenuates invasion *in vitro*. It curtails metastatic colonization *in vivo* without markedly affecting primary tumor size, underscoring the nonredundant role of FAM20C in shaping a permissive metastatic microenvironment[140].

TRPM7 controls the actomyosin machinery that powers cell migration. Clinically, *TRPM7* overexpression is a strong, independent predictor of lymph-node or distant metastasis in breast, nasopharyngeal, pancreatic, and lung cancers[141—143]. Its α-kinase domain phosphorylates the myosin IIA heavy chain, thereby lowering actomyosin contractility and focal adhesion strength, whereas Ca^{2+}/Mg^{2+} influx activates MAPK cascades that enhance ERK phosphorylation and lamellipodial dynamics[144]. TRPM7 knockdown reduces invasion *in vitro* and diminishes spontaneous lung dissemination *in vivo*, and this depletion correlates with decreased lymph-node involvement in patient cohorts[144]. Beyond mechanics, TRPM7-mediated Ca^{2+} entry stabilizes MYC and upregulates caveolin-1, linking ion flux to transcriptional programs that promote epithelial-mesenchymal transition and metabolic adaptation[142,143]. Pharmacologic TRPM7 blockers or channel-dead mutants blunt migratory capacity without broadly affecting viability, positioning TRPM7 as a cytoskeletal rheostat whose inhibition could selectively curb metastatic spread[145].

Overall, PKCι/ζ disrupts PAR-governed polarity to trigger EMT, releasing cells from the epithelial layer; FAM20C phosphorylates secreted matrix regulators, softening the stroma and clearing a migratory path; and TRPM7-mediated Ca^{2+}/Mg^{2+} influx reprograms actomyosin contractility, providing the propulsion for invasion. Together, this polarity—matrix—motility sequence enables efficient tumor dissemination.

3.8. Summary

From genome surveillance to immune escape, every central axis of tumor biology intersects with NCKs. These enzymes function either as oncogenic drivers or as indispensable enablers of malignant traits. NCKs reinforce multiple cancer hallmarks: limitless proliferation is sustained (HASPIN, MELK); cell death is suppressed (TBK1, RIOK1, BRD4); angiogenic and inflammatory circuits are fueled (ALPK1, TBK1); invasion and metastasis are propelled (aPKC isoforms, FAM20C, TRPM7); and cellular metabolism is reprogrammed (mTOR, PDHKs, ADCK3). Positioned at nodal points within signaling networks—and often serving as dual-function enzymes and scaffolds—these kinases integrate diverse stress cues, thereby conferring exceptional plasticity on cancer cells and rendering them compelling therapeutic targets. Several kinases have already been shown to be druggable, and ongoing mechanistic and clinical studies are expected to drive drug discovery further.

4. Pre-clinical small-molecule inhibitors

NCKs have emerged as a promising frontier in drug discovery. Recent advances in chemical biology have yielded potent tool compounds and, for several members of this class, even clinical candidates. The preclinical inhibitors discussed here demonstrate that, with appropriate strategies, even unconventional kinases can be effectively targeted for cancer therapy (Table 1).

4.1. Targeting cancer metabolism and stress adaptation

NCK signaling spans multiple cancer hallmarks. Pharmacologic interrogation of stress-adaptive kinases reveals context-dependent liabilities in tumor metabolism and physicochemical homeostasis that are unmasked under nutrient or energy deprivation. In such conditions, eEF2K throttles translational elongation to conserve ATP; this axis is druggable in both directions. Inhibition at the calmodulin site (NH125), the ATP pocket (A-484954), or the eEF2 substrate interface (oleuropein) curtails adaptive proteostasis, sensitizing tumors to chemotherapy and glucose scarcity. In contrast, pharmacologic hyperactivation with nelfinavir increases eEF2 phosphorylation, driving "adaptation-to-lethality" and apoptosis[94]. Targeted degradation likewise converts dependency into loss-of-function: C1 and optimized analogs (*e.g.*, compound **36**) enhance βTRCP-mediated proteasomal degradation of eEF2K and cooperate with paclitaxel in triple-negative breast cancer (TNBC) organoids and xenografts[164,165]. These interventions address metabolic reprogramming (limiting biosynthetic demand), resistance to cell death (forcing fatal stress), and sustained proliferation (restricting synthesis of growth drivers), with phosphorylated eEF2 as a pharmacodynamic readout; progress remains tempered by the absence of a high-resolution structure and the enzyme's unconventional catalytic core.

PDHK1−4 maintain the Warburg phenotype by phosphorylating the pyruvate dehydrogenase complex (PDC); inhibition reactivates mitochondrial oxidation, thereby affecting metabolic reprogramming, proliferative capacity, and therapy resistance. Beyond low-affinity dichloroacetate, next-generation agents include JX06 (a covalent PDHK1 inhibitor), VER-246608 (an ATP-competitive pan-PDHK inhibitor with the most substantial effects under low glucose and synergy with doxorubicin), and the potent PDHK1-selective compound **17**; additional modalities include AI-predicted chemotypes, DAP derivatives, and repurposed binders such as bagrosin and dehydrocholic acid[166-168]. Loss of PDC-E1α phosphorylation and decreased lactate levels serve as on-target pharmacodynamic biomarkers. Key hurdles include PK/PD optimization and isoform redundancy, which may be best addressed through rational combinations with complementary metabolic or stress-response agents.

WNK kinases couple osmotic and ionic homeostasis to cell motility and survival, thereby linking to invasion, metastasis, angiogenesis, and microenvironmental adaptation. The oral pan-WNK inhibitor WNK463 suppresses isoform phosphorylation and reduces invasiveness and neovascularization in preclinical models but exhibits a narrow therapeutic window owing to electrolyte disturbances; alternative agents, such as closantel and the allosteric inhibitor WNK-IN-11, suggest routes to greater selectivity and clinically acceptable exposure[169,170].

Collectively, these drug classes convert stress-enabled advantages into liabilities, most notably in hypoglycemic, hypoxic, or osmotically fluctuating niches [168,171]. Biomarker-guided patient selection; context-adjusted combinations with chemotherapy, mTOR inhibitors, or proteostasis modulators; and improvements in selectivity and delivery should broaden the therapeutic window.

4.2. Modulating transcriptional and post-transcriptional control

Pharmacologic modulation of transcriptional and post-transcriptional control exposes druggable dependencies that intersect core cancer hallmarks, notably sustained proliferative signaling, resistance to cell death, epigenetic plasticity, and therapy adaptation. TRIM24 is overexpressed across diverse tumors, and first-generation bromodomain ligands—IACS-9571 (a benzimidazolone that also binds Bromodomain and PHD finger containing 1) and Y08624—displace TRIM24 from chromatin but yield only modest antiproliferative effects, echoing the gap between domain occupancy and genetic ablation observed for other readers[148,172]. To achieve loss-of-function, dTRIM24—tethering an IACS-9571 warhead to a VHL ligand—degrades the entire protein and enhances antiproliferative activity in AML, converting chromatin-dependent growth signals into liabilities[172]. TAF1, a transcriptional cofactor that also modulates p53, likewise proves more vulnerable to protein removal than to bromodomain blockade. Although the ATR inhibitor ceralasertib (AZD6738) unexpectedly binds the tandem bromodomains and Tafbromin selectively targets BD2, high-affinity monovalent antagonists such as GNE-371 exhibit limited cytotoxicity[173]. By contrast, cereblon-recruiting TAF1 degraders built from ceralasertib- or GNE-371-based warheads deplete TAF1, activate p53, and induce apoptosis in AML and selected solid tumors, with *in vivo* efficacy in leukemia xenografts—directly addressing the hallmarks of proliferative drive and evasion of apoptosis[174]. Dual-target strategies (TAF1−ATR hybrids; PLK1-based TAF1−BRD4 bromodomain inhibitors derived from BI-2536) further couple transcriptional control to DNA-damage or BET axes, thereby amplifying antitumor effects[173,175].

At the post-transcriptional level, CDC-like kinase 1 (CLK1) regulates alternative splicing programs that sustain oncogenic signaling and phenotypic adaptability. The pan-CLK inhibitor SM08502 (cirtuvivint) entered clinical testing before early termination; nevertheless, in preclinical studies, its combination with paclitaxel suppressed endometrial cancer xenografts, and the tool compounds TG003 and KH-CB19 remodeled splicing and constrained growth in gastric and breast models[154,176]. Class

Table 1 Pre-clinical small-molecule candidates targeting NCKs.

Family	Target	Number of modulators (about)	Compound	Cancer type	Mechanism	Ref.
Atypical-alpha	eEF2K	16	**Inhibitor:**NH125, Rottlerin, A-484954, compound **A1**, compound **A2**, compound **2W**, EC1, EC7, compound **2C**, Fluoxetine, oleuropein, Rhoifolin, TX-1918, Mitoxantrone **Activators:** Nelfinavir, everolimus	Triple-negative breast cancer, breast cancer, cervical cancer, glioma, glioblastoma, melanoma, prostate cancer, pancreatic cancer, colon cancer, osteosarcoma, non-small cell lung cancer, small cell lung cancer	1. Interfering with CaM binding sites, 2. Interfering ATP binding sites 3. Interfering with eEF2 binding sites	94
	TRPM7	34	**Channel blockers:** NS8593, waixenicin A, 2-APB, carvacrol, Midazolam, lidocaine, Spermine, Gd^{3+}, Xyloketal B, Quercetin, TRPM7-IN-1 Kinase inhibitors: TG100-115, VER155008, CCT128930, TG100713, JNJ-7706621 **Multitarget inhibitors:** FTY720, MK886, AA861, Rottlerin, PHA-665752, Butein, Naltriben mesylate, DMS (dimethylsphingosine), Sphingosine, Cholesterol, NDGA, Piperlongumine, Cannabigerolic acid **Natural compounds:** Ginsenoside Rd/Rg3, Xeniafaraunol A (compound **31**), Ulmi Pumilae Cortex, *Buxus Microphylla* var. *Koreana Nakai* extract	Glioblastoma, breast cancer, stomach cancer, leukemia, head and neck cancer, brain cancer, prostate cancer, colon cancer	1. Channel function inhibition, direct blockade of TRPM7 channel activity, inhibition of Mg^{2+} and Ca^{2+} influx, usually acting on channel pore sites or regulating gating mechanisms. 2. Kinase function inhibition, targeting the kinase domain of TRPM7, inhibiting its enzymatic activity rather than channel function.	146,147
Atypical-TIF1	TRIM24/TIF1α	7	IACS-9571, IACS-9571 (trifluoroacetate), IACS-9571 hydrochloride, Y08624, TRIM24-IN-11d, TRIM24-IN-11h, BRPF1B/TRIM24-IN-1 (compound **34**)	Prostate cancer, breast cancer, acute myeloid leukemia, non-small cell lung cancer, multiple myeloma	1. Inhibits the binding of bromodomains to acetylated histones 2. Induced targeted degradation (PROTAC)	148,149
Atypical-other	TAF1	9	CeMMEC13, CeMMEC1 HCl, BAY-299, BAY-364 (BAY-299N), AZD6738, Tafbromin, GNE371, N2817, 3i-1248	Lung adenocarcinoma, acute leukemia, triple-negative breast cancer, acute myeloid leukemia, sinus squamous cell carcinoma, colorectal cancer, pancreatic cancer	1. BrD inhibition: Blocks the binding of BrD1 or BrD2 to histone acetylation modifications of TAF1 2. TAF1 protein degradation (PROTAC). 3. Dual-targeted strategies (single kinase and dual kinase/bromodomain inhibition)	150-153

Table 1 (*continued*)

Family	Target	Number of modulators (about)	Compound	Cancer type	Mechanism	Ref.
Atypical-ePKs	CLK1	24	**Non-selective inhibitors:** CX-4945, Leucettine L41, CC-671, Indazole1, ML106, ML167, ML315, Thiophene 48, KuWal151, TCMDC-135051 **Selectivity inhibitors:** TG003, TG693, KH-CB20, SRI-29329, DB18, K00546, Cpd-2, 3A5, T3, AB1, T-025, MU1210, SGC-CLK-1, Pyrido[3,4-*g*]quinazoline 9m	Gastric cancer, breast cancer, prostate cancer, colorectal cancer, ovarian cancer, uterine cancer, non-small cell lung cancer, lung cancer, bile duct cancer, pancreatic cancer, leukemia, multiple myeloma, glioblastoma, osteosarcoma	1. Targeting CLK1 regulates SR protein phosphorylation, which in turn alters the alternative splicing patterns of tumor-associated genes (*e.g.*, BCL-X, MCL1, MYC) to induce apoptosis or sensitization 2. Synthetic lethality in combination with specific pathway mutations (*e.g.*, MYC overexpression, *SF3B1* mutations, *TP53* inactivation) or known drugs (*e.g.*, EGFR inhibitors). 3. By interfering with multiple oncogenic kinase pathways (*e.g.*, CLK/DYRK/SRPK/CK2) simultaneously, it induces broad-spectrum antitumor effects at the expense of selectivity	154,155
	CDK14-20	17	**CDK14-18:** JA397, FMF-04-159-R, FMF-04-159-2,JNK-IN-7 analogs **CDK8/19:** Senexin A, Senexin B, SEL120-34A, CDK8/19-IN-1, CDK8/19-IN-2 (compound **12**), CDK8/19-IN-3 (compounds **3**−**7**), CDK8-IN-16 (compound **51**), AS2863619, JH-XVI-178, CDK19 probe 1 (compound **10c**) **CDK18:** PF-3758309, **CDK16/17:** CDKi-73 **CDK17:** BMS-387032	Acute myeloid leukemia, myelodysplastic syndrome, triple negative breast cancer, hormone receptor positive breast cancer, colorectal cancer, non-small cell lung cancer, ovarian cancer, prostate cancer, chronic lymphocytic leukemia, multiple myeloma, and solid tumors	1. Competes for the ATP-binding site of CDK kinase, inhibiting its phosphate transfer function 2. Sustained inhibition is achieved by irreversibly binding to the kinase active site by covalent bonds, typically with Cys residues 3. Multi-target inhibition, targeting only partially CDK14−20 while inhibiting other CDKs or other targets	156,157

(*continued on next page*)

Table 1 (*continued*)

Family	Target	Number of modulators (about)	Compound	Cancer type	Mechanism	Ref.
	WNK	6	**WNK1:** WNK1-IN-1, WNK-IN-11, Trihalosulfone 1 **WNK3**: SW120619, **Pan-WNK:** STOCK2S-26016, WNK463, Tyrphostin 47	Breast cancer, non-small cell lung cancer, liver cancer, colorectal cancer, glioblastoma, clear cell renal cell carcinoma, cholangiocarcinoma	1. WATP binding site competition inhibition, blocking its kinase activity, and inhibiting its downstream signaling (such as SPAK/OSR1 pathway); 2. allosteric site inhibition; 3. Interfacial interference or inhibition of protein-protein interactions, blocking the binding of WNK to downstream regulatory proteins (*e.g.*, SPAK, OSR1) or interfering with the dimeric interface required for its activation.	158
	TBK1	23	GSK8612, BX795, MRT67307, MRT68601, TBK1-IN-1, TBK1/IKKε-IN-4, TBK1/IKKε-IN-2, TBK1/IKKε-IN-6 (example 110), TBK1/IKKε-IN-5 (compound 1), TBK1/IKKε-IN-1, BAY-985, S3648 Amlexanox, MRT68601, DMXD-011, WEHI-122 (STING complex disruptor), Idronoxil (IDX), DMX-129, BX795, Amlexanox, GSK319347A, Domainex, CYT387	Lung cancer (KRAS-mutant non-small cell lung cancer), pancreatic cancer (KRAS-driven), prostate cancer, melanoma, hepatocellular carcinoma, endometrial cancer, colorectal cancer, breast cancer, acute myeloid leukemia, multiple myeloma, glioma, osteosarcoma, stomach cancer	1. Competitive binding to the ATP-binding pocket of the TBK1 kinase domain, thereby blocking its kinase activity 2. The exact ATP-site binding mechanism typically achieves inhibition of both TBK1 and its close family IKKε 3. Indirectly inhibited TBK1 function by disrupting the activating signaling complex of TBK1 and affecting its upstream regulation	115
	Haspin	29	Haspin-IN-1 (compound **2a**), Haspin-IN-2 (compound **4**), Haspin-IN-3 (compound **8l**), Haspin-IN-4 (compound **60**), LDN-209929, HSK205, LDN-192960,	Cervical cancer, colorectal cancer, breast cancer, pancreatic cancer, melanoma (especially for RAF/MEK inhibitor-resistant types), Ewing sarcoma, multiple	1. Inhibits Haspin-mediated phosphorylation of histone H3-Thr3 and anti-mitosis	159,160

Table 1 (*continued*)

Family	Target	Number of modulators (about)	Compound	Cancer type	Mechanism	Ref.
			LDN-211898, CHR-6494, CX-6258, MU1920, MELK-8a, LJ4827, compound **22**, compound **19**, Haspin-IN-5/21, 5-Iodotubercidin (5-ITu), SGI-1776, Harmine, Harmol, AnnH75, ARC-3353, ARC-3372, HSD972, **5f**, **5q**, **7h**, **7f**, SCH772984,	myeloma, acute myeloid leukemia, lung cancer, liver cancer, neuroblastoma, prostate cancer (related to dual-targeted inhibitors such as SGI-1776)	2. Multi-target regulation, affecting mitosis and other key cancer signaling pathways (*e.g.*, PIM/ERK/Aurora, etc.). 3. Natural product derivative, broad-spectrum anti-cancer	
Atypical-Fam20	Fam20C	3	Compound **5k**, FL-1607, compound **3r**	Triple negative breast cancer	1. Blocks its ability to phosphorylate substrate proteins by competing with ATP-binding sites in the Fam20C kinase domain	140,161,162
Atypical-PDHK	PDHK1-4	23	**PDHK1:** JX06, PDHK1-IN-1 (compound **17**) **PDHK2:** AZD7545, TM-1, **PDHK4:** PDK4-IN-1, PDK4-IN-2 (compound **8**), GM10395, M77976 **PDHK2/4:** KPLH1130, Sodium dichloroacetate, **Pan-PDHK:** PS10, dichloroacetate (DCA), Leelamine, VER-246608, PDHK-IN-4 (compound **30**), PDHK-IN-5 (compound **19**), 11a, 19n, Huzhangoside A, PDHK-IN-4 (compound **30**), PDHK-IN-5 (compound **19**), PDHK-IN-3 (compound **7**), PDHK-IN-7 (compound **32**),	Multiple myeloma, endometrial cancer, non-small cell lung cancer, lung cancer, prostate cancer, breast cancer, oral cancer, Kidney cancer, pancreatic cancer, neuroblastoma, vestibular schwannoma, esophageal cancer, melanoma, liver cancer	1. Competitive binding to ATP sites inhibits kinase activity; 2. Covalently modified key cysteine residues and irreversibly inhibited PDHK activity. 3. Regulate the conformational or coenzyme binding site to interfere with its binding to the PDC and inhibit phosphorylation function.	163

CDK, cyclin-dependent kinase; CLK1, CDC-like kinase 1; eEF2K, eukaryotic elongation factor 2 kinase; ePKs, eukaryotic protein kinases; ERK, extracellular signal-regulated kinase; Fam20C, family with sequence similarity 20C; JNK, c-Jun N-terminal kinase; KRAS, Kirsten rat sarcoma viral oncogene; PDC, pyruvate dehydrogenase complex; PDHK, pyruvate dehydrogenase kinase; OSR1, oxidative stress-responsive kinase 1; PROTAC, proteolysis-targeting chimera; SPAK, TE20/SPS1-related proline-alanine-rich protein kinase; STING, stimulator of interferon genes; TAF1, TATA-box binding protein-associated factor 1; TBK1, TANK-binding kinase 1; TRPM7, transient receptor potential melastatin 7; WNK, With-No-Lysine (K) kinase.

liabilities persist—including isoform redundancy across CLK1/2/3/4, cross-reactivity with DYRK kinases, and system-wide splicing perturbations that raise safety concerns. More selective chemotypes (*e.g.*, SRI-29329, DB18) point to isoform- or substrate-biased inhibition strategies that could confine activity to tumors addicted to specific splice variants[177].

Collectively, these drug classes rewire transcriptional and splicing dependencies that sustain proliferation and survival, reinforcing a recurring principle: reader/bromodomain occupancy rarely suffices, whereas targeted degradation, dual-node inhibition, and biomarker-guided combinations more effectively convert hallmark-level dependencies into durable therapeutic responses.

4.3. Disrupting mitotic and cell cycle regulation

Pharmacologic disruption of mitosis and noncanonical cell-cycle control reveals liabilities aligned with sustained proliferation and genome instability, while opening avenues to overcome therapy

adaptation. HASPIN, the histone H3 Thr3 kinase that licenses chromosome alignment, is druggable: CHR-6494, CX-6258, and LJ-4827 suppress H3T3 phosphorylation, trigger mitotic catastrophe, and produce robust xenograft activity (colorectal, pancreatic, breast, melanoma) with acceptable tolerability[178-180]. Clinical translation has lagged because many scaffolds exhibit poor pharmacokinetics, metabolic instability, and inadequate intratumoral exposure, and functional redundancy with Aurora B or vaccinia-related kinase 1 (VRK1) can blunt monotherapy, consistent with CHR-6494 resistance reported in breast cancer models [181]. Clinically actionable HASPIN inhibition will likely require biomarker-driven patient selection, for example, in AML, which is characterized by mitotic vulnerabilities[182,183].

Orphan CDKs extend this axis beyond the canonical CDK4/6 pair. Covalent engagement has been a notable advance—FMF-04-159-2 durably targets CDK14/16, enforces G2/M arrest, and preferentially impairs triple-negative and stem-like phenotypes by dampening Wnt/β-catenin signaling[184,185]. The probe JA397 supports mechanistic mapping. In the CDK8/19 space, SEL120-34A has advanced to first-in-human AML studies, demonstrating low-nanomolar potency and STAT1/5 signaling repression[186]. Tool compounds (Senexin A/B, the CDK8/19-IN series, AS2863619, JH-XVI-178) and the selective CDK19 Probe 1 refine selectivity and biology[156]. Programs for CDK16/17 (CDKi-73) and CDK18 (PF-3758309) remain early with limited *in vivo* validation. The CDK20 lacks highly selective inhibitors. The central translational challenge is to achieve target selectivity and sufficient exposure *in vivo* while sparing conventional CDKs to avoid global cell-cycle collapse[156]. Inhibition of the Mediator kinases also raises concerns about on-target effects on standard intestinal transcription.

Overall, HASPIN and CDK14−CDK20 inhibitors convert mitotic control into a tractable dependency. Further progress will hinge on covalent or allosteric chemotypes with improved pharmacokinetics, degrader strategies for recalcitrant nodes, biomarker-guided patient selection, and rational combinations that broaden the therapeutic window without compromising essential proliferative functions in normal tissues.

4.4. Targeting tumor invasion and microenvironment remodeling

Targeting the TRPM7 channel-kinase and the secretory-pathway kinase FAM20C renders invasion, metastasis, and microenvironmental adaptation pharmacologically tractable[142]. TRPM7 integrates divalent-cation flux with atypical Ser/Thr kinase signaling to drive motility and survival. Most agents act on the pore: lidocaine and carvacrol inhibit currents nonselectively; NS8593—a Mg^{2+}-dependent blocker originating from SK-channel programs—reduces the viability of TNBC and breast adenocarcinoma cells *via* STAT3 inhibition and TRAIL sensitization; waixenicin A is more selective and, at 50 μmol/L, halves MCF-7 viability and induces G0/G1 arrest, indicating heightened dependence under nutrient stress[141,187]. Kinase-directed tool compounds corroborate the migratory role of the catalytic domain: TG100-115 competes at the ATP site, lowering CREB phosphorylation and suppressing migration/invasion in breast and pancreatic models, although parallel inhibition of PI3K−p110δ complicates attribution[188]. Structural insights from CCT128930 point to a vanilloid-like pocket that may confer selectivity[146]. Collectively, TRPM7 inhibitors blunt hallmarks of invasion and metastasis, microenvironmental adaptation, and resistance to cell death, yet class liabilities persist—cross-reactivity with other TRP/SK channels, incomplete kinase selectivity, and limited exposure. Next steps include pore blockers with improved selectivity, bona fide kinase inhibitors or degraders, and dual channel/kinase chemotypes; combinations with cytoskeletal or ion-channel modulators and chemotherapy may amplify anti-motility effects.

FAM20C resides in the Golgi and phosphorylates a broad set of extracellular substrates—including basement-membrane components and secreted growth factors—positioning it as a regulator of stromal architecture, growth-factor bioavailability, and metastatic niche formation[12]. First-in-class small molecules validate their druggability: FL-1607 inhibits FAM20C and, in TNBC cells, induces apoptosis and blocks migration[161]; compound **5k** and compound **3r** further suppress proliferation and motility, collectively demonstrating that editing the extracellular phosphoproteome can restrain aggressive phenotypes[162]. These ATP-competitive scaffolds still face hurdles in potency, selectivity, and subcellular delivery; achieving effective Golgi localization while sparing normal secretory pathways (*e.g.*, bone mineralization) is central to maintaining an adequate therapeutic window. Because FAM20A functions as an allosteric activator, disrupting the FAM20C−FAM20A interface or developing non-ATP-site allosteric inhibitors offers a route to selectivity.

Together, TRPM7 and FAM20C inhibitors operationalize invasion- and tumor-microenvironment-centric dependencies that complement cytotoxic or pathway-targeted agents. Pharmacodynamic anchors—ion-flux suppression, STAT3/TRAIL sensitization, and CREB dephosphorylation for TRPM7; loss of extracellular-substrate phosphorylation or migration readouts for FAM20C—can guide patient selection. Further progress will rely on structure-guided design to improve selectivity.

4.5. Overcoming survival signaling and therapeutic resistance

TBK1 sits at the interface between oncogenic and innate immune circuitry. The small-molecule landscape spans dual TBK1/IKKε inhibitors and more selective TBK1 agents[189]. BX-795, an early chemotype, inhibits TBK1/IKKε but also engages PDHK1, blocks IRF3 activation, and induces cell death in selected lines—biologically informative yet confounded by polypharmacology. MRT67307 provides potent dual TBK1/IKKε inhibition, *in vivo* anti-inflammatory activity, and is widely used to probe tumor dependence. GSK8612 achieves high biochemical selectivity for TBK1, although a full *in vivo* profile remains pending[190]. In cancer models, TBK1 blockade reveals context-specific vulnerabilities, including synthetic lethality in VHL-null backgrounds and sensitization of KRAS-driven tumors to MEK inhibitors and cytotoxics[122,191]. Despite these signals, no clinical TBK1 inhibitor has advanced to trials, reflecting concern that systemic blockade may blunt interferon responses and rewire innate pathways; indeed, inhibiting TBK1/IKKε can reroute signaling to other NF-κB kinases[192]. A drug-centric strategy is therefore clear: prioritize selectivity and kinome cleanliness (separating TBK1 from IKKε and PDHK1), use pharmacodynamic anchors (TBK1 autophosphorylation, p-IRF3, interferon-stimulated gene signatures) and genetic context (KRAS mutation, VHL loss) for patient selection, and deploy combinations that exploit network wiring—such as MEK inhibitors in RAS tumors. Executed in this way, TBK1 becomes a tractable node for converting innate-linked survival and resistance into therapeutic liabilities.

4.6. Opportunities and challenges in targeting non-canonical kinases

NCKs reveal tractable dependencies across multiple cancer hallmarks, yet their pharmacology spans a broad spectrum of druggability and translational risk. Pathway redundancy remains a central constraint: PDHK blockade can be metabolically bypassed; other TRP/SK channels can offset TRPM7 pore inhibition; and HASPIN-mediated mitotic control is buffered by Aurora B or VRK1. Rational combinations can convert this liability into leverage—VER-246608 gains activity with DNA-damaging agents or under low-glucose conditions; TBK1/IKKε antagonism sensitizes KRAS-driven tumors to MEK inhibitors and can be combined with immunotherapy; and eEF2K modulation heightens responses to nutrient restriction or mTOR inhibition. High kinome cleanliness is essential to broaden the therapeutic window: GSK8612 refines on-target TBK1 biology, whereas polypharmacology (*e.g.*, BX-795 also inhibiting PDHK1) obscures efficacy and safety. Subcellular and tissue context further shape success: FAM20C inhibitors (*e.g.*, FL-1607, 5k) must achieve Golgi exposure while sparing normal secretory pathways, and potent WNK blockers require strategies to mitigate electrolyte liabilities.

Moreover, several NCKs already demonstrate that mechanistically distinct inhibitor chemotypes can target the same kinase. For PDHK1, for example, the pan-isoform ATP-competitive inhibitor VER-246608 occupies the canonical nucleotide-binding cleft. It makes classical hinge hydrogen bonds in the catalytic domain. In contrast, the covalent inhibitor JX06 exploits a nearby Cys240-containing hydrophobic subpocket adjacent to the ATP site to form an irreversible adduct and lock PDHK1 in an inactive conformation. WNK kinases provide a similar contrast: WNK463 is a type I ATP-competitive inhibitor that binds in the catalytic cleft, while newer back-pocket binders such as WNK-IN-11 engage a lateral cavity formed by the outwardly displaced αC-helix and activation loop next to the ATP site, allosterically stabilizing an inactive conformation and improving isoform selectivity. TBK1 has likewise evolved from broad, dual-kinase scaffolds to highly selective probes: first-generation inhibitors such as BX-795 and MRT67307 are ATP-competitive and potently inhibit both TBK1 and IKKε, whereas the later probe GSK8612 retains an ATP-site binding mode but uses a refined pyrazolopyrimidine scaffold that better complements unique TBK1 hinge and back-pocket residues, dramatically sharpening kinome selectivity.

Reader-type NCKs also illustrate how distinct chemotypes and modalities can address the same structural module. In TRIM24, the monovalent inhibitor IACS-9571 simply occupies the acetyl-lysine binding pocket of the bromodomain. In contrast, PROTAC degraders such as dTRIM24 reuse the same KAc pocket as a warhead but append an E3-ligase ligand to trigger proteasomal degradation, and recently described bivalent ligands bridge the PHD-BRD tandem to engage both the methyl-lysine and acetyl-lysine reader sites simultaneously. In TAF1, GNE-371 is a highly selective monovalent inhibitor that fits into the canonical KAc pocket of BD2, in contrast to ceralasertib-derived dual TAF1−ATR ligands that contact both bromodomains and remodel their open/closed conformational equilibrium. Modular proteins such as TRPM7 can be blocked at different levels: allosteric channel blockers (*e.g.*, NS8593 and related CCT compounds) bind a lipid-exposed pocket in the transmembrane region and displace an endogenous phospholipid, whereas ATP-competitive inhibitors such as TG100-115 and CCT128930 occupy the active site of the cytosolic kinase domain. Even for ostensibly "simple" ATP-site targets such as Haspin, CLK kinases and the secretory kinase FAM20C, scaffold hopping within the catalytic cleft has yielded distinct chemotypes—from planar heteroaromatic hinge binders (*e.g.*, CHR-6494, early CLK inhibitors) to nucleoside-like or diaryl amide/urea scaffolds—that differ in how deeply they penetrate back pockets, how they engage the glycine-rich loop and activation segment, and thus in kinome selectivity, residence time and tolerability.

Taken together, these examples highlight that, even within a single non-canonical kinase, different inhibitors may share the same orthosteric ATP site but use divergent scaffolds and subpocket contacts, or deliberately reroute binding to adjacent cysteine-containing subpockets, allosteric cavities, or non-catalytic reader domains. Pocket choice (ATP cleft *versus* back pocket, cysteine subpocket, or transmembrane allosteric site) and chemotype design (reversible versus covalent, monovalent versus bivalent, or degrader-based) are therefore key levers for tuning on-target efficacy, kinome selectivity, and safety when drugging NCKs.

A development playbook emerges: structure-guided design spanning orthosteric, allosteric, covalent, and degrader-based modalities; biomarker anchors—phosphorylated eEF2, p-PDC/lactate, histone H3 threonine-3 phosphorylation (H3T3ph), interferon-stimulated gene signatures, and extracellular phosphosite readouts for FAM20C—to select patients and titrate dose; and context-tuned combinations aligned with stress, metabolic, mitotic, or innate-immune wiring. With these elements, unconventional kinase biology can be translated into durable therapeutic control while minimizing collateral damage to essential proliferative and secretory functions (Fig. 3).

5. Clinical and approved inhibitors

5.1. DNA damage-related NCKs

DNA damage-related NCKs convert genomic instability into therapeutic leverage by clinically tractably inhibiting ATM, ATR, and DNA-PKcs. Once considered undruggable, ATM has yielded selective ATP-competitive chemotypes (KU-55933, KU-60019, CP-466722, KU-59403, AZ31, AZ32) that enabled combination strategies and informed clinical entrants[193,194]. AZD0156 established oral ATM blockade and synergy with PARP inhibitors and topoisomerase poisons but was halted, likely owing to hematologic toxicity and limited incremental benefit (NCT02588105). The brain-penetrant analog AZD1390 improved CNS exposure, radiosensitized glioblastoma, and activated cGAS−STING with manageable safety in early trials (NCT03423628). Merck's M3541 underperformed due to PK/efficacy gaps; the follow-up agent, M4076, improved solubility and potency, induced xenograft regressions, and is being tested alone and in combination with PARP/ATR inhibitors or immunotherapy[195]. Domestic programs broaden the field: ZN-B-2262 enhances radiosensitivity and irinotecan synergy and is in early trials for head and neck cancer; SYH2051 reflects expanding interest; and WSD-0628, a highly potent, brain-penetrant ATM inhibitor, robustly radiosensitizes glioma and has entered phase I for recurrent high-grade disease[196]. Dual targeting further strengthens repair blockade: XRD-0394 inhibits ATM/DNA-PKcs, simultaneously disabling HR and NHEJ, radiosensitizing glioblastoma and head-and-neck models, and advancing into clinical trials with radiotherapy (NCT05002140). Overall, ATM programs now emphasize CNS-

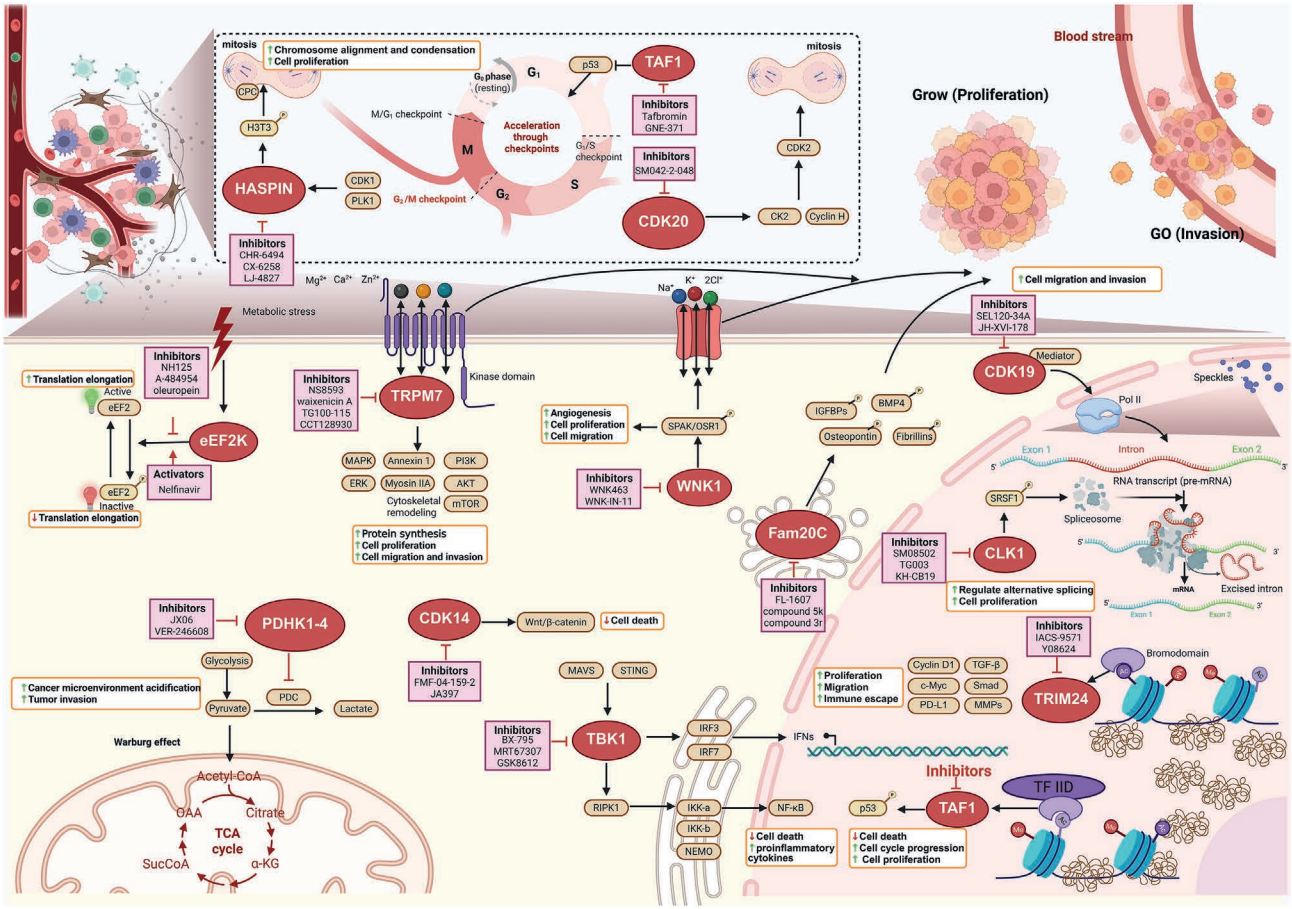

Figure 3 Mechanism and targeting strategy of NCKs in tumors. This figure systematically shows the potential functions and targeted intervention pathways of NCKs currently in preclinical research for the development and progression of cancer, encompassing multiple key pathways, including cell proliferation, metabolic reprogramming, transcriptional regulation, RNA splicing, cell migration/invasion, and immune evasion.

active agents, biomarker selection, and combination regimens to offset modest monotherapy activity[197].

ATR inhibition has advanced rapidly, with more than a dozen agents in clinical trials and activity enriched in biomarker-defined tumors. Ceralasertib (AZD6738) yields durable disease control in ATM- or HR-deficient settings when combined with PARP inhibitors or PD-L1 blockade, although hematologic toxicity is limiting[198]. Elimusertib (BAY 1895344) shows activity in ATM-deficient tumors but causes myelosuppression in combination with cytotoxic agents[199]. Camonsertib (RP-3500) demonstrates efficacy in HR-deficient cancers with intermittent dosing and is being paired with PARP or PKMYT1 inhibitors[200]; Tuvusertib (M1774) achieves exposure-driven target engagement and can be combined with temozolomide or immunotherapies (NCT04170153)[201]. Berzosertib (VX-970) shows clinical activity, but combination-related adverse events curtailed parts of its program[202]; gartisertib (M4344) was discontinued due to UGT1A1-mediated hepatotoxicity[203]. Next-generation entries—ART0380 (reduced CHK1-linked cytopenias), the brain-optimized SC0245, and early-phase agents ATRN-119, ATG-018, IMP9064, TCC1727, and HRS2398—aim to refine selectivity, pharmacokinetics, and CNS access[204-206]; preclinical AD1058 and AI-designed series expand the scope toward DNA damage-driven and CNS indications[207].

DNA-PKcs, a lynchpin of NHEJ, shows its most substantial benefit in combination therapies. AZD7648 synergizes potently with PARP inhibitors and radiation, although monotherapy activity is limited[208].; Peposertib (M3814) is orally bioavailable and well tolerated with radiotherapy, with skin toxicity and fatigue most common[209]; VX-984 demonstrated glioma radiosensitization before discontinuation[210]. Dual inhibitors intensify network pressure: BR101801 targets DNA-PKcs and PI3Kδ/γ to couple repair blockade with immunomodulation[211]; XRD-0394 likewise provides dual blockade of double-strand break repair; and CC-115 co-inhibits DNA-PKcs/mTOR to add metabolic stress. Emerging preclinical agents (DA-143, WNC0901, BAY-8400) further enhance radio- and chemosensitization[212]. Even so, clinical translation has been limited by modest single-agent activity, overlapping toxicities, and the absence of robust predictive biomarkers. The strategic value of NCKs inhibition—particularly in biomarker-defined, DDR-deficient, or combination-driven contexts—remains substantial. Future progress will depend on refined patient stratification, optimized dosing schedules, and rational combinatorial design to fully realize the therapeutic promise of this critical DNA-repair target.

5.2. *Nutrient-sensing NCKs*

mTOR therapeutics exploit tumor nutrient-sensing addiction across metabolic reprogramming, sustained proliferation, and therapy resistance. First-generation rapalogs—sirolimus, everolimus, and temsirolimus—are FKBP12-dependent allosteric

mTORC1 inhibitors with clinical benefit in Lymphangioleiomyomatosis, subependymal giant cell astrocytoma, neuroendocrine tumors, breast cancer, and renal cell carcinoma[69]; ABI-009 (albumin-bound sirolimus) extends use to PEComa, whereas topical NPC-12G and PTX-022 broaden dermatologic applications[213]. Their ceiling reflects preserved mTORC2 signaling and AKT feedback, motivating more profound pathway suppression and combinations. Second-generation ATP-competitive inhibitors (sapanisertib/TAK-228, AZD8055, vistusertib/AZD2014) co-target mTORC1/2, strengthen S6K and 4E-BP blockade, and show activity in non-small cell lung cancer (NSCLC), endometrial carcinoma, glioblastoma, and bladder cancer, albeit with increased mucocutaneous, metabolic, and hematologic toxicities that favor intermittent or exposure-guided dosing[214,215]. Dual PI3K/mTOR agents address network redundancy upstream and downstream: BEZ235 established feasibility despite toxicity[214]; Dual PI3K/mTOR agents address network redundancy upstream and downstream: BEZ235 established feasibility despite toxicity[214]; later entries—gedatolisib in HR-positive breast and endometrial cancers, samotolisib (PI3K/mTOR/DNA-PKcs), omipalisib, paxalisib for glioblastoma, voxtalisib, and apitolisib in ovarian and prostate settings—illustrate the trade-off between breadth and tolerability, underscoring the need for predictive biomarkers. Next-generation designs emphasize selective depth and feedback control. Bi-steric mTORC1 inhibitors (*e.g.*, RMC-6272) combine FRB engagement with catalytic blockade to restore 4E-BP restraint while sparing mTORC2, aiming to curb AKT rebound and metabolic adverse events[216]. Multi-target scaffolds (IBL-302, XL-388), refined ATP-competitive chemotypes from academic pipelines, and natural-product-inspired modulators expand the toolkit[217]. Treatment positioning favors biomarker-guided combinations: endocrine therapy in HR-positive disease; PARP inhibitors or radiotherapy in replication-stressed tumors; KRAS/MEK or CDK4/6 inhibitors to constrain compensatory signaling; and checkpoint blockade in metabolically inflamed microenvironments.

5.3. *Mitotic and polarity-related NCKs*

Mitotic- and polarity-related NCKs create druggable leverage points that intersect proliferation, invasion-metastasis, therapy resistance, genome instability, and immune evasion. Atypical PKC isoforms (PKCζ, PKCι/λ) exemplify this duality: context can render them oncogenic or tumor suppressive, yet several chemotypes already exploit their signaling architecture. Gold-based PB1—Par6 disruptors—such as aurothiomalate and auranofin (and the derivatives ATG and Na-ATM)—dismantle polarity scaffolds and curb tumor growth in NSCLC and ovarian cancer models, with early clinical exploration and signals of heightened responsiveness to immunotherapy, even as metal-associated toxicity narrows the therapeutic window[218]. Catalytic-site ligands push selectivity further: ICA-1S (PKCι-selective) and ζ-Stat (PKCζ-directed) inhibit proliferation across breast, ovarian, colorectal, glioblastoma, and melanoma models, disrupt 14-3-3 coupling and c-RAF/ERK output, and synergize with cisplatin, 5-FU, PI3K inhibitors, or rapamycin—evidence that aPKC blockade can simultaneously throttle growth programs and erode resistance niches[219]. Allosteric PIF-pocket binders such as PS432 add a third axis, potentiating proteasome and PI3K inhibition in lung cancer, although this class remains early in development.

MELK illustrates the volatility of mitotic targets as therapeutic anchors: overexpression and links to FOXM1, G2/M control, and apoptosis propelled OTSSP167 into clinical trials and yielded broad preclinical cytotoxicity and radiosensitization; however, CRISPR-based studies questioned MELK essentiality, and off-target liabilities eroded mechanistic confidence, leading to program termination[220-222]. Nevertheless, OTSSP167 consistently sensitizes tumors to paclitaxel, cisplatin, 5-FU, and radiotherapy across glioma, TNBC, ovarian, and gastric models, positioning MELK as a co-target to overcome therapy resistance; next-generation, cleaner chemotypes (*e.g.*, compound **30e**) aim to restore specificity and context dependence[223].

CDK5, a noncanonical CDK activated by p25, links cytoskeletal dynamics, survival signaling, and immune modulation. Clinical experience has derived mainly from pan-CDK agents: (*R*)-roscovitine and flavopiridol established tractability but lacked selectivity[224]; dinaciclib (CDK1/2/5/9) achieved potent preclinical control and downregulated PD-L1 with increased T-cell infiltration, yet myelosuppression constrained dosing[225]; AT7519 showed activity amid class-wide toxicities, whereas PHA-793887 was discontinued because of hepatotoxicity[226,227]. A precision turn is now evident, with tumor-selective CDK5 inhibitors such as LGR3087, dual CDK5/GSK3β agents like valmerin-19, and PROTAC degraders including TMX-2172 that aim for durable, selective suppression[228-230]. These next-generation compounds are expected to overcome resistance and reduce systemic toxicity. Notably, CDK5 inhibition sensitizes resistant tumors to chemotherapy and immunotherapy: in TNBC, CDK5 blockade reduces cancer stemness and enhances the anti-PD-1 response[231,232]. It also restores chemosensitivity and reshapes the immune microenvironment—effects that may confer advantages over conventional proliferation-focused CDK inhibitors[233,234].

5.4. *Dual-function epigenetic NCKs*

BET-directed therapeutics convert epigenetic addiction into a tractable vulnerability across sustained proliferation, transcriptional plasticity, and therapy resistance. It is worth emphasizing that current BET-directed therapeutics (small-molecule inhibitors and PROTACs) do not modulate a kinase domain of BRD proteins. Instead, they either compete with acetyl-lysine for the conserved KAc pocket within BET bromodomains or drive ubiquitin-dependent degradation of the entire protein. These agents are therefore conceptually distinct from small molecules that inhibit canonical or atypical serine/threonine kinases, even though BRD4 has historically been discussed in the context of non-canonical kinase networks. Pan-BET inhibitors that engage BRD2/3/4 BD1 and BD2—OTX015 (MK-8628), GSK525762 (I-BET762), ABBV-075, and CPI-0610—established on-target transcriptional suppression, with CPI-0610 plus ruxolitinib delivering clinical benefit in myelofibrosis[235-238]. Class liabilities—dose-limiting thrombocytopenia from megakaryocytic dependence and gastrointestinal intolerance—have constrained the intensity of monotherapy. Next-generation agents (PLX51107, FT-1101, INCB057643, BMS-986158/986378, GSK2820151, GS-5829, ZEN003694, BAY1238097, ODM-207) improve pharmacokinetics and broaden testing to AML and solid tumors, often in biomarker-enriched or combination regimens[239]. A precision turn favors isoform- or domain-selective strategies to preserve efficacy while widening the therapeutic window. BD2-selective compounds ABBV-744 and NUV-868 retain antitumor activity with reduced hematologic toxicity, consistent with a greater BD1 contribution to normal hematopoiesis[240,241]. AZD5153, a bivalent BRD4 binder, engages both bromodomains to deepen occupancy[242]; SYHA1801 and PLX-2853 extend BRD4-biased

approaches across solid tumors, and BI894999 targets BRD4-driven nuclear protein in testis (NUT) carcinoma[243,244]. These designs aim to sustain repression of super-enhancer-driven programs (*e.g.*, MYC, E2F) while minimizing off-tumor effects. Degradative modalities push beyond occupancy: the PROTAC ARV-771 achieves more profound BET suppression by catalyzing proteasomal loss, offering a route to overcome adaptive enhancer rewiring, isoform compensation, and kinase-mediated BET phosphorylation that blunt conventional inhibitors[245]. Tumor-selective delivery strategies further promise to confine exposure and mitigate systemic cytopenias[246]. Collectively, these emerging modalities may overcome resistance and broaden the therapeutic window of BET inhibition. The clinical trajectory of BET inhibitors has shifted from broad-spectrum pan-BET blockade toward precision-guided isoform- or domain-selective approaches; although monotherapy efficacy remains modest, rational combinations and enhanced selectivity are expected to unlock the full therapeutic potential of BET-targeted agents in oncology.

5.5. *Emerging immunomodulatory NCKs*

Recent advances underscore the potential of ALPK1 as a target in cancer immunotherapy. Activation of ALPK1 with the small-molecule agonist PTT-936, an ADP-heptose analog, inhibits tumor growth and elevates cytokine levels in peripheral blood mononuclear cells, with synergistic antitumor activity when combined with immune checkpoint inhibitors[247]. PTT-936 is currently being evaluated in a Phase I clinical trial as monotherapy or in combination with checkpoint inhibitors in patients with locally advanced or metastatic solid tumors. Beyond PTT-936, other ALPK1 agonists, such as DF-006, are in clinical trials for noncancer indications, underscoring the therapeutic versatility of ALPK1 modulation[248]. Patents have disclosed benzothiazole and quinoline derivatives as ALPK1 inhibitors with potential applications in lung and colon cancers, although detailed data have not yet been published. Collectively, these findings suggest that both activation and inhibition of ALPK1 may be strategically leveraged in cancer therapy, either as stand-alone treatments or in combination with established immunotherapeutic approaches. Continued research and clinical evaluation are required to define the role of ALPK1 modulators in oncology.

5.6. *Clinical lessons of druggable NCKs*

Several unifying lessons emerge from these clinical efforts. Durable monotherapy responses are uncommon and occur mainly when tumors are highly dependent on a single hallmark-driven pathway, as seen with mTOR in proliferative signaling and ATR in defective DNA repair (NCT00411619, NCT02223923). Consequently, combination therapy has become the dominant paradigm, with positive examples—such as ATR plus PARP inhibitors or BET plus JAK inhibitors—contrasting with toxic failures (*e.g.*, DNA-PKcs plus chemotherapy), underscoring the need for rational, hallmark-guided pairing (NCT03462342, NCT04606446, NCT02516813). Patient selection is essential because biomarker-defined vulnerabilities—such as *HRD*, *ATM*, and *BRCA* status, or transcriptional addiction—strongly influence outcomes (Tables 2 and 3).

At a broader level, the NCKs that have progressed to clinical development share defining properties that distinguish them from less tractable kinases. Despite atypical architectures, many contain features amenable to small-molecule engagement, including

Table 2 Small-molecule inhibitors targeting NCKs in clinical trials.

Family	Target	Compound/drug	Disease	Mechanism	Combination Therapies	Clinical State	NCT Number
PKC	aPKCι	Aurothiomalate (ATM)	Non-small cell lung cancer	Inhibits the binding of the PB1 domain of PKCζ and PKCι to Par6	–	Phase I/II	NCT00575393 NCT01383668
		Auranofin (AUR)	Chronic lymphocytic leukemia (CLL), recurrent epithelial ovarian cancer	Inhibits the binding of the PB1 domain of PKCζ and PKCι to Par6	Sirolimus	Phase I/II	NCT01419691 NCT01747798 NCT01737502 NCT02126527
PIKK	mTOR	PTX-022 (Qtorin)	Lymphatic malformations, basal cell carcinoma	Novel formulation of sirolimus	–	Phase III	NCT05050149 NCT06653842
		Sapanisertib (TAK228)	Advanced KEAP1/NRF2 mutation lung squamous cell carcinoma, endometrial cancer, non-small cell lung cancer, bladder cancer, acute lymphoblastic leukemia, solid	ATP-competitive inhibitors inhibit both mTORC1 and mTORC2	Ziv-Aflibercept, paclitaxel, alisertib	Phase II	NCT05275673 NCT06463028 NCT04479306 NCT02417701

		tumors, glioblastoma, etc.				
	AZD8055	Recurrent glioma, advanced solid tumor, etc.	ATP-competitive mTOR inhibitors	αCD40 agonistic antibody, ABT-737	Phase I	NCT01316809
	Vistusertib (AZD2014)	Bladder cancer, non-small cell lung cancer, B-cell lymphoma, etc.	ATP-competitive mTOR inhibitors	BTKi (Calquence)	Phase II	NCT03334617
mTOR + PI3K	BEZ235 (dactolisib)	HR-positive breast cancer, endometrioma, primary neuroectodermal tumor, perivascular epithelioid cell tumor, urothelial carcinoma, breast cancer, leukemia	Inhibits mTORC1, mTORC2 and PI3Kα/γ/d/β	Radiotherapy	Phase III	NCT01756118 NCT01690871 NCT01628913 NCT01495247 NCT01290406 NCT01288092
	Gedatolisib	HR-positive breast cancer, endometrioma, colorectal cancer, acute myeloid leukemia, HER2-positive breast cancer, non-small cell lung cancer, breast cancer, etc.	Inhibits mTORC1, mTORC2 and PI3Kα/γ/d/β	Carboplatin + paclitaxel, CDK4/6i (palbociclib) + the aromatase inhibitor letrozole,	Phase III	NCT06757634 NCT02438761 NCT06190899 NCT05501886 NCT03698383
	Samotolisib (LY3023414)	Relapsed or refractory advanced solid tumors, non-Hodgkin lymphoma	Inhibits PI3Kα/β/δ/γ, DNA-PK, and mTORC1/2	Enzalutamide	Phase II	NCT03213678
	Omipalisib (GSK2126458)	Advanced solid tumors	Inhibits p110α/β/δ/γ and mTORC1/2	−	Phase I	NCT00972686 NCT01248858
	Paxalisib (GDC-0084)	Relapsed or refractory primary central nervous system lymphoma	Inhibits PI3Kα/β/δ/γ and mTOR	Radiotherapy	Phase II	NCT04906096 NCT03522298
	Voxtalisib (XL765)	Ovarian cancer, malignant tumors	Inhibits PI3K/mTOR	Low intensity pulsed ultrasound, navitoclax, rituximab + bendamustine	Phase II	NCT01936363 NCT01587040
	Apitolisib (GDC-0980)	Prostate cancer, ovarian cancer	Inhibits PI3K/mTOR	Abiraterone	Phase II	NCT01485861
ATM	AZD1390	Metastatic solid tumors, glioblastoma, and brain tumors	Prevent the repair of DSBs of cancer cells and enhance the anti-cancer effect of radiotherapy/ chemotherap	Radiotherapy, immune checkpoint inhibitors	Phase I	NCT05678010 NCT05182905 NCT03423628

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Table 2 (*continued*)

Family	Target	Compound/drug	Disease	Mechanism	Combination Therapies	Clinical State	NCT Number
		AZD0156	Advanced solid tumor	Prevent the repair of DSBs in cancer cells	Olaparib, irinotecan	Phase I	NCT02588105
		M4076 (Lartesertib)	Metastatic or advanced solid tumors	Prevent the repair of DSBs in cancer cells	PARPi, ATRi, ICI	Phase I	NCT05396833 NCT04882917
		M3541	Solid tumor	Prevent the repair of DSBs in cancer cells	Cisplatin	Phase I	NCT03225105
		WSD0628	Glioblastoma, metastatic brain cancer	Prevent the repair of DSBs in cancer cells	Radiotherapy	Phase I	NCT05917145
		SYH2051	Advanced solid tumors, locally advanced head and neck cancer	Prevent the repair of DSBs in cancer cells	Radiotherapy	Phase I	NCT06011291
		ZN-B-2262	Solid head and neck cancer	Prevent the repair of DSBs in cancer cells	Irinotecan	Phase I	CTR20222750
	ATR	ART0380	Solid tumor	Inhibit ATR-driven phosphorylation of chk1 and prevent DSB repair	Irinotecan	Phase II	NCT05798611 NCT04657068
		Berzosertib (VX970)	Solid tumors, small cell lung cancer, squamous non-small cell lung cancer, HER2-negative breast cancer, gastric cancer, prostate cancer, ovarian cancer, colorectal cancer, neuroendocrine tumors, head and neck cancer, bladder urothelial carcinoma, etc	Prevent DSB repair	Chemotherapy (DNA crosslinkers: Cisplatin and carboplatin, and topoisomerase inhibitors: Topotecan and irinotecan), PARPis, immune checkpoint inhibitors, radiotherapy	Phase II	NCT02567409 NCT03517969 NCT03641313 NCT03896503
		Camonsertib (RP-3500)	Advanced solid tumor	Prevent DSB repair	PARPi, RP-6306, radiotherapy	Phase II	NCT04972110 NCT04497116
		Tuvusertib (M1774)	Ovarian cancer, urothelial carcinoma, solid tumor, skin cancer, non-small cell lung cancer	Prevent DSB repair	Temozolomide, PARPi, immunotherapy combinations, peposertib	Phase II	NCT06433219 NCT06424717 NCT05947500 NCT05882734
		Ceralasertib (AZD6738)	Non-small-cell lung cancer, triple-negative breast cancer, advanced solid tumor, melanoma, osteosarcoma, pancreatic cancer	Prevent DSB repair	Paclitaxel, gemcitabine, trastuzumab, deruxtecan, PARPi, immunotherapy combinations, acalabrutinib	Phase III	NCT06732401 NCT05450692

	Elimusertib (BAY1895344)	Advanced or refractory solid tumors, fallopian tube cancer, ovarian cancer	Prevent DSB repair	Cisplatin, cisplatin + gemcitabine, irinotecan, topotecan, FOLFIRI, PARPi, immunotherapy combinations	Phase I	NCT05071209
	Gartisertib (M4344)	Advanced solid tumors, breast cancer	Prevent DSB repair	Carboplatin, PARPi	Phase I/II	NCT04655183
	ATRN-119	Advanced solid tumor	Prevent DSB repair	–	Phase I/II	NCT04905914
	ATG-018	Advanced solid tumors and hematological malignancies	Prevent DSB repair	–	Phase I	NCT05338346
	IMP9064	Advanced solid tumor	Prevent DSB repair	–	Phase I	NCT05269316
	SC0245	Small cell lung cancer	Prevent DSB repair	Irinotecan	Phase I/II	NCT05731518
	TCC1727	Advanced solid tumor	Prevent DSB repair	–	Phase I	NCT05970016
	HRS2398	Advanced solid tumor	Prevent DSB repair	HRS2398	Phase I	NCT06439589 NCT05144061
DNA-PK	AZD7648	Advanced malignancy	Selectively inhibits DNA-PK, blocks the NHEJ pathway, and enhances the sensitivity to radiotherapy/ chemotherapy.	Pegylated liposomal doxorubicin, PARPi (olaparib)	Phase I/II	NCT03907969
	Nedisertib (M3814, Peposertib, MSC2490484A)	Solid tumors, advanced sarcomas, neuroendocrine tumors, glioblastoma, head and neck squamous cell carcinoma, pancreatic cancer, ovarian cancer, rectal cancer, etc	Oral administration of DNA-PKcs inhibitors targeting the ATP-binding pockets of the kinase domain	Anthracycline/TOPO II	Phase I/II	NCT05711615 NCT05687136 NCT04750954
	VX-984 (M9831)	Solid tumors	Selectively inhibits DNA-PK, blocks the NHEJ pathway, and enhances the sensitivity to radiotherapy/ chemotherapy.	–	Phase I	NCT02644278
DNA-PK + PI3Kδ/γ	BR101801	Hematologic malignancies	Targets both DNA-PK and PI3Kδ/γ kinases	Radiotherapy	Phase I/II	NCT04018248
DNA-PK+ATM	XRD-0394	Solid tumors, gliomas	ATM/DNA-PK dual	Radiotherapy, PARPi, and	Phase I	NCT06829173

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Table 2 (*continued*)

Family	Target	Compound/drug	Disease	Mechanism	Combination Therapies	Clinical State	NCT Number
				inhibitors, which achieve dual-target inhibition by sharing the core structure of imidazole-2-one	targeted delivery of topoisomerase I inhibitors		NCT05002140
	DNA-PK + mTOR	CC-115	Prostate cancer, glioblastoma, and head and neck cancer	Targets both DNA-PK and mTOR kinases	−	Phase I	NCT02833883 NCT01353625
CAMK	MELK	OTS167	Breast cancer, acute myeloid leukemia, and solid tumors	Inhibits MELK-dependent signaling pathways, reduces the expression of FOXM1 and its downstream targets, and induces apoptosis and G2/M phase arrest	−	Phase I/II	NCT02926690 NCT02795520 NCT02768519 NCT01910545
CDK	CDK5	(*R*)-Roscovitine (Seliciclib)	Breast cancer, advanced solid tumors, non-small cell lung cancer	Inhibits CDK5, Cdc2 and CDK2 and eliminates the interaction of the CDK5/p35 complex	PXD101, liposomal doxorubicin	Phase II	NCT03774446 NCT00372073
		Dinaciclib (MK7965)	Acute myeloid leukemia, pancreatic cancer, myeloma, breast cancer, lymphoma, melanoma, solid tumors, non-small cell lung cancer	Inhibits CDK1/2/5/9	Venetoclax, pembrolizumab, Akti MK2206, bortezomib + dexamethasone, rituximab	Phase III	NCT00732810 NCT00798213 NCT00871546
		AT7519	Solid tumors	Inhibits CDK1/2/4/5/6/9	Onalespib	Phase I	NCT02503709
		PHA-793887	Solid tumors	Inhibits CDK2/5/7	−	Phase I	NCT00996255
Alpha	ALPK1	PTT-936	Solid tumors	ADP-heptose analog, which activates an innate immune response	PD-1/L1	Phase I/II	NCT06244992
BRD	BET (BRD2/3/4/T)	ABBV-744	Acute myeloid leukemia	Selective BD2 inhibitor	Venetoclax	Phase I	NCT02391480
		PLX51107	Acute myeloid leukemia, solid tumors	Pan-BET inhibitor; disrupts acetyl-lysine recognition by BET bromodomains, leading to MYC repression.	Azacitidine	Phase I	NCT04022785 NCT02683395
		ABBV075	Breast cancer, non-small cell lung cancer,	Pan-BET inhibitor; broad inhibition of	Venetoclax, BCL2 inhibitors	Phase I	NCT02391480

	etc.	BET family proteins leading to apoptosis in cancer cells			
OTX015/MK-8628	Solid tumors, hematologic malignancies	Pan-BET inhibitor; displaces BET proteins from chromatin to reduce transcription of oncogenes like MYC.	Decitabine	Phase II	NCT01713582 NCT02259114 NCT02296476 NCT02698189 NCT02698176
ODM-207	Solid tumors	Pan-BET inhibitor; inhibits BET bromodomain interactions with chromatin	–	Phase I	NCT03035591
PLX-2853	Advanced uveal melanoma, metastatic castration-resistant prostate cancer, epithelial ovarian cancer, acute myeloid leukemia, etc.	Inhibits BRD2/3/4; disrupts chromatin binding, suppressing oncogenic transcriptional programs	Olaparib, abiraterone	Phase I/II	NCT05677373 NCT04556617 NCT04493619 NCT03787498 NCT03297424
ODM-207	Solid tumors	Pan-BET inhibitor; inhibits BET bromodomain interactions with chromatin	–	Phase I	NCT03035591
GSK2820151/I-BET151	Solid tumors	Pan-BET inhibitor; blocks BET bromodomain binding to acetylated chromatin, disrupting transcription	–	Phase I	NCT02630251
GSK525762/I-BET762	Solid tumors, hematologic malignancies	Pan-BET inhibitor; impairs BET protein binding to chromatin, downregulating oncogenic pathways	Fulvestrant	Phase II	NCT03266159 NCT01943851
FT-1101	Acute myeloid leukemia	Pan-BET inhibitor; disrupts BRD4 chromatin association, leading to transcriptional repression in cancer	–	Phase I	NCT02543879
ZEN003694	Metastatic castration-resistant prostate cancer, triple-negative breast cancer, solid tumors, ovarian	BET inhibitor; interferes with BRD binding to chromatin, reducing AR and MYC signaling	Enzalutamide	Phase II	NCT05607108 NCT05327010 NCT05071937 NCT04986423 NCT04471974

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Table 2 (*continued*)

Family	Target	Compound/drug	Disease	Mechanism	Combination Therapies	Clinical State	NCT Number
			cancer, lymphoma, colorectal cancer, endometrial cancer, squamous cell lung cancer, colorectal adenocarcinoma, etc.				NCT03901469
		INCB057643	Advanced myeloid tumors, solid tumors	Pan-BET inhibitor; inhibits BRD-chromatin interaction, downregulating inflammatory and oncogenic genes.	Ruxolitinib	Phase I/II	NCT04279847 NCT02711137
		BMS986158	Solid tumors, advanced tumors	Pan-BET inhibitor; broadly disrupts BET-mediated transcription in multiple solid tumor types.	Nivolumab, ruxolitinib, fedratinib	Phase I/II	NCT03936465 NCT02419417
		BMS-986378	Solid tumors, lymphomas, and brain tumors	Pan-BET inhibitor; targets BET protein function in lymphoma and brain tumor models.	–	Phase I	NCT03936465
		GS5829	Advanced estrogen receptor-positive HER2-breast cancer, metastatic castration-resistant prostate cancer, solid tumors, and lymphomas	BET inhibitor; blocks BET interaction with estrogen receptor signaling in hormone-sensitive tumors	Fulvestrant	Phase I/II	NCT02983604 NCT02607228 NCT02392611
		BAY1238097	Solid tumor	Pan-BET inhibitor; inhibits BRD2/3/4-mediated transcription by displacing BET from acetylated chromatin.	–	Phase I	NCT02369029
		CPI-0610	Lymphoma, leukemia, peripheral nerve oma	Pan-BET inhibitor; synergizes with JAK inhibition to modulate fibrosis and cytokine gene expression.	Ruxolitinib	Phase II	NCT02986919 NCT02158858 NCT02157636
	BRD4	SYHA1801	Advanced solid tumors, gastric cancer	Selective inhibition of BRD4 bromodomains blocks binding to acetylated histones, suppressing MYC-driven transcription.	–	Phase I	NCT04309968

BI894999	NUT carcinoma	Selective BRD4 inhibitor; blocks recruitment of transcriptional elongation factors at key gene promoters	–	Phase I	NCT02516553
AZD5153	Malignant solid tumors	Bivalent BRD4 inhibitor binds both BD1 and BD2 domains; enhances binding affinity and MYC suppression.	Olaparib	Phase I	NCT03205176
NUV-868	Solid tumor	Selective BD2 inhibitor; targets BRD4 BD2 to reduce AR- and PARP-driven transcription in resistant tumors	Olaparib, enzalutamide	Phase I/II	NCT05252390

Data from clinical.trial ALPK1, alpha-protein kinase 1; aPKC, atypical protein kinase C; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; BET, bromodomain and extra-terminal; BRD, bromodomain-containing protein; CAMK, calcium/calmodulin-dependent protein kinase; CDK, cyclin-dependent kinase; DNA-PK, DNA-dependent protein kinase; HER2, human epidermal growth factor receptor 2; HR, homologous recombination; MELK, maternal embryonic leucine zipper kinase; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; NHEJ, non-homologous end joining; PARP, poly(ADP-ribose) polymerase; PIKK, phosphatidylinositol 3-kinase-related kinase.

Table 3 Approved small-molecule inhibitors.

Target	Generic Name	Trade Name	Indications	Mechanism	Original research/ production	Approval time
mTOR	Sirolimus	Rapamycin	Renal cell carcinoma, lymphangioleiomyomatosis, organ transplant rejection (immunosuppression)	mTORC1 inhibitor, immunosuppressant	Wyeth (now Pfizer)	1999 (FDA)
	Sirolimus	Hyftor	Facial angiofibroma	Gel formulation containing sirolimus	Nobelpharma	2018 (PMDA)
	Sirolimus	Fyarro	Malignant perivascular epithelioid cell tumor (PEComa)	Albumin-bound sirolimus nanoparticle formulation targeting mTOR	Aadi Bioscience	2021 (FDA)
	Everolimus	Afinitor	Advanced hormone receptor-positive, HER2-negative breast cancer, renal cell carcinoma, and neuroendocrine tumors	mTORC1 inhibitor	Novartis	2009 (FDA)
	Temsirolimus	Torisel	Advanced renal cell carcinoma	mTORC1 inhibitor (prodrug of sirolimus)	Wyeth (now Pfizer)	2007 (FDA)
CDK5	Flavopiridol	Alvocidib	Relapsed/refractory chronic lymphocytic leukemia (CLL)	Inhibits CDK1/CDK2/CDK4 and inhibits the formation of CDK5/p25	Sanofi/Tolero pharmaceuticals	2014 Orphan drug (FDA)

CDK, cyclin-dependent kinase; FDA, U.S. Food and Drug Administration; HER2, human epidermal growth factor receptor 2; mTORC1, mammalian target of rapamycin complex 1; PMDA, Pharmaceuticals and Medical Devices Agency.

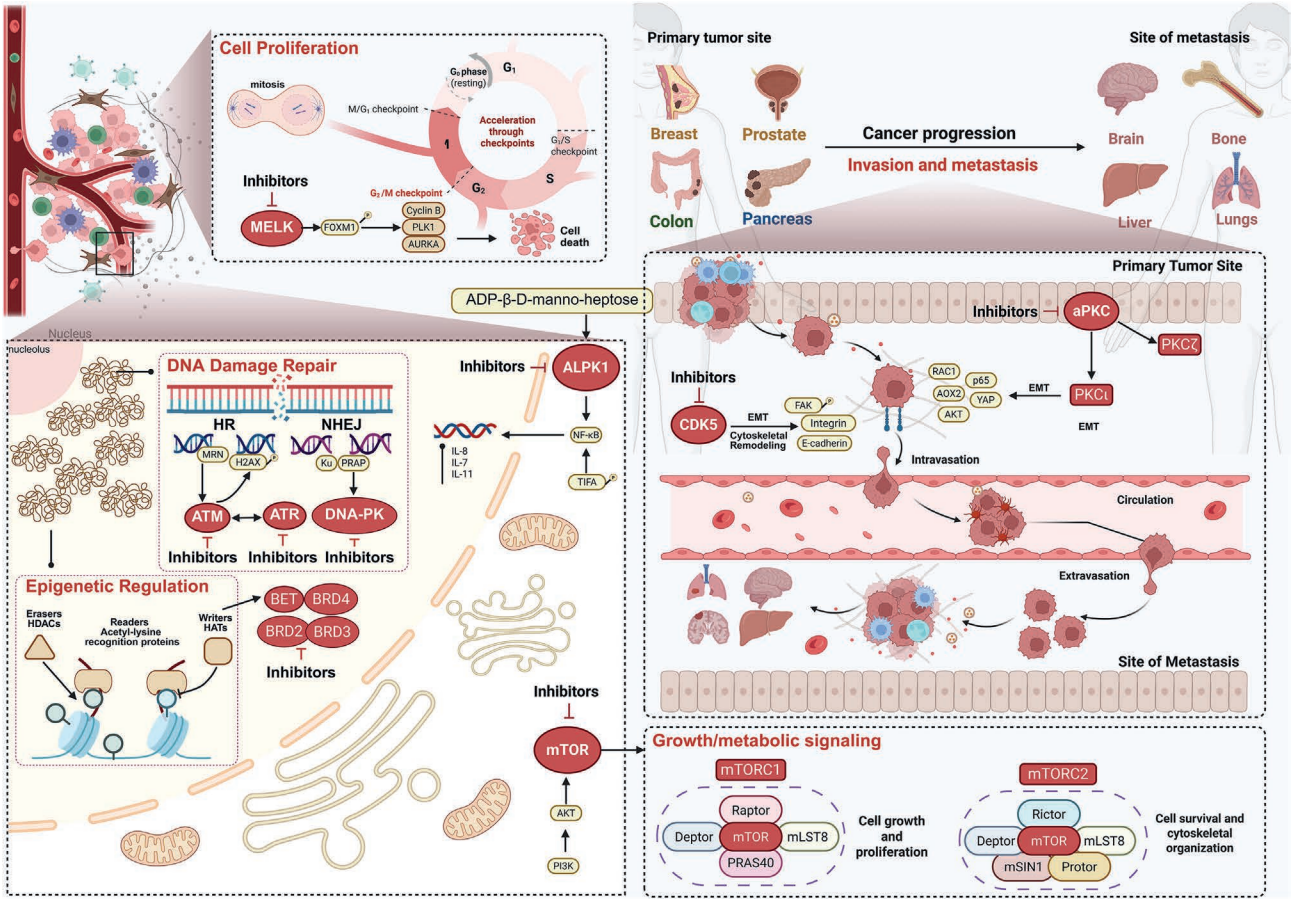

Figure 4 Mechanism and targeting strategy of NCKs in tumors. The figure comprehensively demonstrates the functional links among several NCKs in tumorigenesis and development, including cell proliferation, DNA damage repair, epigenetic regulation, metabolic signaling pathways, and tumor invasion and metastasis. The NCK targets highlighted in the figure have all entered the clinical stage of small-molecule inhibitors, reflecting their potential and translational value in tumor treatment.

Table 4 Summary of non-canonical kinase targets and representative modulators.

Target	Modality	Binding site	Representative agents	Notes/Status
mTOR	Allosteric	FRB-FKBP12 complex (C1-biased)	Sirolimus/Everolimus/Temsirolimus	Approved—C1-selective; preserves mTORC2 (feedback control).
mTOR	ATP-competitive (C1/2)	Orthosteric ATP pocket	AZD8055, sapanisertib, vistusertib	Clinical/Preclinical—broader mTORC1/2 suppression; toxicity-managed by intermittent dosing.
mTOR	Bi-steric (C1-selective)	FRB anchor + ATP site	RMC-6272	Clinical/preclinical—restores 4E-BP1 while limiting AKT rebound.
ATR	ATP-competitive	PIKK catalytic/ATP region	Camonsertib (ATRi)	Clinical—synthetic-lethal in HR/ATM-deficient tumors; combo strategies.
ATM	ATP-competitive	PIKK catalytic pocket	AZD0156	Clinical—radiosensitization and PARP combinations.
DNA-PKcs	ATP-competitive	PIKK catalytic pocket	Peposertib (M3814), AZD7648	Clinical—radiosensitizer focus; combo emphasis.
SMG1	ATP-competitive/allosteric	PIKK-like catalytic module/UPF1 interface	Tool leads/emerging inhibitors	Preclinical—links NMD to checkpoint control; targetable in specific tumors.
TRRAP	PPI/scaffold targeting (degrader)	SAGA/Tip60 docking interfaces (non-catalytic)	PROTAC-like tools (preclinical)	Preclinical—scaffold disruption restores the balance between repair and transcription.
TRIM family (TRIM24)	PPI/reader pocket	Chromatin reader/cofactor interfaces	Tool compounds/inhibitors (preclinical)	Preclinical—modulates chromatin and transcriptional co-activation.
TRIM family (TRIM28)	Post-translational modulation	Phospho-switch at Ser824 (damage-regulated)	Genetic/RNAi tools	Preclinical—involved in damage-induced chromatin relaxation and repair.
PRPK (TP53RK)	ATP-competitive/complex disruption	KEOPS complex active site/PPI interfaces	Tool inhibitors reported	Preclinical—affects tRNA modification and p53 modulation; concerns about therapeutic window.
TAF1	ATP-competitive/bromodomain (dual)	Kinase ATP pocket and bromodomain pockets	TAF1 ligands/degraders (preclinical)	Preclinical—couples transcription initiation to growth programs; degrader approaches promising.
RIOKs (RIOK1−3)	ATP-competitive	PKL-type ATP pocket (RIO-specific features)	RIOK inhibitor leads	Preclinical—inhibit ribosome maturation → nucleolar stress; structural basis for optimization.
HASPIN	ATP-competitive	Active site near H3T3 substrate pocket	CHR-6494	Preclinical—antimitotic; synergizes with taxanes/PLK inhibitors.
MELK	ATP-competitive	Kinase ATP pocket (contested biology)	OTSSP167 (historical), cleaner chemotypes	Preclinical/terminated trials—target-essentiality debated; combination utility noted.
BRD4	Bromodomain inhibitors/PROTAC degraders	Acetyl-lysine binding pockets (BD1/BD2)	OTX015, GSK525762, ARV-771 (PROTAC)	Clinical/Preclinical—transcriptional addiction; thrombocytopenia limits; degrader strategies.
TBK1	ATP-competitive	Kinase ATP pocket (TBK1/IKKε region)	Tool compounds (BX-795 class)	Preclinical—innate immunity/NF-κB hub; immune/toxicity considerations.
ALPK1	Allosteric/ligand pocket	ADP-heptose sensing pocket/	Agonist/antagonist leads (preclinical)	Preclinical—microbial metabolite

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Table 4 (*continued*)

Target	Modality	Binding site	Representative agents	Notes/Status
		activation surface		sensor; immunomodulatory strategy.
FAM20C	ATP-competitive/secretory-pocket	Golgi luminal kinase pocket	FL-1607, compound 3r (preclinical)	Preclinical—remodels secretome; strategy: Inhibit extracellular phospho-signaling to reduce metastasis.
TRPM7	Channel pore blockers & ATP-site kinase inhibitors	Channel pore/α-kinase ATP pocket	Waixenicin A (pore), NS8593 (blocker)	Preclinical—dual channel/kinase biology; pore blockers reduce migration/invasion.
eEF2K	Mixed modalities (allosteric/CaM-site/ATP)	Calmodulin regulatory site; shallow ATP pocket	NH125, A-484954 (tool compounds)	Preclinical—regulates translation elongation; multiple targeting strategies and PROTAC ideas.
PDHKs (PDHK1−4)	ATP-competitive/covalent	ATP pocket/PDC-binding conformational sites	VER-246608, JX06, DCA (repurposed)	Preclinical/Clinical repurposing—metabolic reprogramming target; isoform redundancy challenge.
ADCK3/ADCK4	Allosteric/cofactor groove binders	Atypical aarF/quinone cofactor groove	Emerging chemical probes	Preclinical—mitochondrial/CoQ biology probes enabling functional studies.
WNK1−4	Allosteric/regulatory-site modulators	Cl^-/water network and regulatory pockets	WNK463, other allosteric leads	Preclinical—electrolyte toxicity risk; allosteric strategies to widen therapeutic window.
aPKC (PKCι/PRKCI)	ATP-competitive (catalytic)	Kinase ATP pocket; PB1/PPI interfaces	ICA-1S (PKCι-selective), ζ-stat (PKCζ)	Preclinical—polarity disruption; PPI/metal-based PB1-Par6 disruptors also used (aurothiomalate).
aPKC (PKCζ)	Allosteric/PIF-pocket	PIF-like pocket/regulatory interfaces	PS432 (PIF-pocket binder)	Preclinical—allosteric modulation potentiates proteasome/PI3K inhibition; early stage.
CDK5	ATP-competitive/PROTAC	Kinase ATP pocket/degrader approaches	LGR3087, TMX-2172 (PROTAC, preclinical)	Preclinical—tumor-selective CDK5 inhibitors and degraders aim to reduce systemic toxicities.

ADCK, aarF domain-containing kinase; ALPK1, alpha-protein kinase 1; aPKC, atypical protein kinase C; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related protein; BRD, bromodomain-containing protein; CDK, cyclin-dependent kinase; CoQ, coenzyme Q; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; eEF2K, eukaryotic elongation factor 2 kinase; FAM20C, family with sequence similarity 20C; HR, homologous recombination; MELK, maternal embryonic leucine zipper kinase; mTORC1, mammalian target of rapamycin complex 1; PDC, pyruvate dehydrogenase complex; PDHK, pyruvate dehydrogenase kinase; PIKK, phosphatidylinositol 3-kinase-related kinase; PLK, polo-like kinase; PPI, protein−protein interaction; PROTAC, proteolysis-targeting chimera; PRPK, p53-related protein kinase; RIOKs, right open reading frame kinases; SMG1, suppressor with morphological effect on genitalia 1; TBK1, TANK-binding kinase 1; TAF1, TATA-box binding protein-associated factor 1; TRIM, tripartite motif-containing protein (TRIM) family; TRPM7, transient receptor potential melastatin 7; TRRAP, transformation/transcription domain-associated protein; WNK, With-No-Lysine (K) kinase.

conserved ATP-binding pockets (ATM, ATR, DNA-PKcs, mTOR) or well-characterized interaction domains (BRD4, aPKC). They also sit at central nodes of hallmark-related pathways—DNA repair, metabolism, cell-cycle regulation, and transcriptional control—so their inhibition produces broad downstream effects, particularly in tumors with contextual vulnerabilities such as HRD or transcriptional addiction. Moreover, many of these NCKs participate in resistance mechanisms, making them rational partners for combination therapy. Finally, the availability of predictive biomarkers enables patient stratification and facilitates clinical translation.

The defining traits of druggable NCKs—structural tractability, functional centrality, and hallmark-driven contextual vulnerability—will continue to guide therapeutic discovery. Advances such as PROTACs, brain-penetrant scaffolds, AI-guided design, and dual-target strategies are expected to expand the druggability landscape, enabling previously inaccessible kinases to be redirected against hallmark vulnerabilities. Collectively, these insights position NCKs not only as precision-oncology targets but also as essential foundations of future combination regimens (Fig. 4).

6. Conclusion and prospect

NCKs play a key role in tumor adaptation by dynamically allocating resources across multiple cancer hallmarks: DNA-damage-responsive NCKs such as the PIKK family convert genomic instability and replication stress into therapeutic vulnerabilities; mitotic and translational NCKs support sustained proliferative drive; metabolic and stress-sensing NCKs reshape cellular bioenergetics; and innate immune and epigenetic NCKs modules coordinate apoptotic escape, inflammatory rewiring and immune evasion. Targeting these NCKs can, under specific contexts, alter tumor cell fate (*e.g.*, inducing synthetic lethality, reprogramming the microenvironment, or causing translational overload collapse), providing multiple intervention points for precision therapy[4,249].

Compared to canonical ePKs, NCKs differ in structure and dynamics from the classic ATP competitive mode: they more frequently have unconventional pockets, allosteric grooves, ion/lipid-phase channels, or protein-protein interfaces, which naturally provide greater selectivity and allosteric modulation[250]. Furthermore, in some cases when ePKs are targeted and tumors evade treatment through alternative pathways, the bypass is mediated by NCKs, which has led to combination strategies based on mechanistic complementarity[251]. Additionally, many NCKs occupy "bottleneck nodes", and inhibiting a single hub can impose systemic costs on tumor adaptation. This is why NCK inhibition triggers context-dependent synthetic lethality more readily. It also indicates that the balance between efficacy and safety requires more precise biomarker stratification. At the same time, high-efficacy scenarios raise safety concerns: DDR inhibition can cause hematopoietic, gastrointestinal, and skin burdens; profound mTOR suppression may lead to metabolic toxicity; systemic TBK1 blockade could impair type I interferon defense; and FAM20C inhibition might affect secretion pathways and physiological measures of bone mineralization[252].

However, the lack of structural and functional information remains a bottleneck in drug discovery: many NCKs fall into the "dark kinome/understudied kinases" category, where high-resolution ligand-bound structures are scarce, leading to unstable pocket boundaries, conformational ambiguity, and poor homolog mapping—all of which hinder functional studies and structure-based drug design[253]. Additionally, for many NCKs, the substrates, sites, and pathways remain partially undefined, so the evidence for functional annotation and disease association is still being developed[254]. In the PIKK family, catalytic cores are highly conserved, and historically, many inhibitors have shown cross-inhibition among ATM/ATR/DNA-PKcs/mTOR, further complicating candidate selectivity.

Studies of NCK-targeting small molecules demonstrate that, although NCKs have atypical structures, they still hold significant "druggability" potential. Across the NCK landscape, catalytically active members such as PIKKs (mTOR, ATR, ATM, DNA-PKcs, SMG1), PDHKs, WNK kinases, eEF2K, Haspin, MELK, ADCK3/COQ8, and TBK1 harbour well-formed ATP-binding clefts and, in some cases, additional ligandable allosteric cavities (for example, the FRB domain of mTOR, the lipoamide pocket of PDHKs, or the chloride-sensing site of WNK1−4), which classical ATP-competitive or allosteric inhibitors have already exploited. By contrast, pseudokinase scaffolds such as FAM20A and TRRAP, and epigenetic readers such as TIF1/TRIM24/28/33 and BET proteins, lack a bona fide catalytic pocket and are instead addressed through bromodomain or PHD-finger reader pockets, protein-protein interaction interfaces, or PROTAC-mediated degradation. Between these extremes, structurally characterized but chemically underexplored pockets in NCKs such as ADCK1/2/4, SMG1, and the TRPM6/7 channel-kinase module represent potential opportunities for future pocket-centric discovery. Various preclinical small molecules—from allosteric inhibitors, reversible-covalent inhibitors, bi-steric dual-site binders, to molecular degraders (PROTACs)—have shown that unconventional pockets can enable precise, high-affinity engagement. For clarity, representative targets and modulators are summarized by modality and binding site in Table 4.

αAs NCK small-molecule drugs enter clinical use, their developmental approach is gradually shifting from "maximum inhibition" toward "precision combination". Monotherapy benefits are limited, but through biomarker stratification and combination therapies, both efficacy and safety have significantly improved. DDR/PIKK axis drugs (*e.g.*, ATR, ATM, DNA-PK inhibitors) with intermittent dosing and radiotherapy/PARP combinations have achieved manageable toxicity; bi-steric mTORC1 inhibitors *via* dual-site binding restore potent 4E-BP1 suppression while reducing AKT rebound, expanding options for post-resistance and maintenance therapy; BD2-selective BET inhibitors and ALPK1 agonists are opening new avenues in epigenetic and immune research[240]. In the future, NCK's small-molecule drugs' success will no longer depend solely on single-target hits. Instead, it will rely on the integrated system of functional selectivity engineering, early PD validation, and platform-based combination — this will transform "druggable target" into "useable drug" and create new opportunities for post-resistance strategies, microenvironment modulation, and multi-modal therapy[255].

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Author contributions

Xuelan Ma wrote the manuscript. Zhifeng Wen and Jun Wang revised the manuscript. Zhiwen Wang and Zhiqi Peng made the figures. Dongbo Wu and Bo Liu polished the language. Bo Liu and Jun Wang proofread the manuscript. All the authors approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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