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Breaking the oncogenic alliance: advances in disrupting the MTDH–SND1 complex for cancer therapy

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Metadherin (MTDH/AEG-1/LYRIC) partners with Staphylococcal Nuclease Domain-Containing Protein 1 (SND1) to form an oncogenic hub that drives proliferation, survival and metastasis in many tumors. Interrupting this interaction dampens pivotal pathways—including NF-κB, PI3K/Akt and Wnt/β-catenin—and simultaneously promotes SND1 degradation, yielding broad antitumor effects. This review consolidates current knowledge of the MTDH–SND1 axis and highlights preclinical studies showing that genetic knock-out or pharmacologic blockade of the complex can sharply reduce primary growth and metastatic spread. We summarize structural studies that map the binding interface, emphasizing the essential MTDH tryptophan pair and the SN1/SN2 barrels of SND1, and we survey therapeutic approaches designed to exploit these determinants. Candidate disruptors range from phage-derived stapled peptides to small molecules unearthed by high-throughput and structure-guided screens; several demonstrate potent cytotoxicity in cell lines and xenografts, particularly when delivered through cell-penetrating motifs or nanoformulations. We also examine hurdles that protein–protein interaction inhibitors must overcome, such as off-target toxicity, metabolic instability and limited bioavailability, and discuss combination regimens that may amplify efficacy. Finally, we outline emerging avenues—PROTAC-mediated degraders, rational biomarker selection and advanced drug-delivery technologies—that could sharpen specificity and accelerate clinical translation. Together, these data validate MTDH–SND1 disruption as a versatile strategy against treatment-refractory cancers.

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1. Introduction

Cancer remains a leading global health concern, driven in large part by complex molecular networks that facilitate uncontrollable cell growth, metastasis, and resistance to therapy.[1] Among the wide range of molecular players identified over recent decades, Metadherin (MTDH), also called AEG-1 or LYRIC, has emerged as a significant oncoprotein implicated in the progression of many tumor types, including breast, liver, and prostate cancers.[2,3] As illustrated in Fig. 1, MTDH is frequently over-expressed in human malignancies and has been linked to invasion, metastasis, immune evasion (for example, *via* PD-L1 up-regulation), and resistance to chemotherapy.[4,5] Its pervasive involvement in oncogenic pathways has prompted extensive research aimed at clarifying its molecular underpinnings and exploring avenues for therapeutic intervention.[4] One of MTDH's most important functional partnerships is with Staphylococcal Nuclease Domain-Containing Protein 1 (SND1).[6] SND1 is a multifunctional protein that participates in RNA metabolism, stress responses and the regulation of several oncogenic signaling cascades.[7] When bound together, MTDH and SND1 establish a signaling hub that sustains tumour-cell proliferation, stemness and metastasis by modulating pathways such as NF-κB, PI3K/Akt and Wnt/β-catenin.[4] Genetic ablation studies demonstrate that disrupting this complex compromises tumor initiation in various models, underscoring the potential of the MTDH–SND1 interface as a high-value therapeutic target.[8]

Despite this promise, disrupting protein–protein interactions (PPIs) in general—and MTDH–SND1 in particular—poses substantial scientific challenges.[9] Unlike enzyme active sites or receptor-binding pockets, PPI interfaces are often relatively flat, less structured, and feature few deep "hot spots," making them notoriously difficult to inhibit with traditional small-molecule drugs.[10] Overcoming these obstacles has required creative

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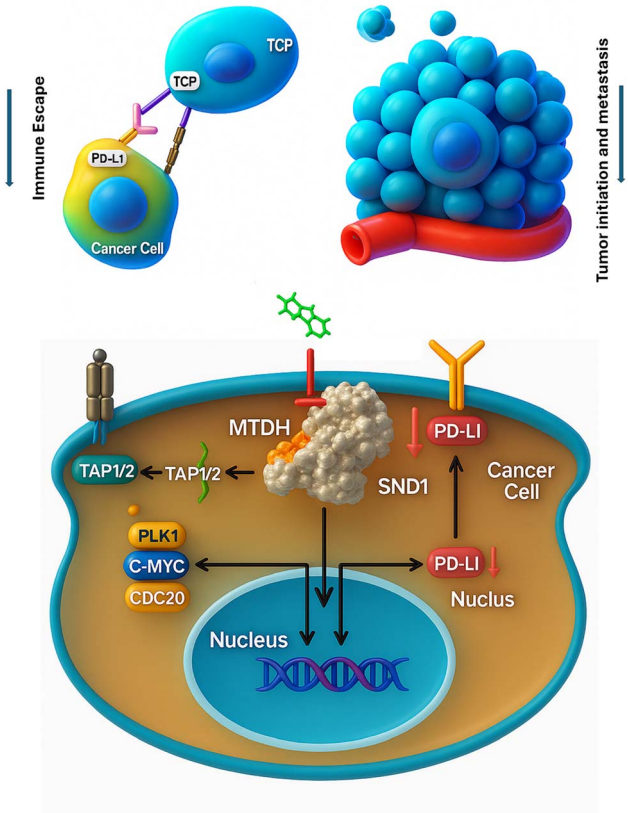

Fig. 1 Multifaceted oncogenic functions of the MTDH–SND1 axis and avenues for therapeutic intervention. Top left: Over-expressed MTDH induces PD-L1 on cancer cells, allowing them to escape T-cell-mediated cytotoxicity. Top right: The MTDH–SND1 complex fosters tumor initiation, angiogenesis and metastatic outgrowth. Bottom: Inside a representative cancer cell, membrane-associated MTDH (orange) recruits SND1 (grey) to form a scaffold that (i) transcriptionally up-regulates oncogenic drivers such as PLK1, c-MYC and CDC20, (ii) suppresses antigen presentation by down-modulating TAP1/2, and (iii) further increases PD-L1 expression. A putative small-molecule inhibitor (green) illustrates the druggability of the MTDH–SND1 interface; red "T" symbols indicate points of therapeutic blockade, reproduced from ref. 9 with permission from American Chemical Society, copyright 2025.

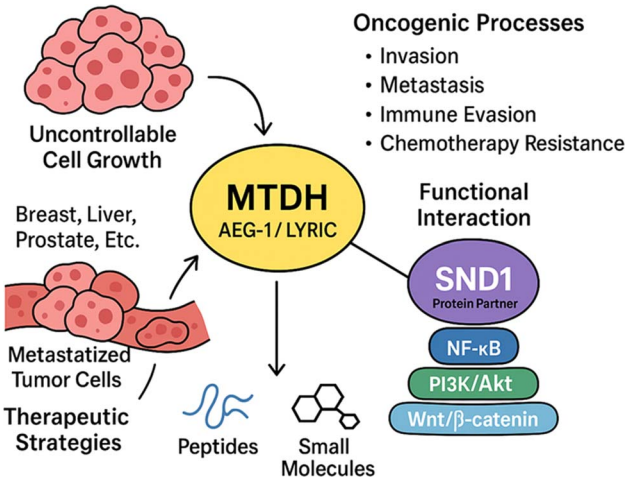

Fig. 2 Network view of Metadherin (MTDH/AEG-1/LYRIC) oncogenic signaling and opportunities for interface-directed therapy. A central yellow oval depicts MTDH, an oncoprotein over-expressed in numerous solid tumors. Left: Outward arrows link MTDH to two key phenotypes—uncontrolled proliferation (top cluster of rapidly dividing cells) and metastatic dissemination (bottom clusters), underscoring its role in both primary-tumor growth and systemic spread. Right: MTDH engages its obligate partner SND1 (Staphylococcal Nuclease Domain-Containing Protein 1), illustrated in purple; together the complex activates a signaling stack comprising NF-κB, PI3K/Akt, Wnt/β-catenin, and MAPK/ERK. These pathways drive the oncogenic processes listed—invasion, metastasis, immune evasion, chemoresistance, stem-like renewal, and angiogenesis (bullet panel). Bottom: Two classes of experimental therapeutics aim to block the shallow MTDH–SND1 interface: blue squiggle icon for stapled peptides and hexagon/benzene icon for structure-guided small molecules; a red "T" bar symbolizes pharmacological inhibition of the complex.

approaches, including the design of specialized peptides and the identification of novel small molecules that can slip into or destabilize critical interfaces.[10] These strategies have started to yield encouraging proof-of-principle inhibitors. Early-generation peptides demonstrated that direct disruption of MTDH–SND1 is feasible, while subsequent small-molecule efforts have revealed distinct chemical scaffolds capable of binding SND1 and hindering complex formation (Fig. 2).[11]

This review provides a comprehensive look at the biology underlying the MTDH–SND1 axis, the structural nuances that enable their interaction, and the types of inhibitors that have begun to emerge. We will examine the peptide- and small-molecule-based approaches developed to obstruct MTDH–SND1 binding, the rational design strategies that guide these inhibitors, and *in vitro* as well as *in vivo* data demonstrating their cancer-suppressive potential. By encapsulating the latest advances in this area, we aim to highlight both the promise and remaining hurdles in transforming MTDH–SND1 inhibitors from intriguing laboratory findings into robust clinical tools against cancer.

2. Structural and mechanistic insights into MTDH–SND1 interaction

Understanding how MTDH (AEG-1/LYRIC) and SND1 bind to one another is central to appreciating why their partnership drives tumor progression so effectively.[2] Although each protein has multiple domains and interacts with several other regulators, their direct contact point forms a tightly knit interface that underpins many of the pro-oncogenic effects attributed to them.[12] Below, we explore the salient features of this interaction by highlighting both the structural organization of these proteins and the functional impacts that arise once they are bound together. The results of molecular docking analysis of MTDH–SND1 with an alkaloid are shown in Fig. 3 to depict the binding mode of an inhibitor with MTDH–SND1.

2.1 Structural features of MTDH and SND1

2.1.1 MTDH's binding region. MTDH is traditionally regarded as a membrane-associated protein, but its

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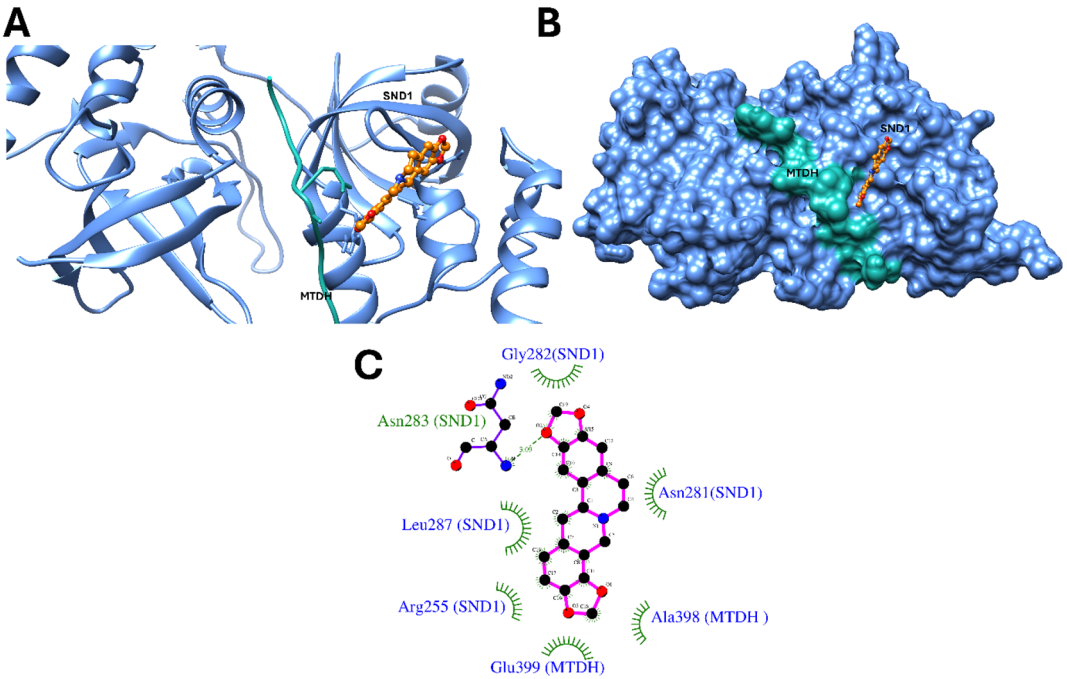

Fig. 3 The binding mode of an alkaloid with MTDH–SND1 (PDB ID: 4QMG). (A) Ligand position within the binding site of the target protein, (B) surface representation of MTDH–SND1 showing the disruptor in the binding site, and (C) ligplot presentation of residues from MTDG and SND1 involved in polar and hydrophobic interactions with the inhibitor.

functionality extends far beyond simple localization. Its oncogenic activity is partly driven by a compact C-terminal motif (residues 393–403) that engages the staphylococcal-nuclease domains of SND1 (Fig. 4).[13] Within this short stretch, Trp394 and Trp401 act as anchor residues, burrowing into two hydrophobic pockets on SND1. Even conservative substitutions at either position reduce binding by >90%.[14] Underscoring their role as a dual "hot-spot" module. Although MTDH contains other regions that govern nuclear shuttling and post-translational control, these two tryptophans are indispensable for forming a stable MTDH–SND1 complex.[15,16]

2.1.2 The SN domains of SND1. SND1 is a multifunctional effector in RNA metabolism and gene regulation.[5] Structurally it comprises four staphylococcal-nuclease-like lobes (SN1–SN4) arrayed around a central linker.[17] The first two lobes, SN1 and SN2, create a continuous groove punctuated by hydrophobic pockets that perfectly accommodate the MTDH motif (Fig. 4A).[6] Disruptive mutations within either lobe destabilize peptide binding and attenuate downstream oncogenic signaling, indicating that both proteins contribute complementary surfaces that must remain conformationally intact.[7]

2.1.3 Interface topology and hot spots. Like many protein–protein interfaces, the MTDH–SND1 surface is relatively planar; nevertheless, structural analysis reveals discrete hot spots centered on Trp394, Trp401 and their surrounding hydrophobic contacts (Fig. 4B).[9] These pockets combine favorable van-der-Waals contacts, hydrogen bonds and π–π stacking interactions to drive high affinity. Because mutation of any one hot-spot residue markedly weakens the complex,[16] these sites provide footholds for inhibitor design. Indeed, both peptide mimetics and small molecules that target the Trp-lined pockets have already demonstrated proof-of-concept disruption in biochemical and cellular assays.[18]

2.2 Mechanistic implications of complex formation

2.2.1 Stabilization of SND1 and MTDH. An intriguing and critical outcome of MTDH–SND1 binding is the mutual stabilization it confers on both partners (Fig. 5). Specifically, MTDH appears to protect SND1 from proteolytic degradation, while SND1 in turn prolongs MTDH's half-life inside cells.[19] This interaction enhances the stability of both proteins, enabling them to persist at elevated levels, which in turn reinforces oncogenic signaling pathways, particularly in cancer cells.[20] The prolonged presence of MTDH and SND1 significantly magnifies their impact on tumor biology, especially in cellular contexts with high co-expression levels.[7] This mutual stabilization underpins their roles in promoting malignancy by ensuring sustained activation of key oncogenic processes, including cell proliferation, survival, and metastasis.[2] Additionally, this stabilization may make both proteins potential targets for therapeutic interventions aimed at disrupting their interaction to impair cancer progression.[8]

2.2.2 Cross-talk with major signaling pathways. Together, MTDH and SND1 serve as critical mediators of a broad range of downstream effects that influence cancer cell behavior.[2] They have been shown to play pivotal roles in modulating key signaling pathways, including NF-κB and PI3K/Akt—pathways that are integral to promoting cell proliferation, survival, inflammation, and the evasion of apoptosis.[21] By influencing these pathways, the MTDH–SND1 partnership enhances tumor

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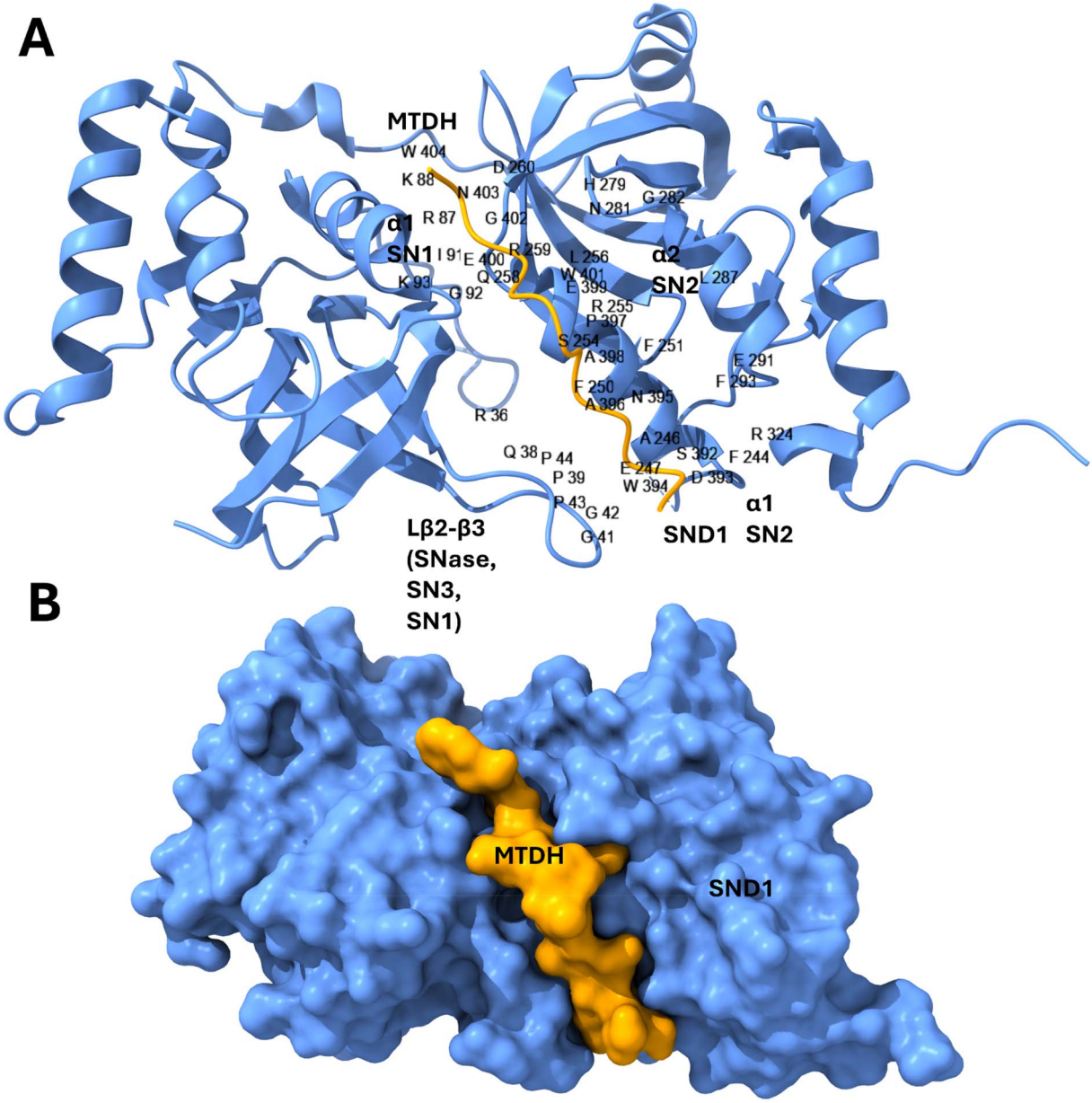

Fig. 4 Structural basis of the MTDH–SND1 interaction (PDB ID 4QMG).[16]. (A) Ribbon representation of the tandem SN1/SN2 domains of SND1 (blue) bound to the minimal 11-residue MTDH motif (orange). Side-chains are shown for the two indispensable hot-spot residues Trp394 and Trp401, which insert into hydrophobic pockets created by the SN1 and SN2 lobes. Key SND1 contact residues are labelled for reference. (B) Molecular-surface view of the same complex, highlighting the contiguous shallow groove on SND1 that cradles the MTDH peptide. The orange surface corresponds to the buried MTDH residues, illustrating the complementary shape and chemistry that enable high-affinity binding.[16]

cells' ability to resist apoptotic signals, endure metabolic stress, and bypass immune surveillance mechanisms, thereby contributing to the progression of malignancy.[22] The activation of these pathways also aids in the establishment of a tumor microenvironment that supports sustained cancer cell survival and growth, even in harsh conditions such as hypoxia and nutrient deprivation.[22]

Moreover, emerging evidence suggests that SND1's role in RNA processing and ribonuclease activity is partially co-opted by MTDH to facilitate oncogenic processes.[23] Specifically, MTDH may redirect SND1's ribonucleolytic properties to target and degrade tumor-suppressive RNAs, thus disrupting critical tumor-suppressor pathways.[24] This manipulation of RNA stability and turnover not only further skews the intracellular equilibrium in favor of tumor growth but also contributes to the acquisition of additional hallmarks of cancer, including enhanced angiogenesis, metastasis, and resistance to chemotherapeutic agents.[2] Additionally, the interplay between MTDH and SND1 may regulate other transcriptional factors such as STAT3, c-Myc, and HIF-1α, which are involved in driving the oncogenic phenotype.[4] This suggests that the MTDH–SND1 complex may act as a central node in integrating multiple pro-

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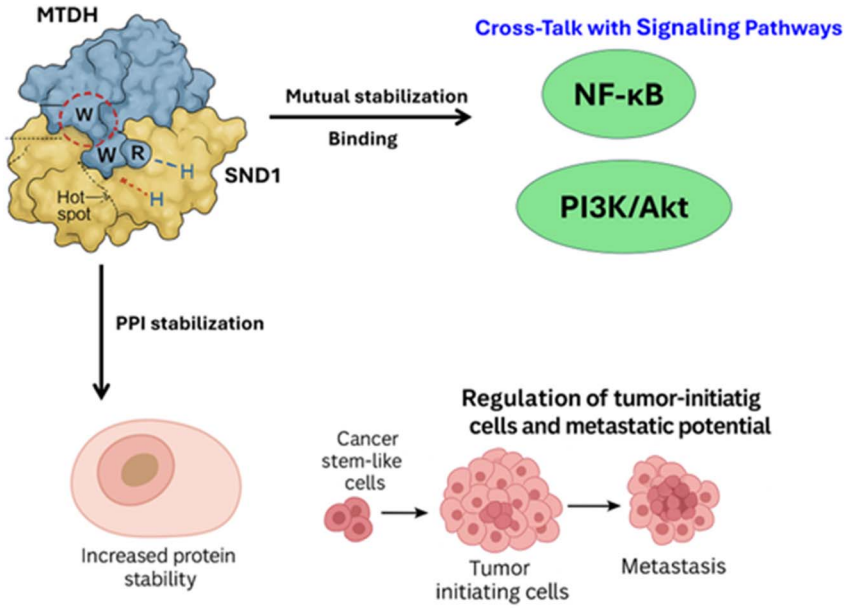

Fig. 5 Mechanistic implications of MTDH–SND1 complex formation.

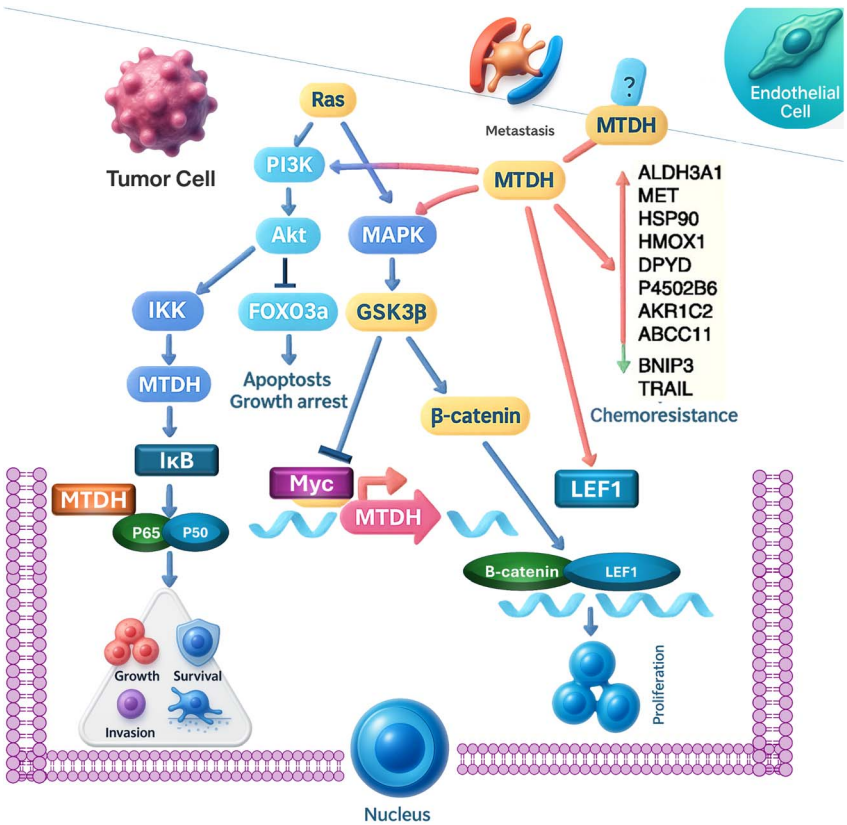

Fig. 6 MTDH orchestrates a nexus of oncogenic pathways that converge on proliferation, invasion, and drug resistance.[26] A tumor cell (upper left) activates Ras, which in turn stimulates both the PI3K/Akt and MAPK cascades. PI3K/Akt axis: Akt suppresses the pro-apoptotic transcription factor FOXO3a and activates IKK, leading to degradation of IκB and nuclear translocation of the NF-κB (p65/p50) heterodimer. Together with membrane-associated MTDH, NF-κB drives genes that promote growth, survival and invasion (grey triangle). MAPK axis: MAPK inhibits GSK3β, allowing cytoplasmic accumulation of β-catenin. Stabilized β-catenin partners with LEF1 in the nucleus to induce proliferative gene expression (right). c-Myc feed-forward loop: NF-κB, LEF1/β-catenin and MAPK collectively boost c-Myc, which in turn transcriptionally up-regulates MTDH, establishing a positive-feedback circuit. Chemoresistance module: MTDH transcriptionally elevates drug-metabolizing enzymes (ALDH3A1, CYP family members) and transporters (ABCC11), while suppressing pro-apoptotic BNIP3 and TRAIL, conferring broad chemoresistance. Metastatic signaling: secreted or endothelial-cell-derived MTDH further enhances metastatic spread.[26]

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tumorigenic signals, making it a potential therapeutic target for disrupting tumor cell survival and growth.[25]

The breadth of this cross-talk is illustrated in Fig. 6, which places MTDH at the intersection of Ras-PI3K/Akt, MAPK, NF-κB and Wnt/β-catenin modules, creating a feed-forward network that simultaneously suppresses pro-apoptotic FOXO3a, amplifies c-Myc transcription, and drives β-catenin/LEF1-dependent proliferation.[26] In parallel, MTDH transcriptionally up-regulates drug-metabolizing enzymes (*e.g.*, ALDH3A1, CYP2B6) and efflux transporters (ABCC11), while down-modulating pro-death mediators (BNIP3, TRAIL), providing a mechanistic basis for the broad chemoresistance observed in MTDH-high tumors (Fig. 6).[26] Although SND1 is not depicted for clarity, genetic and biochemical studies indicate that SND1 is required for full activation of these downstream programs, serving as the effector through which MTDH redirects RNA-processing machinery to reinforce oncogenic signaling. Collectively, these intertwined pathways underscore why the MTDH–SND1 complex represents a central node for therapeutic interception.[26]

2.2.3 Regulation of tumor-initiating cells and metastatic potential. Mechanistic studies indicate that the MTDH–SND1 complex plays a central role in regulating cancer stemness, particularly influencing the pool of tumor-initiating cells (TICs).[2,27] By modulating key transcription factors such as OCT4, Sox2, and Nanog, which are critical for maintaining stem cell-like properties, the MTDH–SND1 interaction promotes the initiation of primary tumors and the ability of cancer cells to undergo epithelial-to-mesenchymal transition (EMT), a crucial process for metastatic spread. In particular, the complex has been shown to maintain a subpopulation of TICs with enhanced self-renewal, resistance to chemotherapy, and the ability to colonize distant organs.[28]

Cell culture and xenograft models have demonstrated that silencing either MTDH or SND1, or disrupting the domains through which they interact, results in a marked reduction in tumorigenic potential and a diminished ability to metastasize.[9,22] This underscores the critical role of the MTDH–SND1 partnership in driving not only primary tumor growth but also in promoting the aggressive metastatic behavior that characterizes advanced cancer stages.[25] Furthermore, the disruption of this complex has been associated with a reduction in the expression of key metastasis-related molecules, including integrins and matrix metalloproteinases (MMPs), which are essential for invasion and dissemination of tumor cells.[24] These findings suggest that targeting the MTDH–SND1 interaction may be a promising therapeutic strategy for reducing both tumor initiation and metastasis, offering new avenues for cancer treatment.[11,29]

2.3 Impacts on clinical outcomes

High expression of both MTDH and SND1 has been consistently associated with poor clinical prognosis across a range of malignancies, including breast cancer, hepatocellular carcinoma (HCC), colorectal cancer, and prostate cancer.[3,28,30] This co-overexpression correlates with more aggressive tumor phenotypes, higher tumor grade, and advanced clinical staging.[31] As illustrated in Fig. 7, MTDH can stabilize SND1 during cellular stress, thereby preserving tumor-initiating cells (TICs); this mechanistic link helps explain why tumours with high MTDH–SND1 expression exhibit aggressive clinical behavior.[2] In breast cancer specifically, elevated levels of MTDH and SND1 have been linked to shorter disease-free survival (DFS) and overall survival (OS), particularly in triple-negative breast cancer (TNBC) subtypes, which are known for their therapeutic resistance and poor prognosis.[32,33] From a clinical perspective, the MTDH–SND1 interaction axis has emerged as a prognostic biomarker.[34] Several transcriptomic analyses from patient cohorts (*e.g.*, TCGA, METABRIC) have shown that tumors with high co-expression of these proteins demonstrate upregulation of oncogenic signaling pathways (*e.g.*, PI3K/Akt, NF-κB, Wnt/β-catenin), as well as enrichment in stemness-

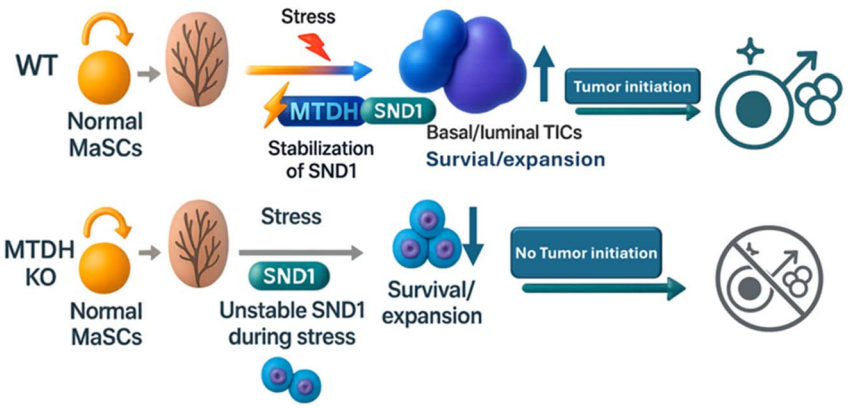

Fig. 7 Stress-induced stabilization of SND1 by MTDH sustains tumor-initiating cells and drives tumor onset.[2] Top (WT scenario): In wild-type (WT) mammary stem cells (MaSCs), oncogenic or micro-environmental stress (lightning bolt) triggers formation of the MTDH–SND1 complex (blue–green bar), which stabilizes SND1. Stabilized SND1 enables the survival and expansion of basal/luminal tumour-initiating cells (TICs, blue cluster) and markedly increases the probability of tumor initiation. Bottom (MTDH-knock-out scenario): In MaSCs lacking MTDH (MTDH-KO), stress fails to protect SND1 from degradation (grey bar). Loss of functional SND1 compromises TIC survival/expansion (downward arrow), resulting in failure of tumor initiation.[2]

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associated gene signatures.[35] These findings align with preclinical studies showing that the MTDH–SND1 complex enhances cancer stem cell maintenance, metastasis, and resistance to conventional chemotherapeutic agents.[2,8] Moreover, high MTDH–SND1 activity has been implicated in drug resistance mechanisms.[2,8] In HCC and breast cancer models, MTDH overexpression reduces sensitivity to doxorubicin, paclitaxel, and sorafenib, partly through upregulation of survival pathways and modulation of apoptotic thresholds.[36,37] SND1, in turn, contributes to post-transcriptional gene silencing of tumor suppressors and facilitates miRNA processing, further tipping the balance toward tumor progression.[38,39] In metastatic settings, elevated MTDH–SND1 levels are predictive of early relapse and organ-specific dissemination, particularly to the lungs and liver.[8] These observations support the inclusion of this protein complex in risk stratification models, and suggest that patients with high MTDH–SND1 expression may benefit from more aggressive treatment regimens or targeted therapeutic interventions.[2,8] Collectively, the clinical data reinforce the notion that the MTDH–SND1 complex is not only a mechanistic driver of tumorigenesis but also a clinically actionable node that could be leveraged for diagnosis, prognosis, and treatment personalization.[2,22]

3. Therapeutic rationale for targeting the MTDH–SND1 complex

Targeting the MTDH–SND1 PPI has garnered increasing attention as evidence accumulates showing that this interaction is a linchpin of several pro-tumor pathways. By binding and stabilizing each other, MTDH and SND1 drive multiple processes that underlie tumor initiation, cancer stemness, immune evasion, and metastasis.[2,22] The rationale for disrupting their partnership is therefore rooted in both fundamental genetic studies and promising preclinical interventions that curb cancer progression.[2]

3.1 Why this PPI is a prime therapeutic target

MTDH is frequently overexpressed in various tumor types, including breast, prostate, and liver cancers, and often correlates with poor prognosis.[40,41] Meanwhile, SND1 contributes to oncogenesis through its roles in RNA metabolism and transcriptional regulation.[42,43] When MTDH binds to the SN1/SN2 domains of SND1, it effectively safeguards SND1 from degradation while benefiting from SND1's broad network of regulatory effects on gene expression.[44] This reciprocal stabilization amplifies

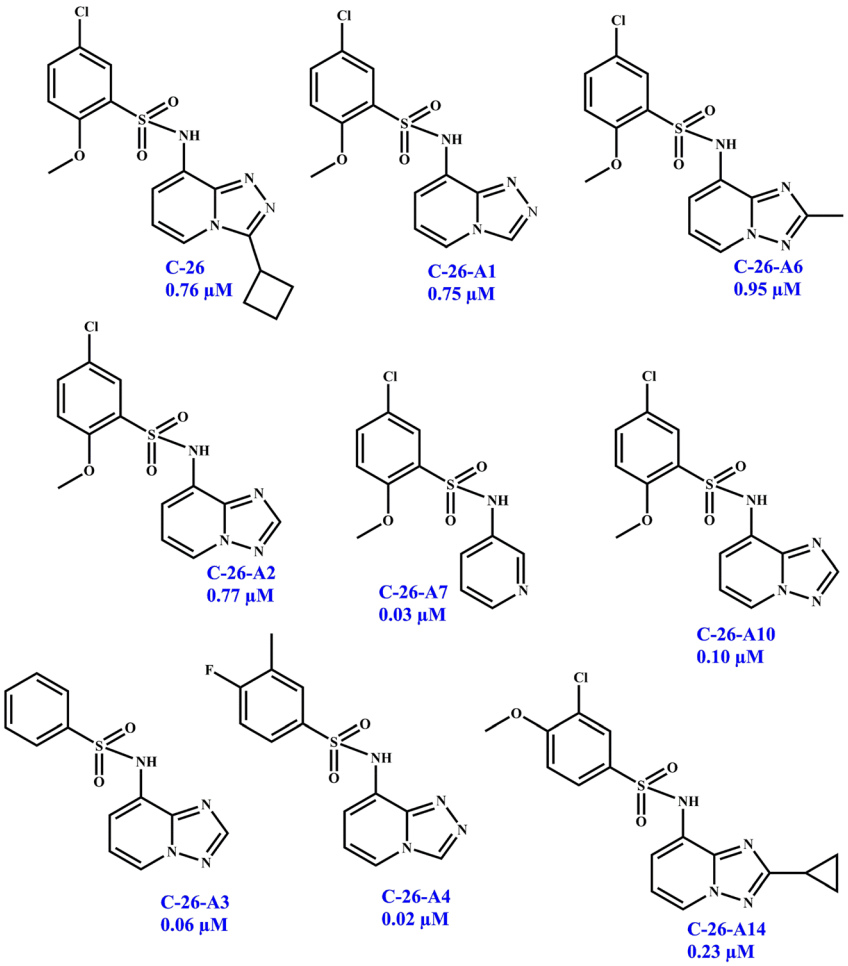

Fig. 8 Structures of compound C26 series MTDH/SND1 complex disruptors and their corresponding blocking ability (50 μM).[8]

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oncogenic signals and promotes cellular phenotypes such as invasiveness and chemotherapy resistance.[44] From a clinical standpoint, high co-expression of MTDH and SND1 frequently marks aggressive tumors.[7] Disrupting their complex, therefore, addresses a convergence point for multiple malignancy-promoting pathways. Rather than inhibiting a single downstream signaling cascade (*e.g.*, NF-κB, PI3K/Akt, or Wnt/β-catenin), blocking the MTDH–SND1 hub can, in principle, weaken several pro-survival and pro-metastatic pathways simultaneously.[7,45]

3.2 Evidence from knockdown or genetic ablation studies

Early evidence for the importance of the MTDH–SND1 axis came from genetic approaches in which one or both proteins were silenced.[8,46] *In vitro* experiments have shown that silencing MTDH or SND1 individually is enough to attenuate cell proliferation, increase apoptosis, and reduce invasive potential.[8,47] These observations are consistent with the idea that each partner is essential for the other's maximal pro-tumor function. Studies using mouse models of breast cancer reinforce these conclusions.[48] Complete or partial deletion of MTDH slows tumor initiation and can significantly reduce lung metastases. Likewise, SND1 knockout animals display delayed tumor progression and smaller tumor sizes.[8] In certain models, simply mutating the MTDH residues necessary for binding SND1 can yield effects comparable to full knockout—underscoring that MTDH's tumorigenic activity often relies on this specific interaction rather than just the presence of the MTDH protein.[8,47] Collectively, these results highlight that an intact MTDH–SND1 complex is indispensable for robust tumor growth and spread.

3.3 Preclinical data showing reduced tumor growth and metastasis upon disruption

Building upon genetic studies, multiple groups have designed molecules—ranging from engineered peptides to synthetic small molecules—that specifically interfere with the MTDH–SND1 interface.[8,47] These inhibitors block the physical

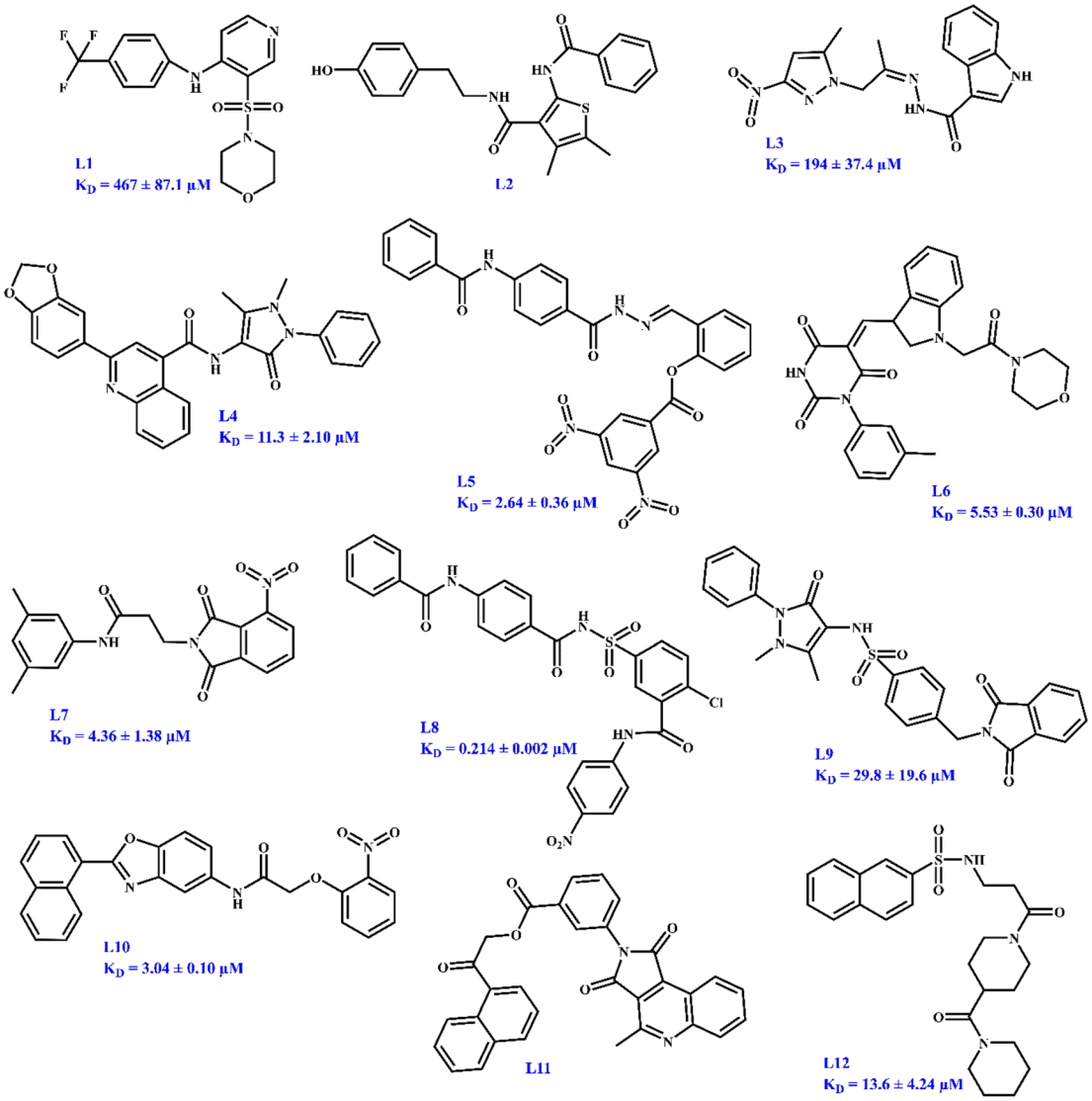

Fig. 9 Assessment of small molecule inhibitors binding strength and kinetics *via* surface plasmon resonance analysis.

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association of the two proteins, leading to reduced levels of SND1 or preventing MTDH from initiating its downstream oncogenic pathways (Fig. 8–10).[8,47]

3.3.1 Peptide-based inhibitors. Preliminary peptide inhibitors, such as CPP-4-2 and MS2D-cyc4, were derived from phage display experiments followed by macrocyclization and stability optimization.[8,11] These structures incorporate amphipathic helices and cell-penetrating domains, enabling intracellular delivery. Mechanistically, they engage the SND1 SN1/SN2 domain to destabilize the MTDH–SND1 complex, promoting proteasomal degradation of SND1. *In vitro*, these peptides exhibit cytotoxicity toward breast and liver cancer cells; *in vivo*, they slow breast tumor growth and, in certain cases, diminish metastatic spread.[49,50]

3.3.2 Small-molecule inhibitors. Structure-based virtual screens have identified small molecules such as C26-A6 and C19, featuring key pharmacophore motifs—chloro-methoxyphenyl (A fragment) and triazolopyridine (B fragment)—that fit into the hydrophobic groove of SND1.[8,22] These ligands form hydrogen bonds with R255 and hydrophobic interactions with adjacent residues, effectively competing with MTDH binding. Early derivatives like L5 improved potency and

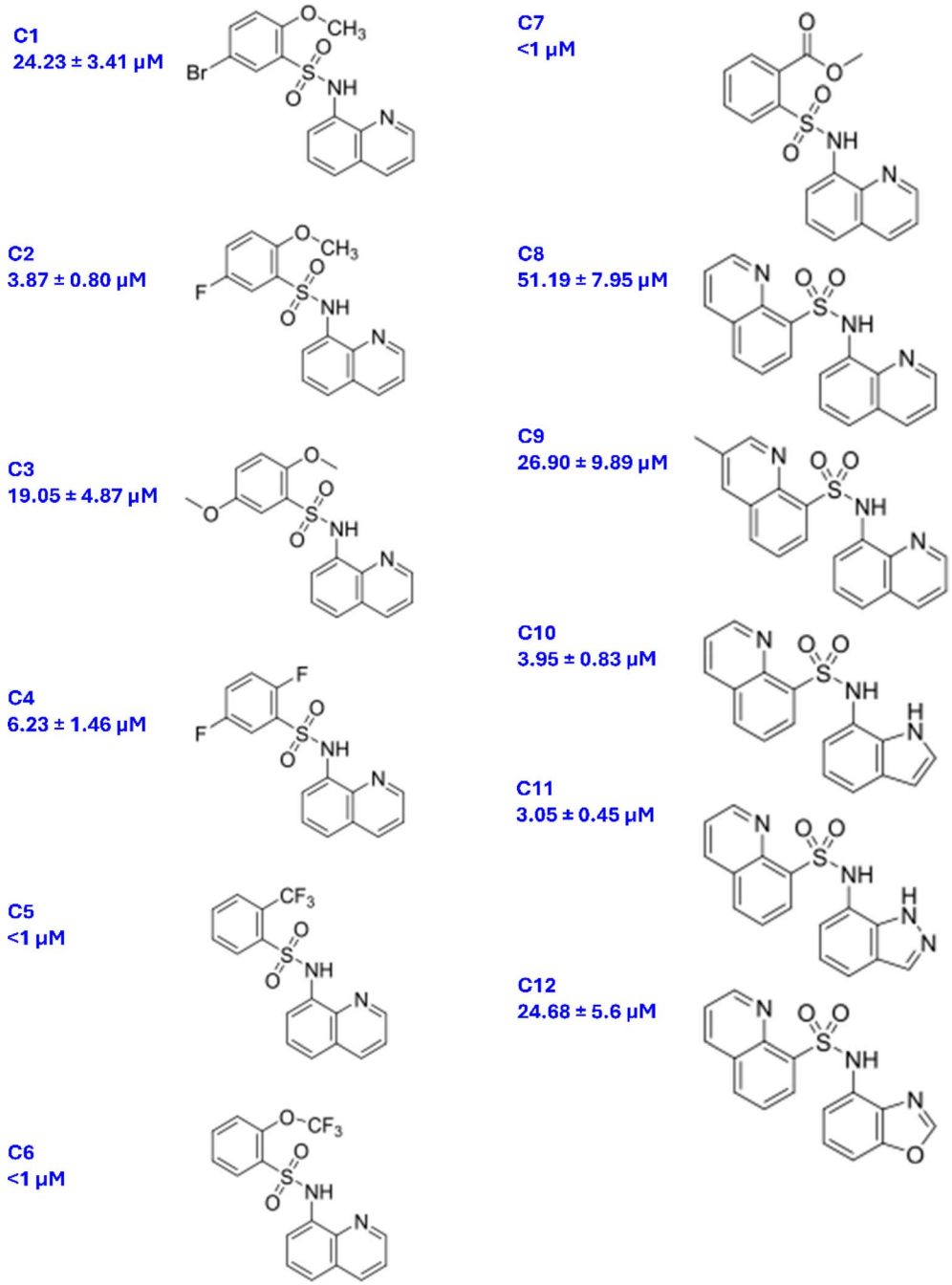

Fig. 10 Chemical structure and inhibitory activity against MTDH–SND1 PPI of compounds C1–C12. The value of inhibitory efficiency% (1 μM) of C1–12 are represented in μM as the mean with SD of triplicate measurements.

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metabolic stability. *In vitro*, these compounds reduce viability of triple-negative breast cancer and hepatocellular carcinoma cells, while in *vivo* xenograft studies show suppressed tumor growth and reduced metastasis.[9,22] Collectively, these preclinical results confirm that pharmacological disruption of MTDH–SND1 not only blocks key molecular pathways but also produces tangible antitumor benefits in experimental settings.[9,22]

3.4 Advantages and challenges of PPI drugging

3.4.1 Flat and extensive interaction surfaces *vs.* well-defined "Hot spots". One hallmark of PPIs is the presence of large, relatively flat interfaces with scattered pockets of energetic "hot spots."[51] MTDH–SND1 exemplifies this: the central interface can be quite broad, but a handful of highly conserved sites (including tryptophan residues on MTDH and corresponding hydrophobic patches on SND1) are essential for complex stabilization.[52,53] From a drug discovery angle, these hot spots provide a foothold for targeted disruption—either through peptide-based binding motifs or small-molecule designs that slip into critical hydrophobic regions.[54] However, the expansive surfaces common to PPIs also complicate traditional small-molecule discovery, as these interactions do not always present deep grooves akin to an enzyme active site. This reality can demand innovative approaches, such as fragment-based lead discovery, specialized computational modeling, or macrocyclic peptide scaffolds.[55]

3.4.2 Lessons learned from other PPI inhibitors. Research on well-characterized protein–protein interactions (PPIs), such as MDM2–p53 and BCL2-family interactions, provides valuable insights that can inform strategies for targeting the MTDH–SND1 interaction. One critical lesson is the importance of hot spot identification, where detailed structural studies—such as mutational mapping and crystallographic analyses—are essential for pinpointing the most functionally significant residues at the interface.[56,57] Another key consideration is the therapeutic window, as PPIs often influence multiple signaling pathways, necessitating careful evaluation of on-target toxicity and potential secondary effects.[58,59] Additionally, target conformational flexibility plays a crucial role, since many PPIs exhibit dynamic structural changes; this flexibility can be leveraged to discover transient binding pockets using approaches like molecular dynamics simulations.[60,61] Moreover, combination therapies have emerged as a promising strategy, wherein PPI inhibitors are paired with agents that block downstream signaling or compensate for parallel pathways.[62,63] Altogether, these lessons suggest that although targeting PPIs remains challenging, it is achievable—especially when the focus is directed toward structurally and functionally vital interface residues.[64,65]

4. Peptide-based disruptors of MTDH–SND1

Protein–protein interactions (PPIs) are particularly amenable to peptide-based approaches because peptides can mimic or competitively block the precise regions involved in binding.[66] The interaction between MTDH and SND1 is a crucial pathway for MTDH to exert its tumorigenic functions, and therefore, therapeutic approaches that block the MTDH–SND1 PPI hold significant research value.[8,9] Peptides derived from the binding regions of MTDH and SND1 have emerged as an effective strategy to block the MTDH–SND1 complex.[8] Over the past few years, researchers have made substantial progress in identifying and optimizing such peptides for greater potency, stability, and *in vivo* functionality.[67,68]

4.1 Discovery and early validation of peptide inhibitors

4.1.1 Phage display screening and peptide 4-2. One of the earliest peptide disruptors of the MTDH–SND1 complex emerged from a phage display screening, which utilized the SN1/SN2 domains of SND1 as bait to identify potential binding peptides.[9,11] Phage display, a technique that allows the display of peptides on the surface of bacteriophages, was employed to screen a large candidate library of peptides for those with high affinity to SND1. After screening thousands of peptides, a 12-amino acid peptide—often referred to as "peptide 4-2"—was identified as a high-affinity binder to the SN1/SN2 domains of SND1.[9,11] This peptide showed a strong interaction with SND1 in biochemical assays, confirming its ability to target the binding interface between MTDH and SND1.[11] Further analysis of peptide 4-2 revealed that it effectively disrupted the MTDH–SND1 interaction, preventing the complex from forming *in vitro*.[11,47] The disruption of this complex resulted in a significant reduction of SND1 protein levels within cancer cells, likely due to increased proteasomal degradation and loss of stability of the unbound SND1 protein.[47,69] This reduction in SND1 levels was accompanied by a marked induction of cytotoxicity in breast cancer cell lines, specifically those overexpressing the MTDH–SND1 complex. Cell viability assays, such as MTT and cell counting, demonstrated a dose-dependent decrease in cell proliferation upon treatment with peptide 4-2.[8,47] Additionally, the peptide induced apoptotic cell death, as indicated by caspase activation and TUNEL assay results. These findings not only validated the biological importance of the MTDH–SND1 interaction in maintaining cancer cell survival but also provided proof of concept for targeting this protein–protein interaction (PPI) with relatively short peptides.[8,9,11] The success of peptide 4-2 highlighted the feasibility of developing peptide-based inhibitors as a therapeutic strategy for targeting the MTDH–SND1 complex in cancer therapy.[11,12]

4.1.2 Critical tryptophan residues and mutagenesis studies. In follow-up work, alanine scanning revealed that tryptophan at position 10 (W10) of peptide 4-2 is pivotal for forming a stable peptide–SND1 complex.[6,11] This residue plays a crucial role in stabilizing the interaction by mediating hydrophobic contacts with key hydrophobic residues on the SND1 protein.[6] Additionally, W10 appears to fit into a specific pocket on the SND1 surface, where it interacts with key amino acids that are critical for the protein's structural integrity and function.[70,71] This binding mode mirrors the critical role of specific tryptophan residues in MTDH, which anchor onto the SN1/SN2 domains of SND1, facilitating the formation of the

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MTDH–SND1 complex.[9] The tryptophan side chain is highly aromatic and bulky, which allows it to stabilize the binding interface through both van der Waals interactions and π–π stacking with aromatic residues on SND1.[72] Furthermore, the size and flexibility of the tryptophan residue enable it to fit snugly into a hydrophobic groove within SND1, creating a stable and energetically favorable interaction.[6,11] Mutating W10 to other amino acids, such as alanine, glutamine, or phenylalanine, significantly diminished both the peptide's binding affinity for SND1 and its cytotoxic potency.[11,47] The reduced binding affinity was confirmed through surface plasmon resonance (SPR) and fluorescence polarization (FP) assays, which showed a significant decrease in the dissociation constant (KD) for the mutated peptides.[73] Additionally, these mutations led to a decrease in apoptotic induction and cell cycle arrest in breast cancer cell lines, further validating the functional importance of this residue.[74] These results underscore the pivotal role of W10 in peptide–SND1 interaction, suggesting that it is a critical hotspot for disrupting the MTDH–SND1 complex and highlighting the potential for further optimization of this region to enhance peptide efficacy.[11,47]

4.1.3 Peptide design based on MTDH structure. In addition, Chen *et al.* designed and modified a series of peptides based on the structure of the MTDH template, utilizing a cross-linking strategy.[4] By studying the amino acid sequence of MTDH that binds to the SND1 1/2 domain, Dap and iso-Asp were introduced to form cyclic peptides.[4] Fluorescence polarization (FP) assays confirmed that MS2D with a WVDE motif had the optimal SND1 dissociation constant (KD).[18] These modifications improved the peptide's affinity for SND1. The antitumor activity of the cyclic peptides MS2D-cyc4 and MS2D-cyc6 was evaluated *in vitro*, showing promising results.[11] A GST-mediated pull-down assay and co-immunoprecipitation (co-IP) verified the inhibitory activity of the modified peptides on the MTDH–SND1 interaction.[11] Furthermore, combination treatment of these peptides with paclitaxel demonstrated significant tumor cell cycle arrest and migration inhibition effects. Despite these positive *in vitro* results, the study lacked *in vivo* experimental data, underscoring the importance of further investigations into peptide stability, antigenicity, and pharmacokinetic properties for developing effective *in vivo* peptide anti-tumor inhibitors.

4.2 Improving cellular uptake and stability

Peptides generally suffer from limitations such as poor membrane permeability and susceptibility to proteolytic degradation.[75] As a result, multiple strategies have been explored to enhance both delivery and half-life.

4.2.1 Cell-penetrating peptide (CPP) fusions. To overcome low intracellular accumulation, some studies fused peptide 4-2 to a CPP sequence.[76] One such derivative, commonly called CPP-4-2, demonstrated improved uptake by breast cancer cells, thus increasing its cytotoxic effects.[47] The IC_{50} values for CPP-4-2 were measured at 22.4 ± 1.0 μmol L^{-1} in MDA-MB-231-GFP-Red-FLuc cells, 18.7 ± 0.2 μmol L^{-1} in MCF-7 cells, and 15.9 ± 6.2 μmol L^{-1} in MDA-MB-468 cells.[47] Although the covalent link to a CPP can slightly alter the peptide's overall charge and conformation, well-chosen linkers can preserve core binding while conferring better tissue penetration.[47]

4.2.2 Cyclization and helical stabilization. Another tactic has been to enforce secondary structure, often through cyclization or the incorporation of noncanonical amino acids (*e.g.*, D-amino acids, stapled side chains, or lactam bridges).[77] For instance, a new generation of stabilized peptides—sometimes described as "cyclic peptides" or "stapled peptides"—is designed to anchor the key binding motif in a conformation that optimizes contact with SND1's interface.[78] This approach can confer increased proteolytic resistance, higher target affinity, and better *in vivo* stability.

4.2.3 Terminal aspartic acid cross-linking. A more specialized strategy reported in recent literature involves "terminal aspartic acid cross-linking," which introduces artificial linkages at peptide termini to reinforce an α-helical conformation.[47] Peptides derived from the known MTDH-binding region have been stabilized in this way, yielding variants (*e.g.*, "MS2D-cyc4" and "MS2D-cyc6") with significantly improved affinity and half-life, as well as notable activity in reducing tumor cell growth *in vitro*.[47]

4.3 Mechanisms of action and downstream effects

By binding to the same or overlapping regions on SND1 that are normally occupied by MTDH, these peptides act as competitive inhibitors, effectively displacing MTDH and thereby disrupting the formation of the MTDH–SND1 complex.[11] The resulting loss of a stable MTDH–SND1 interaction appears to have several significant effects. First, it promotes SND1 degradation, as the absence of MTDH's stabilizing influence renders SND1 more susceptible to proteolytic turnover. Second, it blocks oncogenic signaling pathways, leading to diminished activation of key pathways such as NF-κB, PI3K/Akt, and Wnt/β-catenin. Third, it lowers metastatic potential, particularly in models where the MTDH–SND1 axis plays a central role in driving tumor cell migration and invasion, with inhibition of the interaction correlating with a reduction in metastatic lesions.[11]

4.4 *In vivo* efficacy and delivery challenges

4.4.1 Xenograft studies. Animal models, particularly xenografts, have been instrumental in validating the anti-tumor benefits of peptide disruptors targeting the MTDH–SND1 complex.[22] In these studies, intravenous or intraperitoneal administration of CPP-4-2 or other engineered peptide inhibitors has demonstrated promising anti-tumor efficacy.[47] In breast cancer xenograft models, for example, treatment with CPP-4-2 resulted in a significant reduction in tumor volume compared to controls. The therapeutic concentrations of the peptides were sufficient to induce tumor growth inhibition without the need for excessively high doses, which is a crucial consideration for minimizing potential side effects.[47]

Further, the administration of CPP-4-2 was shown to reduce the proliferation of tumor cells, as evidenced by a decrease in Ki-67 expression (a marker for cell proliferation) within the tumor tissue.[47] Histopathological analysis revealed that tumors from peptide-treated animals exhibited higher levels of

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apoptosis (programmed cell death), as indicated by increased caspase-3 activity and a higher percentage of TUNEL-positive cells, a hallmark of apoptotic cells.[79] Additionally, there was a significant reduction in angiogenesis, as shown by decreased microvessel density in tumors treated with peptide inhibitors.[80] This suggests that the peptides not only affect tumor cell proliferation but may also disrupt the tumor's ability to sustain itself through new blood vessel formation.[81] In some models, a combination of CPP-4-2 with traditional chemotherapy agents, such as paclitaxel, further enhanced the anti-tumor effects, leading to synergistic reductions in tumor volume.[18,47] The combination treatment also resulted in tumor cell cycle arrest and migration inhibition, suggesting that peptide inhibitors could potentiate the effects of existing chemotherapy agents by targeting complementary pathways involved in tumor progression.[18,47] Importantly, these studies confirmed that properly formulated peptides can achieve effective concentrations in tumor tissue, even at relatively low doses, thereby providing a more targeted and less toxic approach compared to conventional chemotherapies.[18,47] Despite these successes, challenges remain in improving the pharmacokinetics and bioavailability of the peptides, as well as minimizing potential off-target effects, which are areas for further investigation.[65] Moreover, while these findings are promising, additional *in vivo* studies involving different cancer models, long-term treatments, and monitoring of potential side effects are essential for translating these results into clinical practice.

4.4.2 Formulation strategies and combination approaches. Despite the promising anti-tumor activity demonstrated by peptide disruptors, there are several challenges that need to be addressed before these peptides can become viable therapeutic agents. Peptides often suffer from issues related to serum stability, immune recognition, and distribution, which can significantly limit their effectiveness *in vivo*.[82] These challenges are primarily due to peptides' susceptibility to enzymatic degradation, poor bioavailability, and rapid clearance from the bloodstream.[83] To overcome these limitations, several formulation strategies have been developed and are being actively explored.

4.4.2.1 Nanoparticle encapsulation. One promising approach to improve the stability and bioavailability of peptides is encapsulating them within nanoparticles.[84] Nanoparticles offer several advantages, including enhanced protection of the peptide from enzymatic degradation and extended circulation time in the bloodstream.[85] By encapsulating peptides in biocompatible nanoparticles, their half-life is increased, which allows for more sustained therapeutic effects. Additionally, nanoparticles can be engineered to target specific tissues or tumor sites, improving the selectivity of peptide delivery.[86] These formulations can be tailored to release the peptide in a controlled manner, ensuring that the drug is delivered directly to the tumor microenvironment, minimizing systemic exposure and potential side effects.

4.4.2.2 PEGylation. PEGylation, the attachment of polyethylene glycol (PEG) molecules to peptides, is another widely used strategy to enhance their pharmacokinetic properties.[87] The addition of PEG molecules increases the peptide's size, which reduces renal clearance and prolongs circulation in the bloodstream.[88] PEGylation also helps mask the peptide from the immune system, thus decreasing immune recognition and preventing the rapid clearance of the peptide by the mononuclear phagocyte system.[89] This strategy improves the peptide's half-life, bioavailability, and ability to accumulate at tumor sites *via* the enhanced permeability and retention (EPR) effect, a phenomenon that allows macromolecules to accumulate in tumor tissues more efficiently than in normal tissues.[90]

4.4.2.3 Liposomal carriers. Another advanced formulation strategy involves encapsulating peptides in liposomal carriers, which are lipid-based vesicles that can deliver both hydrophilic and hydrophobic drugs.[91] Liposomes can provide a controlled release of peptides, improving their stability and reducing off-target effects.[92] Liposomal formulations can be further optimized by surface modification with targeting ligands, such as antibodies or small molecules, to enhance tumor specificity.[93] This approach has been successfully applied to several peptide-based therapies, increasing their efficacy while minimizing systemic toxicity.

4.4.2.4 Combination with chemotherapy and immunotherapy. An exciting avenue for enhancing the therapeutic potential of MTDH–SND1-targeting peptides is their combination with conventional chemotherapy or immunotherapy.[12] Combining peptide inhibitors with chemotherapeutic agents, such as paclitaxel, doxorubicin, or cisplatin, can produce synergistic effects by simultaneously blocking complementary oncogenic pathways involved in tumor progression.[94] For example, while chemotherapy drugs target rapidly dividing tumor cells, peptides like CPP-4-2 specifically inhibit the MTDH–SND1 complex, which plays a role in promoting metastasis, drug resistance, and stemness.[55] This combined approach could enhance the overall anti-tumor response by addressing multiple aspects of tumor biology concurrently. Furthermore, combining peptides with immunotherapies (such as immune checkpoint inhibitors or monoclonal antibodies) could improve the activation of the immune system.[95] Peptides that inhibit MTDH–SND1 may reduce the tumor's ability to evade immune detection, thus making tumor cells more susceptible to immune attack.[55] This combination approach could also enhance the efficacy of adoptive T-cell therapy or immune checkpoint blockade, which aim to reactivate the body's immune response against tumors.[55,96] Moreover, dual-targeted therapies, where peptide disruptors are combined with therapies targeting other key signaling pathways such as PI3K/Akt, NF-κB, or Wnt/β-catenin, are being explored to overcome resistance and further suppress tumor growth and metastasis.[97] The simultaneous targeting of multiple molecular mechanisms could prevent the compensatory activation of alternative pathways that often undermine the effectiveness of monotherapies.[98]

4.4.2.5 Challenges. Despite the progress in formulation strategies and combination approaches, there are still challenges to overcome in translating these strategies to clinical use. The cost and complexity of developing and manufacturing peptide-based formulations remain significant hurdles.[99] Additionally, ensuring consistent and reproducible delivery to tumor sites, particularly in patients with different types of cancers or varying tumor microenvironments, remains an area of active research.[100,101]

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4.5 Future directions for peptide development

While peptide-based MTDH–SND1 inhibitors have already demonstrated clear proof of concept, ongoing research aims to refine and optimize them for clinical use. Several innovative approaches are currently being explored to enhance the potency, stability, and therapeutic efficacy of these peptides, as well as to overcome the challenges associated with their clinical translation.

4.5.1 Macrocyclic libraries. One promising direction for peptide development is the generation of macrocyclic libraries through high-throughput screening.[102] Macrocyclic peptides, which are characterized by a covalently closed ring structure, offer several advantages over linear peptides, including improved stability and higher binding affinity to their targets.[103] The cyclic structure provides resistance to proteolytic degradation, making these peptides more suitable for *in vivo* applications.[104] Researchers are screening synthetic macrocyclic libraries to identify novel peptide candidates that exhibit tighter affinity for the MTDH–SND1 complex.[11] This strategy aims to enhance the overall efficacy and specificity of peptide inhibitors, potentially leading to new, more potent therapeutic agents with better pharmacokinetic properties.

4.5.2 Multi-epitope targeting. Another exciting avenue for improving peptide-based therapies is multi-epitope targeting, which involves designing peptides that simultaneously target multiple interface regions of SND1 or MTDH.[105] By targeting more than one region of the protein complex, these peptides may increase the likelihood of disrupting the MTDH–SND1 interaction and provide a more comprehensive blockade of the functional interaction.[6,11] Multi-epitope peptides can also reduce the risk of resistance, as the tumor would have to overcome multiple binding sites simultaneously.[106] Additionally, such peptides could potentially offer greater selectivity and reduced off-target effects, enhancing their safety profile while improving therapeutic outcomes.[107]

4.5.3 Dual-function peptides. Dual-function peptides are a particularly promising strategy for increasing the therapeutic impact of peptide inhibitors.[108] These peptides are designed to serve dual roles—as both inhibitors of the MTDH–SND1 complex and as carriers of cytotoxic payloads or reporter moieties.[55] By incorporating a cytotoxic agent, such as a chemotherapeutic drug, or a radioactive isotope, into the peptide, researchers can combine the ability of peptides to inhibit the MTDH–SND1 interaction with direct tumor cell killing mechanisms.[28] For example, conjugating peptide inhibitors to chemotherapeutic agents could deliver the drug directly to tumor sites, ensuring that high concentrations of the drug are locally available while minimizing systemic toxicity.[109] Similarly, linking peptides to reporter molecules or fluorescent tags could facilitate real-time tracking of peptide delivery and therapeutic effects, allowing for personalized and optimized treatment regimens.[110]

4.5.4 Peptide-mediated immune modulation. Emerging research is also exploring peptide-mediated immune modulation as a complementary strategy to enhance anti-tumor immunity.[111] MTDH and SND1 are known to play roles in immune evasion by regulating immune checkpoints and modulating the tumor microenvironment.[22] Therefore, peptides that disrupt the MTDH–SND1 complex may also enhance the body's immune response against the tumor.[47] In addition, peptides can be engineered to stimulate immune cells, such as T-cells or natural killer (NK) cells, improving their ability to recognize and attack cancer cells.[112] By combining peptide inhibitors with immune checkpoint inhibitors or vaccines, researchers aim to develop immunotherapy strategies that offer synergistic benefits.[113]

4.5.5 Optimizing pharmacokinetics and bioavailability. Despite the promising *in vitro* and *in vivo* results, one of the ongoing challenges with peptide-based therapies is optimizing their pharmacokinetics and bioavailability.[114] Peptides often have poor oral bioavailability and are rapidly cleared from circulation.[115] To address this, researchers are investigating strategies to enhance peptide stability, such as PEGylation, liposomal encapsulation, and the use of prodrug approaches to prolong their action.[116] Additionally, efforts are underway to improve their tissue penetration and targeted delivery to tumors, reducing off-target effects and enhancing treatment efficacy. The development of long-acting peptide formulations, which can provide sustained release and minimize the need for frequent dosing, is also a key focus of current research.[117]

4.5.6 Combination therapies. As mentioned earlier, combining peptide inhibitors with conventional chemotherapy, immunotherapy, or targeted therapy represents a strategic approach to overcome resistance and improve treatment outcomes.[118] Future studies are expected to investigate a broader range of combination therapies that could enhance the efficacy of MTDH–SND1-targeting peptides, including their combination with small molecule inhibitors targeting other critical pathways like PI3K/Akt, NF-κB, and Wnt/β-catenin.[47] Additionally, combining peptides with novel immunomodulatory agents could help overcome the immunosuppressive tumor microenvironment and improve overall therapeutic efficacy.[119]

4.5.7 Personalized medicine and biomarker identification. The future of peptide-based therapies for targeting the MTDH–SND1 complex may also lie in the development of personalized treatment regimens.[11] By identifying specific biomarkers that predict which patients will benefit most from MTDH–SND1-targeting peptides, clinicians could optimize therapeutic strategies.[11] The use of genomic profiling, proteomics, and biomarker panels will allow for more accurate patient stratification and enhance the clinical outcomes of peptide therapies.[120] Personalized approaches can ensure that the right peptide inhibitors are used for the right patients, based on their individual tumor biology and molecular profiles.

5. Small-molecule inhibitors of MTDH–SND1

While peptide-based inhibitors offer high specificity for disrupting the MTDH–SND1 complex, the pharmacokinetic and delivery limitations associated with peptides have catalyzed growing interest in small-molecule alternatives.[9,22] Small molecules typically demonstrate better oral bioavailability, chemical

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stability, and tissue penetration, which makes them more amenable to clinical translation.[121] Additionally, small molecules can be fine-tuned for selectivity, solubility, and metabolic stability through medicinal chemistry optimization.[122] Recent progress in chemical biology, biophysical assay development, and computational modeling has enabled the rational design and screening of potent small-molecule inhibitors that target the MTDH–SND1 interaction interface, particularly the hydrophobic SN1/SN2 pocket of SND1.[8,9]

5.1 Early leads and proof-of-concept screens

A major breakthrough in small-molecule screening for MTDH–SND1 inhibitors came from Shen *et al.*, who developed a split-luciferase complementation assay tailored to detect the interaction between MTDH and SND1 in living cells.[8,9] This assay leveraged a library of ~50 000 compounds and utilized a bioluminescent output to report on MTDH–SND1 binding status.[8,9] Hits from this screen included the compound C26 series (notably C26-A2 and C26-A6), which disrupted the complex with an IC_{50} of ~2.4 μM.[8] Subsequent microscale thermophoresis (MST) confirmed binding to the SND1 interface (Fig. 8). Importantly, co-crystal structures revealed that these compounds occupy the hydrophobic pocket of the SND1 SN1/SN2 domain where MTDH W401 normally anchors.[8,9] These compounds demonstrated selective interference with MTDH–SND1 without broadly inhibiting SND1's unrelated RNA-processing functions—an essential consideration for therapeutic safety.[8,9]

5.2 Structure-based design and virtual screening

Capitalizing on available co-crystal structures and mutagenesis data, researchers applied virtual screening and molecular dynamics simulations to identify more refined scaffolds.[53] This led to compounds such as compound C19, which filled the MTDH anchoring pocket on SND1, and compound L5, discovered by simulating conformational flexibility in SND1 to identify cryptic binding sites (Fig. 9, 10, and Table 1).[9,18] Compound C19 demonstrated submicromolar potency in biochemical assays, with strong activity in xenograft models. Compound L5, though less potent (IC_{50} ~ 57 μM in MDA-MB-231 cells), showed clear intracellular target engagement, verified *via* immunofluorescence assays.[18] Notably, compound L5's binding mode suggested hydrogen bonding interactions with SND1 R255, further validated by molecular dynamics simulations, underscoring the role of polar contacts and pocket dynamics in SND1 ligand recognition.[18] The integration of ensemble docking, ligand field energy modeling, and free energy perturbation (FEP) simulations represents an important frontier for refining these leads. Compounds L2 and L11 displayed no binding signals.

To further elucidate the binding mode of small-molecule inhibitors, molecular docking studies were performed using the crystal structure of the SND1 SN1/SN2 domain (PDB ID: 4QMG) (Fig. 11).[16] Compound C19 fitted deeply into the hydrophobic groove, forming hydrogen bonds with Arg255 and Glu399, π–π stacking with Trp401, and van der Waals contacts with residues such as Phe251 and Ala398. The binding pocket was well-occupied, suggesting strong shape complementarity and favorable energetics. Similarly, compound L5 exhibited a comparable binding orientation, establishing hydrogen bonds with Arg255 and Glu291, π–π interactions with Trp401, and hydrophobic contacts with Phe251 and Ala398. The similarity in binding modes supports the hypothesis that both C19 and L5 disrupt the MTDH–SND1 interface by competitively occupying the SN1/SN2 hydrophobic pocket, thereby blocking MTDH recruitment and destabilizing oncogenic SND1 complexes.

5.3 Mechanisms of action and key findings

Despite their chemical diversity, most validated MTDH–SND1 small-molecule inhibitors function by occupying or deforming the hydrophobic binding pocket within SND1's SN1/SN2 domain, thereby blocking MTDH recruitment, which is critical for stabilizing SND1 in oncogenic contexts. Inhibitors such as compounds C26-A6 and C19 have been shown to induce proteasomal degradation of SND1 due to the loss of MTDH's stabilizing interaction, downregulate key oncogenic signaling cascades—notably NF-κB, PI3K/Akt, and Wnt/β-catenin, all of which are hyperactivated in MTDH-driven tumors—and impair migration, invasion, and stemness phenotypes in aggressive cancer cells. Additionally, C26-A6 interferes with the MTDH–SND1–TAP1/2 axis, restoring tumor antigen presentation and reversing immune evasion, underscoring the role of MTDH–SND1 as a dual oncogenic-immunosuppressive hub.

5.4 *In vitro* and *in vivo* evaluations

In vitro studies of these inhibitors have consistently demonstrated dose-dependent inhibition of cancer cell proliferation, particularly in triple-negative breast cancer (TNBC) and hepatocellular carcinoma (HCC) cells, along with suppression of epithelial-to-mesenchymal transition (EMT) markers and cancer stem cell signatures, and induction of apoptosis as evidenced by elevated cleaved caspase-3 and PARP cleavage. *In vivo*, xenograft models treated with compounds such as C26-A6 or C19 showed tumor volume reduction, slower growth kinetics, and reduced metastasis to the lungs in breast cancer models. These compounds also exhibited synergistic efficacy when combined with paclitaxel, resulting in improved tumor suppression and fewer metastatic lesions compared to monotherapy. Furthermore, combining C26-A6 with anti-PD-1 therapy significantly enhanced $CD8^+$ T-cell infiltration and reduced T-cell exhaustion, further confirming the immune relevance of the MTDH–SND1 axis.[8,9,12,14,18]

5.5 Challenges, opportunities, and next steps

The shallow and hydrophobic nature of the MTDH–SND1 interface makes it classically "undruggable," requiring ligands with precise three-dimensional complementarity and hydrogen-bonding patterns.[18] In addition, SND1's pleiotropic role in post-transcriptional regulation poses selectivity risks, as global inhibition of SND1 could impair normal RNA processing.[38] Current leads also face challenges related to solubility, metabolic stability, and tumor-specific accumulation, which limit systemic delivery and long-term exposure.[123] To address these

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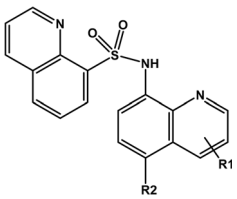
Table 1 Chemical structure and inhibitory activity against MTDH–SND1 PPI of C23–C31. The IC_{50} values are represented in μM as the mean with SD of triplicate measurements



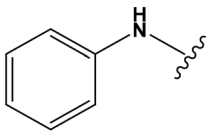
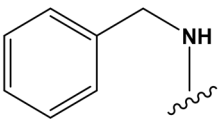
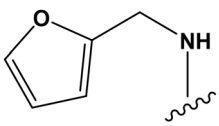
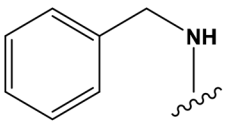
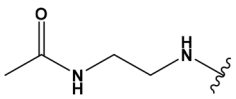
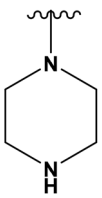
Compound	R1	R2	Inhibitory efficiency IC_{50} (μM)
C13	2-CH_3	H	2.087 ± 0.310
C14	2-Cl	H	>5
C15	3-Br	H	1.530 ± 0.233
C16	5-OMe	H	0.994 ± 0.130
C17	5-Cl	H	1.247 ± 0.108
C18	5-Br	H	1.699 ± 0.214
C19	6-F	H	0.487 ± 0.099
C20	6-Cl	H	0.914 ± 0.077
C21	6-Br	H	1.423 ± 0.212
C22	6-OMe	H	2.081 ± 0.216
C23	7-Me	H	>5
C24	3- 	H	2.577 ± 0.254
C25	 3-	H	>5
C26	3- 	H	>5
C27	H		>5
C28	H		>5
C29	H		3.568 ± 0.858

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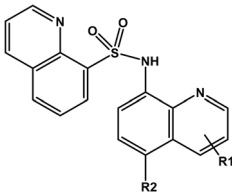
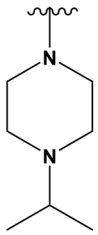
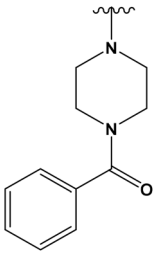
Table 1 (*Contd.*)



Compound	R1	R2	Inhibitory efficiency IC_{50} (μM)
C30	H		>5
C31	H		>5

issues, several opportunities have emerged. Fragment-based drug design (FBDD) and structure-guided scaffold hopping may help overcome interface limitations by building multi-site occupancy ligands.[124] Combination therapies involving MTDH–SND1 inhibitors with checkpoint blockade, such as anti-PD-1, or DNA-damaging agents could amplify efficacy and broaden applications across immune-resistant tumors.[22] PROTAC technology offers a means to selectively degrade SND1 or MTDH *via* recruitment to E3 ubiquitin ligases, bypassing the need for competitive inhibition.[125] Structure–activity relationship (SAR) studies on the C26 scaffold have identified key pharmacophores—chloromethoxyphenyl (A fragment) and triazolopyridine (B fragment)—with hydrogen bonding between R255 of SND1 and the triazole/pyridylamine moieties of C26-A2/A6 being critical for binding and function.[8] Furthermore, incorporating lipophilic efficiency metrics and plasma protein binding predictions can guide improvements in absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties.[126]

6. Delivery systems and formulation advances

While identifying potent inhibitors of the MTDH–SND1 complex is a critical step, achieving efficient delivery and sustained bioactivity *in vivo* poses its own set of challenges. Peptide-based inhibitors can suffer from limited serum stability and membrane permeability, whereas small molecules, although typically more drug-like, still require formulations that maximize tumor localization and minimize off-target effects.[22] Overcoming these hurdles has driven researchers to explore an array of delivery strategies—from fusion peptides and nanocarriers to specialized chemical modifications—to ensure that MTDH–SND1 inhibitors reach their intracellular target in sufficient concentrations.[114]

6.1 Peptide delivery strategies

6.1.1 Cell-penetrating peptide (CPP) conjugates. One of the most direct methods of enhancing intracellular uptake for peptide inhibitors is tethering them to cell-penetrating peptides.[127] A notable example is the derivatization of the peptide "4-2" (originally identified through phage display) into "CPP-4-2," which improved cellular internalization and resulted in enhanced cytotoxicity against breast cancer cells.[47] Similar conjugate strategies often utilize short, positively charged sequences (*e.g.*, TAT or poly-arginine motifs) to facilitate crossing the plasma membrane. Studies have shown that these CPP fusions reduce tumor volume in mouse models, particularly for MTDH–SND1–dependent cancers, confirming that

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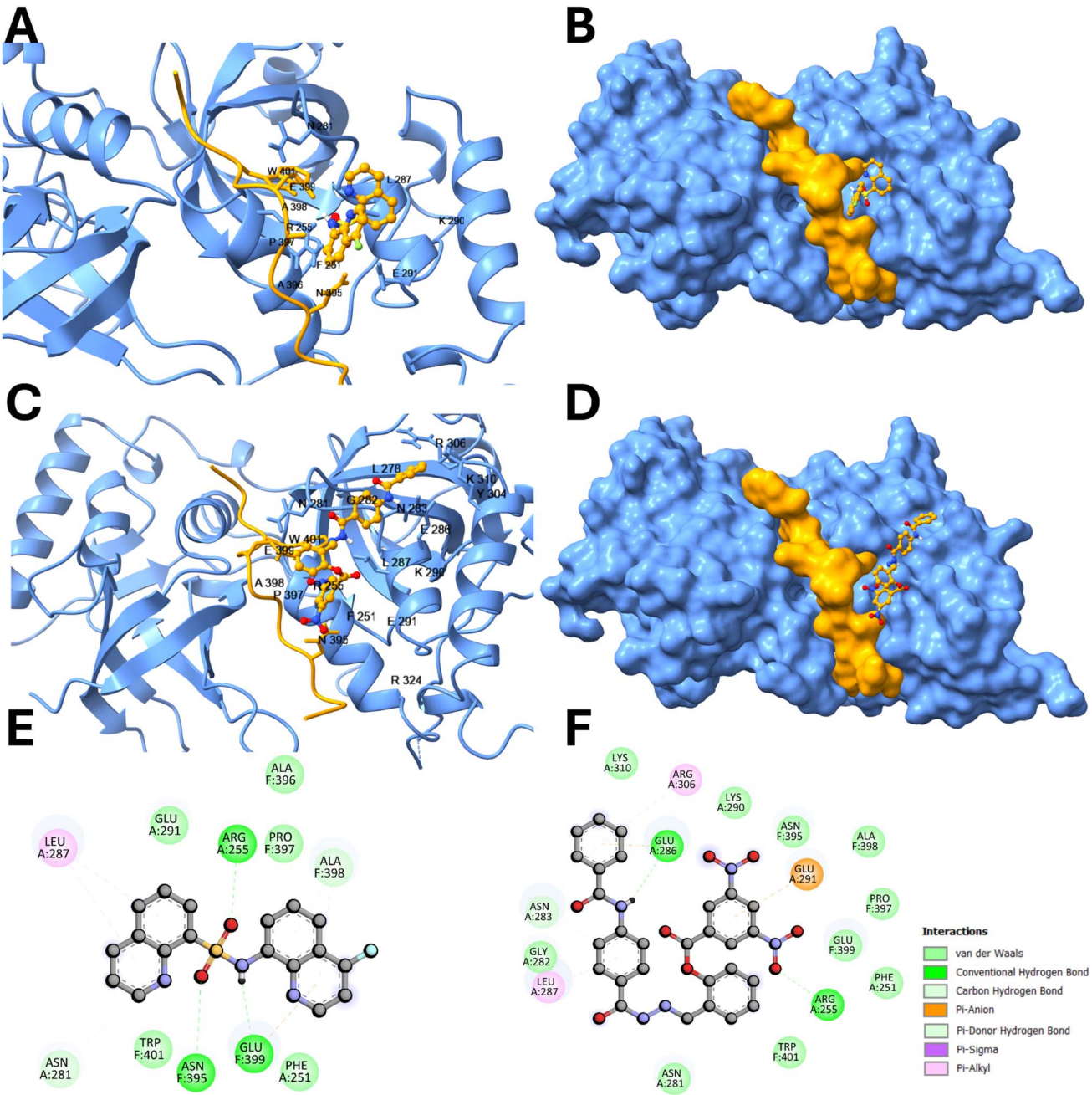

Fig. 11 Molecular docking analysis of compounds C19 and L5 with the SND1 SN1/SN2 domain (PDB ID: 4QMG).[16] (A, B and E) Docking pose and interaction analysis of compound C19. Panel A shows the ribbon representation of SND1 (blue) with C19 bound in the hydrophobic groove (yellow sticks). Panel B illustrates the surface view highlighting the binding pocket (yellow surface) accommodating C19. Panel E depicts the 2D interaction map showing hydrogen bonds, π-interactions, and van der Waals contacts between C19 and surrounding residues, with key interactions involving Arg255, Glu399, and Trp401. (C, D and F) Docking pose and interaction analysis of compound L5. Panel C displays the ribbon representation of SND1 (blue) with L5 bound in the hydrophobic groove (yellow sticks). Panel D shows the surface representation with the binding site highlighted. Panel F presents the 2D interaction map, revealing key contacts such as hydrogen bonding with Arg255 and π–π stacking with Trp401, along with hydrophobic interactions involving Phe251 and Ala398.

improved intracellular access can significantly increase therapeutic efficacy.[47]

6.1.2 Sulfonium-based peptide delivery system. Recent work has also introduced a sulfonium-based delivery approach that noncovalently complexes peptides with cationic sulfonium moieties.[128] By carefully balancing charge interactions, investigators were able to enhance the stability and uptake of a stabilized peptide derived from MTDH sequences (*e.g.*, MS2D-based peptides).[6] *In vivo* experiments demonstrated that sulfonium–peptide complexes led to stronger tumor growth inhibition in triple-negative breast cancer xenografts compared to unformulated controls, highlighting how specialized chemical

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carriers can help surmount the cell permeability and plasma stability barriers that often plague peptide therapeutics.[128]

6.1.3 Macrocyclic and stapled formulations. Beyond carrier systems, stabilizing the peptide itself is another route to improved delivery.[129] Stapled peptides—or macrocyclic peptides containing intramolecular bonds that fix them in a helical conformation—resist proteolysis and display higher cellular uptake relative to linear analogs.[128] Studies on "stapled" or "cyclized" versions of MTDH-binding peptides, such as MS2D-cyc4 and MS2D-cyc6, suggest that cyclization confers both enhanced potency and better metabolic stability, leading to more robust *in vivo* antitumor effects.[11]

6.2 Small-molecule formulation approaches

6.2.1 Nanoparticle encapsulation. While small molecules typically permeate cells more easily than peptides, optimal tumor delivery and reduced off-target toxicity can still benefit from nanoparticle-based encapsulation.[130] Liposomal formulations of small-molecule MTDH–SND1 inhibitors (for instance, early derivatives akin to C26-A2 and C26-A6) have been proposed to prolong circulation time and concentrate payloads within the tumor microenvironment through the enhanced permeability and retention (EPR) effect.[8,9] Although published data remain limited, preliminary findings indicate that nanoencapsulation can mitigate the dose-dependent side effects observed with unformulated compounds.[131]

6.2.2 PEGylation and prodrug strategies. A more traditional approach involves PEGylating small molecules or creating prodrugs that undergo enzymatic or chemical cleavage in the tumor milieu.[132] While direct evidence for PEGylated MTDH–SND1 inhibitors is still emerging, similar methods have been successful for other PPI-targeted agents. By extending half-life and lowering systemic clearance, PEGylation or site-specific prodrug activation could help maintain steady intracellular levels of the inhibitor, crucial for continuous disruption of MTDH–SND1.[55]

6.3 Efficacy in preclinical models

Researchers have evaluated various formulation and delivery strategies in multiple *in vivo* models, primarily murine xenografts derived from breast cancer cell lines known to overexpress MTDH.[133] These studies have consistently demonstrated enhanced tumor uptake, with agents delivered *via* cell-penetrating peptide (CPP) conjugation or nanoencapsulation accumulating at higher concentrations within tumors compared to free compounds.[134] Additionally, these formulations have been shown to reduce off-target toxicity by limiting nonspecific tissue distribution and thereby minimizing adverse effects on normal cell populations.[135] Treatment synergy is also improved; whether administered as monotherapy or in combination with chemotherapy, these delivery systems often result in deeper tumor regression and reduced metastatic spread relative to standard therapies.[136] For instance, peptides formulated with a sulfonium-based system have significantly reduced tumor volume in animal models, exhibiting superior pharmacokinetic profiles and potent inhibition of MTDH–SND1-driven signaling pathways.[12] Similarly, small molecules such as compound C19, when packaged in nanosized carriers, have shown promising antitumor effects alongside reduced systemic toxicity.[9]

6.4 Future outlook and combination therapies

Despite these advances, several challenges remain. One critical need is the development of high-loading formulations capable of carrying sufficient quantities of peptides or hydrophobic small molecules to achieve clinically effective doses.[109] Another area of focus is active targeting, where the incorporation of tumor-specific ligands or antibodies onto nanoparticle surfaces may improve the localization of MTDH–SND1 inhibitors to metastatic sites, thereby enhancing their therapeutic index. Moreover, synergistic treatment regimens are being explored, including the combination of MTDH–SND1 inhibitors with immune checkpoint inhibitors or PI3K/Akt pathway blockers, as such approaches could produce enhanced outcomes due to the convergence of these agents on multiple pro-tumorigenic signaling pathways.[137] In parallel, novel technologies like PROTAC-based degraders, which exploit the ubiquitin–proteasome system, are being investigated as a means to selectively degrade MTDH or SND1.[138] Although still in early development for this particular PPI, the potential synergy between advanced degrader platforms and innovative delivery systems highlights a broad and promising frontier for future research.[139]

7. Translational considerations and future directions

Having established the feasibility of disrupting the MTDH–SND1 interaction through both peptide- and small-molecule-based approaches, the next major step lies in transitioning these discoveries from preclinical models to clinical implementation. While this target holds considerable promise—given its essential role in multiple oncogenic pathways—several questions must be resolved to facilitate progress toward therapeutic approval. In addition, emerging technologies and synergistic treatment paradigms could propel MTDH–SND1 inhibition into a new class of precision cancer therapies.

7.1 Pharmacokinetic and pharmacodynamic challenges

A recurring obstacle in PPI drug discovery is ensuring adequate drug exposure and potency within the complex tumor microenvironment. Even some of the most advanced MTDH–SND1 inhibitors (*e.g.*, C19 or stabilized peptides like CPP-4-2) display variability in half-life, tissue distribution, and metabolic stability across animal studies.[12,47] Achieving and sustaining therapeutically active levels of peptide disruptors can be difficult. Despite demonstrated *in vivo* efficacy, formulations such as CPP-conjugates or nanoencapsulated peptides often require repeated administrations.[140] Previous xenograft experiments, for instance, showed that while weekly dosing of certain cell-penetrating peptides can slow tumor growth, drug clearance remains relatively rapid, necessitating further PK/PD optimization.[82] The complexity of SND1's involvement in RNA

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metabolism means broad off-target effects are possible if an inhibitor excessively disrupts normal SND1 functions.[141] Early leads for small-molecule MTDH–SND1 inhibitors sometimes exhibited dose-limiting toxicity, likely due to partial selectivity issues.[9,12] Continual structure-guided design, informed by high-resolution structural data of the SN1/SN2 interface, will be essential for sharpening selectivity and reducing adverse effects *in vivo*.[142]

7.2 Biomarker-driven clinical application

Because MTDH and SND1 are implicated in several cancer types, patient selection and biomarker profiling are poised to become integral parts of any future clinical trial strategy.

Multiple studies have correlated high MTDH/SND1 co-expression with poor prognosis in breast and liver cancers.[31] As these data accumulate, it becomes feasible to use MTDH–SND1 expression signatures as a biomarker to identify patient subgroups most likely to benefit from targeted inhibition. For instance, mice bearing high-MTDH–expressing breast tumors showed robust responses to experimental inhibitors, whereas low-expressing tumors were less sensitive.[133]

The MTDH–SND1 axis frequently intersects with NF-κB, PI3K/Akt, and other key signaling routes.[47] Tumors harboring hyperactivating mutations in these pathways (*e.g.*, PIK3CA or PTEN loss) might respond more vigorously when the upstream MTDH–SND1 hub is dismantled.[24] In one line of preclinical research, combining MTDH–SND1 peptide inhibitors with a PI3K inhibitor produced stronger tumor control than either agent alone, suggesting synergy in pathway blockade.[11] Evidence from knockdown studies indicates that MTDH–SND1 is tied to metastatic progression and the maintenance of tumor-initiating cells.[2,4] Monitoring circulating tumor cells (CTCs) or relevant stemness markers may help gauge how effectively an inhibitor is impacting the metastatic process.[143] Early xenograft data show that even a partial disruption of the MTDH–SND1 interaction can significantly reduce micrometastatic lesions, suggesting a promising angle for controlling or preventing recurrence.[2]

7.3 Next-generation inhibitors and combination strategies

7.3.1 PROTACs and degrader approaches. In light of the complex's importance, an emerging concept is to create proteolysis-targeting chimeras (PROTACs) or molecular glues that not only block MTDH–SND1 binding but also recruit E3 ubiquitin ligases to degrade one or both proteins.[144] Although PROTACs targeting this specific interaction have not yet been broadly reported, progress in related PPI systems (such as MDM2-p53 or BCL-xL-BCL2) suggests the methodology could be adapted.[145] Any success here would have the added benefit of permanently eliminating MTDH or SND1 from cells, as opposed to transiently inhibiting their interaction.

7.3.2 Combination therapies. Mounting evidence suggests that MTDH–SND1 inhibitors may act synergistically with existing cancer treatments. In the context of chemotherapy and radiotherapy, disruption of the MTDH–SND1 complex can impair tumor cell survival pathways, thereby sensitizing cells to DNA damage and enhancing the efficacy of standard cytotoxic agents.[2] Preclinical studies have demonstrated, for instance, that drug-resistant breast cancer cells can regain sensitivity to doxorubicin following inhibition of MTDH–SND1.[146] In terms of immunotherapy, MTDH overexpression is linked to the development of immunosuppressive tumor microenvironments. Targeting the MTDH–SND1 axis may improve the effectiveness of immune checkpoint inhibitors by relieving MTDH–SND1-mediated suppression of antigen presentation and cytokine signaling, thereby restoring immune cell activity.[147] Furthermore, combination strategies involving targeted pathway inhibitors have shown promise; simultaneous inhibition of downstream effectors such as NF-κB and PI3K/Akt has produced greater tumor regression in both *in vitro* and *in vivo* models compared to monotherapy approaches.[148]

7.3.3 Personalized and RNA-based therapeutics. Another frontier is the integration of RNA interference (RNAi) or antisense oligonucleotides to knock down MTDH or SND1 mRNA directly, in combination with small-molecule or peptide inhibitors.[149] Although these therapies each have intrinsic delivery and stability challenges, combined modalities might exploit synergy between gene-level silencing and protein-level inhibition.

7.4 Moving toward clinical trials

With growing evidence of safety and efficacy in animal models, a logical next step is to conduct formal toxicity studies followed by Phase I trials in selected patient cohorts. Key aspects for clinical transition include ensuring robust pharmacokinetic (PK) properties for either peptides or small molecules so that safe and effective plasma exposures are achievable;[109] utilizing biomarker-driven endpoints—such as MTDH–SND1 expression levels, response rates, or progression-free survival—to capture the earliest signals of clinical activity;[150] and performing thorough safety evaluations to detect any potential immunological or hematopoietic toxicities, given that MTDH–SND1 inhibitors may have pleiotropic effects.[22] Encouragingly, ongoing research demonstrates that improved structural knowledge, rational combination regimens, and advanced delivery platforms are mitigating many of the obstacles once deemed insurmountable in PPI targeting. With sufficient support, the MTDH–SND1 axis could become an actionable therapeutic target in multiple tumor settings, particularly for patients who do not respond well to current standards of care.

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8. Outlook and path forward

The MTDH–SND1 interaction has emerged as a pivotal node in tumor biology, profoundly impacting processes such as cellular

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proliferation, metastasis, drug resistance, and immune evasion.[14] From early genetic knockdown studies demonstrating the essential nature of this complex for tumor survival, to recent strides in rational inhibitor design, the story of MTDH–SND1 has transformed from an abstract molecular mechanism to a concrete therapeutic target with expanding clinical relevance.[9]

8.1 Lessons learned from structural and functional studies

A wealth of structural insights has illuminated the critical residues on both MTDH and SND1 that anchor their interaction—most notably, the tryptophans on MTDH and complementary hydrophobic sites within the SN1/SN2 domains of SND1.[9] These discrete "hot spots" are indispensable for the stability of the MTDH–SND1 partnership, offering an attractive foothold for inhibitors.[9] Studies using peptides, small molecules, and genetic manipulations consistently reinforce the conclusion that blocking this interface can cripple multiple oncogenic signals in pathways as diverse as NF-κB, PI3K/Akt, and Wnt/β-catenin.[97] At the same time, the reciprocal stabilization phenomenon—where each protein bolsters the other's half-life—underscores a major reason this pair exerts such a profound oncogenic effect. Interventions that dismantle the complex tend not only to reduce signaling outputs but also promote degradation or inactivation of SND1.[38] This duality amplifies the therapeutic impact, making MTDH–SND1 blockade an especially potent approach to undermine tumors' adaptive capabilities.[22]

8.2 Progress and promises in therapeutic development

Research groups have demonstrated that MTDH–SND1 is indeed druggable despite some inherent challenges in PPI targeting. Peptide inhibitors such as CPP-4-2, MS2D-cyc4, and other stabilized constructs have shown high specificity and strong target engagement. Although delivery remains a major hurdle, innovative carrier systems—including cell-penetrating peptides, sulfonium-based carriers, and macrocyclization strategies—have significantly improved *in vivo* stability and efficacy.[47,128] Small-molecule inhibitors also provide compelling evidence, with early hits such as C26-A2 and C26-A6 proving the concept, and more recent refined leads like compound C19 and L5 demonstrating enhanced potency and improved pharmacological profiles. *In vivo* models have yielded encouraging tumor growth inhibition, and combining small-molecule disruptors with standard therapies or immunotherapies may further amplify clinical benefits.[8,9,18] Nanoencapsulation, PEGylation, and prodrug strategies aim to enhance tumor-specific delivery, reduce toxicity, and prolong half-life.[116,132] Trials in murine xenografts point to robust synergy when MTDH–SND1 inhibition is paired with chemotherapy or targeted pathway blockers (*e.g.*, PI3K/Akt inhibitors).[9] Collectively, these strategies highlight a rapidly maturing field that is poised to translate into meaningful clinical outcomes as optimization continues.

8.3 Persisting challenges

While the potential is evident, multiple challenges warrant attention. Regarding selectivity and toxicity, SND1's extensive roles in RNA metabolism raise the possibility of on-target toxicity, making it crucial to strike a balance between potency and the preservation of normal cellular processes.[14] In terms of complex tumor biology, tumors often evolve redundancy in signaling, meaning that simultaneously shutting down MTDH–SND1 might require parallel blockade of compensatory pathways to achieve durable responses.[14] Finally, translational hurdles remain, as moving from promising xenograft data to human trials demands thorough toxicological evaluations, robust biomarker strategies, and large-scale manufacturing capacity for specialized formulations.[151]

8.4 Path forward: toward clinical trials and beyond

A few logical trajectories define the next phase of MTDH–SND1 research. In clinical trial design, defining ideal patient populations—such as tumors with high MTDH–SND1 co-expression—and establishing early proof-of-mechanism endpoints, including SND1 levels or changes in tumor-initiating cell markers, will be critical for Phase I/II trials.[3] Synergy with emerging modalities also holds promise; mitigating immune–evasive properties fostered by MTDH–SND1 could open new avenues for checkpoint inhibitors, while harnessing the specificity of small-molecule binders to degrade MTDH or SND1 entirely through molecular glues or PROTACs may dramatically lower the risk of treatment escape.[138] Deepened structural insights, such as additional co-crystal structures and advanced simulation models, could further refine small-molecule design and push potency into the high-affinity range needed for clinical success. Expansion to other cancers is another important direction, as although most research has focused on breast, liver, and prostate cancers, the high incidence of MTDH overexpression across many tumor subtypes suggests broader therapeutic potential. Ultimately, the MTDH–SND1 axis stands at the crossroads of numerous cancer-driving processes, and as more potent, selective, and clinically viable inhibitors emerge, the prospect of meaningfully affecting treatment-resistant malignancies grows increasingly tangible.[152] Through iterative optimization, advanced delivery solutions, and rational combination therapies, targeting the MTDH–SND1 complex may redefine success in oncology, offering more effective strategies against some of the toughest malignancies known.[2,9,12,14,18]

9 Conclusion

Over a decade of intensive research has painted a compelling picture of MTDH–SND1 as a central signaling hub driving malignancy in various cancers, most notably breast cancer. From basic mechanistic discoveries to the development of peptides and small-molecule inhibitors, this PPI has transitioned from an elusive target to a tangible candidate for therapeutic intervention. Preclinical evidence indicates that dismantling MTDH–SND1 diminishes key oncogenic pathways, reduces tumor growth, and can synergize with existing treatments. Advances in formulation technologies—ranging from cell-penetrating peptides to nanoparticle encapsulation—have

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meanwhile addressed some inherent barriers to drug delivery, thereby broadening the scope of clinically relevant applications. Despite these advances, challenges remain. The essential roles of SND1 in normal cellular functions mean that careful attention to toxicity and off-target effects will be critical in future clinical testing. Additionally, identifying the patient populations most likely to benefit from MTDH–SND1 inhibition—based on tumor expression profiles, co-occurring mutations, or other biomarkers—could help maximize therapeutic benefit while minimizing unnecessary interventions. The field will also need to refine the pharmacokinetics and manufacturing scale-up for novel peptides and chemical scaffolds, paving the way for more seamless transitions from the laboratory to the clinic. Nevertheless, the momentum gathered thus far underscores the enormous potential of MTDH–SND1 – targeted therapies to transform cancer care. As refinements in structure-based design, delivery platforms, and combination regimens continue, MTDH–SND1 blockade stands poised to address unmet needs in aggressive, therapy-resistant tumors. Ultimately, success in this domain would mark an important milestone in the broader effort to transform PPI modulators into robust, lifesaving treatments.

Conflicts of interest

The authors report there are no competing interests to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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References

1 F. Weiss, D. Lauffenburger and P. Friedl, *Nat. Rev. Cancer*, 2022, **22**, 157–173.
2 L. Wan, X. Lu, S. Yuan, Y. Wei, F. Guo, M. Shen, M. Yuan, R. Chakrabarti, Y. Hua, H. A. Smith, M. A. Blanco, M. Chekmareva, H. Wu, R. T. Bronson, B. G. Haffty, Y. Xing and Y. Kang, *Cancer Cell*, 2014, **26**, 92–105.
3 M. Khan and D. Sarkar, *Genes*, 2021, **12**, 308.
4 Y. Chen, H. Sheng, G. Rong and D. Chen, *Biomarkers Med.*, 2021, **15**, 1769–1783.
5 H. Shen, J. Ding, J. Ji, B. Jiang, X. Wang and P. Yang, *Overcoming MTDH and MTDH-SND1 complex: driver and potential therapeutic target of cancer*, 2023.
6 S. Liu, X. Hao, D. Miao and Y. Zhang, *J. Phys. Chem. B*, 2024, **128**, 9074–9085.
7 S.-Y. Liao, D. Rudoy, S. B. Frank, L. T. Phan, O. Klezovitch, J. Kwan, I. Coleman, M. C. Haffner, D. Li, P. S. Nelson, A. Emili and V. Vasioukhin, *Nat. Commun.*, 2023, **14**, 7435.
8 M. Shen, Y. Wei, H. Kim, L. Wan, Y.-Z. Jiang, X. Hang, M. Raba, S. Remiszewski, M. Rowicki, C.-G. Wu, S. Wu, L. Zhang, X. Lu, M. Yuan, H. A. Smith, A. Zheng, J. Bertino, J. F. Jin, Y. Xing, Z.-M. Shao and Y. Kang, *Nat. Cancer*, 2022, **3**, 43–59.
9 H. Shen, J. Ding, J. Ji, L. Hu, W. Min, Y. Hou, D. Wang, Y. Chen, L. Wang, Y. Zhu, X. Wang and P. Yang, *J. Med. Chem.*, 2025, **68**, 1844–1862.
10 H. Nada, Y. Choi, S. Kim, K. S. Jeong, N. A. Meanwell and K. Lee, *Signal Transduct. Targeted Ther.*, 2024, **9**, 341.
11 H. Chen, M. Zhan, J. Liu, Z. Liu, M. Shen, F. Yang, Y. Kang, F. Yin and Z. Li, *J. Med. Chem.*, 2022, **65**, 12188–12199.
12 H. Chen, M. Zhan, Y. Zhang, J. Liu, R. Wang, Y. An, Z. Gao, L. Jiang, Y. Xing, Y. Kang, Z. Li and F. Yin, *JACS Au*, 2024, **4**, 139–149.
13 D. Davda, M. A. El Azzouny, C. T. M. B. Tom, J. L. Hernandez, J. D. Majmudar, R. T. Kennedy and B. R. Martin, *ACS Chem. Biol.*, 2013, **8**, 1912–1917.
14 F. Guo, L. Wan, A. Zheng, V. Stanevich, Y. Wei, K. A. Satyshur, M. Shen, W. Lee, Y. Kang and Y. Xing, *Cell Rep.*, 2014, **8**, 1704–1713.
15 L. Yu, Y. Di, L. Xin, Y. Ren, X. Liu, X. Sun, W. Zhang, Z. Yao and J. Yang, *Oncogene*, 2017, **36**, 3903–3914.
16 F. Guo, L. Wan, A. Zheng, V. Stanevich, Y. Wei, K. A. Satyshur, M. Shen, W. Lee, Y. Kang and Y. Xing, *Cell Rep.*, 2014, **8**, 1704–1713.
17 S. Lehmusvaara, T. Haikarainen, J. Saarikettu, G. Martinez Nieto and O. Silvennoinen, *Cancers*, 2022, **14**, 3100.
18 Y. Xu, X. Guo, D. Yan, X. Dang, L. Guo, T. Jia and Q. Wang, *J. Chem. Inf. Model.*, 2023, **63**, 3614–3627.
19 Z.-X. Li, Z.-Q. Zheng, P.-Y. Yang, L. Lin, G.-Q. Zhou, J.-W. Lv, L.-L. Zhang, F. Chen, Y.-Q. Li, C.-F. Wu, F. Li, J. Ma, N. Liu and Y. Sun, *Cell Death Differ.*, 2022, **29**, 1137–1151.
20 V. Gureghian, H. Herbst, I. Kozar, K. Mihajlovic, N. Malod-Dognin, G. Ceddia, C. Angeli, C. Margue, T. Randic, D. Philippidou, M. T. Nomigni, A. Hemedan, L.-C. Tranchevent, J. Longworth, M. Bauer, A. Badkas, A. Gaigneaux, A. Muller, M. Ostaszewski, F. Tolle, N. Pržulj and S. Kreis, *Cancer Gene Ther.*, 2023, **30**, 1330–1345.
21 M. Mustafa, R. Ahmad, I. Q. Tantry, W. Ahmad, S. Siddiqui, M. Alam, K. Abbas, M. I. Hassan, S. Habib and S. Islam, *Cells*, 2024, **13**, 1838.
22 M. Shen, H. A. Smith, Y. Wei, Y.-Z. Jiang, S. Zhao, N. Wang, M. Rowicki, Y. Tang, X. Hang, S. Wu, L. Wan, Z.-M. Shao and Y. Kang, *Nat. Cancer*, 2022, **3**, 60–74.
23 M. Cappellari, P. Bielli, M. P. Paronetto, F. Ciccosanti, G. M. Fimia, J. Saarikettu, O. Silvennoinen and C. Sette, *Oncogene*, 2014, **33**, 3794–3802.
24 A. He, S. He, C. Huang, Z. Chen, Y. Wu, Y. Gong, X. Li and L. Zhou, *Aging*, 2020, **12**, 1465.
25 L. Wan, Dissecting the roles of MTDH/AEG-1 during multiple steps of cancer development, PhD thesis, Princeton University, 2014.

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26 G. Hu, Y. Wei and Y. Kang, *Clin. Cancer Res.*, 2009, **15**, 5615–5620.
27 M. U. J. Oliphant, D. Kong, H. Zhou, M. T. Lewis and H. L. Ford, *J. Mammary Gland Biol. Neoplasia*, 2020, **25**, 85–102.
28 P. Li, Inhibiting breast cancer progression by targeting SND1 using a novel peptide identified from phage display, PhD thesis, The Hong Kong Polytechnic University, 2019.
29 J.-L. Wan, B. Wang, M.-L. Wu, J. Li, R.-M. Gong, L.-N. Song, H.-S. Zhang, G.-Q. Zhu, S.-P. Chen, J.-L. Cai, X.-X. Xing, Y.-D. Wang, Y. Yang, C.-Z. Cai, R. Huang, H. Liu and Z. Dai, *Cancer Lett.*, 2022, **541**, 215750.
30 N. Jariwala, *SND1 Mediated Downregulation of PTPN23 in Hepatocellular Carcinoma*, Virginia Commonwealth University, 2014.
31 N. Wang, X. Du, L. Zang, N. Song, T. Yang, R. Dong, T. Wu, X. He and J. Lu, *Mol. Biol. Rep.*, 2012, **39**, 10497–10504.
32 H. Zhang, M. Gao, W. Zhao and L. Yu, *Breast Cancer Res.*, 2023, **25**, 129.
33 L. Hu, Y. Zeng, L. Xin and J. Yang, *FEBS J.*, 2023, **290**, 5759–5772.
34 L. Niu, W. Yang, L. Duan, X. Wang, Y. Li, C. Xu, C. Liu, Y. Zhang, W. Zhou, J. Liu, Q. Zhao, L. Hong and D. Fan, *Mol. Ther. Nucleic Acids*, 2021, **23**, 42–54.
35 N. Al-Zeheimi and S. A. Adham, in *Latest Research on Breast Cancer*, ed. A. C. Monteiro and L. Wang, IntechOpen, Rijeka, 2024, DOI: 10.5772/intechopen.1007394.
36 X. Liu, Y. Zhang, X. Wu, F. Xu, H. Ma, M. Wu and Y. Xia, *Front. Pharmacol*, 2022, **13**, DOI: 10.3389/fphar.2022.963054.
37 F. Rahdan, A. Saberi, N. Saraygord-Afshari, M. Hadizadeh, T. Fayeghi, E. Ghanbari, H. Dianat-Moghadam and E. Alizadeh, *Heliyon*, 2024, **10**(20), e39489.
38 B. Ochoa, Y. Chico and M. J. Martínez, *Front. Oncol.*, 2018, **8**, DOI: 10.3389/fonc.2018.00606.
39 K. Huang, L. Yu, D. Lu, Z. Zhu, M. Shu and Z. Ma, *Front. Oncol.*, 2024, **14**, 1437698.
40 A. Sultan, N.-E. Sahar, S. K. Riaz, J. Qadir, S. H. Waqar, F. Haq, T. Khaliq and M. F. A. Malik, *Mol. Biol. Rep.*, 2021, **48**, 7999–8007.
41 P.-Y. Chu, S.-M. Wang, P.-M. Chen, F.-Y. Tang and E.-P. I. Chiang, *J. Clin. Med.*, 2020, **9**, 3153.
42 H. Navarro-Imaz, B. Ochoa, I. García-Arcos, M. J. Martínez, Y. Chico, O. Fresnedo and Y. Rueda, *Biochim. Biophys. Acta*, 2020, **1865**, 158589.
43 X. Cui, X. Zhang, M. Liu, C. Zhao, N. Zhang, Y. Ren, C. Su, W. Zhang, X. Sun, J. He, X. Gao and J. Yang, *Genomics*, 2020, **112**, 3958–3967.
44 S. Ganskih, 2023.
45 L. Hu, Y. Zeng, L. Xin and J. Yang, *FEBS J.*, 2023, **290**, 5759–5772.
46 A. He, S. He, C. Huang, Z. Chen, Y. Wu, Y. Gong, X. Li and L. Zhou, *Aging*, 2020, **12**, 1465–1487.
47 P. Li, Y. He, T. Chen, K. Y. Choy, T. S. Chow, I. L. K. Wong, X. Yang, W. Sun, X. Su, T. H. Chan and L. M. C. Chow, *Mol. Cancer Ther.*, 2021, **20**, 76–84.
48 D. Wu, C. Huang and K. Guan, *Biochem. Pharmacol.*, 2024, **226**, 116406.
49 S. Twafra, C. G. Sokolik, T. Sneh, K. D. Srikanth, T. Meirson, A. Genna, J. H. Chill and H. Gil-Henn, *Oncogene*, 2023, **42**, 278–292.
50 Y. Wang, F. Ye, Y. Liang and Q. Yang, *Br. J. Cancer*, 2021, **125**, 1056–1067.
51 S. Monteleone, D. G. Fedorov, A. Townsend-Nicholson, M. Southey, M. Bodkin and A. Heifetz, *J. Chem. Inf. Model.*, 2022, **62**, 3784–3799.
52 S. Liu, X. Hao, D. Miao and Y. Zhang, *J. Phys. Chem. B*, 2024, **128**, 9074–9085.
53 Y. Xu, X. Guo, D. Yan, X. Dang, L. Guo, T. Jia and Q. Wang, *J. Chem. Inf. Model.*, 2023, **63**, 3614–3627.
54 K. Vrbnjak and R. N. Sewduth, *Pharmaceutics*, 2024, **16**, 1486.
55 P. Li, Y. He, T. Chen, K.-Y. Choy, T. S. Chow, I. L. K. Wong, X. Yang, W. Sun, X. Su, T.-H. Chan and L. M. C. Chow, *Mol. Cancer Ther.*, 2021, **20**, 76–84.
56 J. K. Morrow and S. Zhang, *Curr. Pharm. Des.*, 2012, **18**, 1255–1265.
57 M. Leander, Z. Liu, Q. Cui and S. Raman, *eLife*, 2022, **11**, e79932.
58 A. M. B. Amorim, L. F. Piochi, A. T. Gaspar, A. J. Preto, N. Rosário-Ferreira and I. S. Moreira, *Chem. Res. Toxicol.*, 2024, **37**, 827–849.
59 L. Hartl, M. A. Fink and S. Beer-Hammer, *Principles of Biomedical Sciences and Industry: Translating Ideas into Treatments*, 2022, pp. 7–35.
60 H. Wang, R. S. Dawber, P. Zhang, M. Walko, A. J. Wilson and X. Wang, *Chem. Sci.*, 2021, **12**, 5977–5993.
61 A. U. Rehman, B. Khurshid, Y. Ali, S. Rasheed, A. Wadood, H. L. Ng, H. F. Chen, Z. Wei, R. Luo and J. Zhang, *Expet Opin. Drug Discov.*, 2023, **18**, 315–333.
62 W. Cabri, P. Cantelmi, D. Corbisiero, T. Fantoni, L. Ferrazzano, G. Martelli, A. Mattellone and A. Tolomelli, *Front. Mol. Biosci.*, 2021, **8**, 697586.
63 Y. Chen, H. Zhu, Y. Luo, S. Tong and Y. Liu, *Biomed. Pharmacother.*, 2024, **175**, 116624.
64 C. H. M. Rodrigues, D. E. V. Pires, T. L. Blundell and D. B. Ascher, *Briefings Bioinf.*, 2022, **23**, bbac165.
65 A. L. Afonso, C. T. Cavaleiro, M. A. R. B. Castanho, V. Neves and M. Cavaco, *Int. J. Mol. Sci.*, 2025, **26**, 3117.
66 X. Wang, D. Ni, Y. Liu and S. Lu, *Front. Chem.*, 2021, **9**, 682675.
67 L. Wang, N. Wang, W. Zhang, X. Cheng, Z. Yan, G. Shao, X. Wang, R. Wang and C. Fu, *Signal Transduct. Targeted Ther.*, 2022, **7**, 48.
68 O. Al Musaimi, L. Lombardi, D. R. Williams and F. Albericio, *Pharmaceuticals*, 2022, **15**, 1283.
69 J. Wu, Y. Jiang, Q. Zhang, X. Mao, T. Wu, M. Hao, S. Zhang, Y. Meng, X. Wan, L. Qiu and J. Han, *Nucleic Acids Res.*, 2024, **52**, 7665–7686.
70 P. Pang, L. Senchen, H. Xiafei, T. Yuxin, G. Shuyue, M. Dongqiang and Y. Zhang, *J. Biomol. Struct. Dyn.*, 2024, **42**, 5536–5550.
71 N. Makki Almansour, *Saudi Pharm. J.*, 2023, **31**, 101751.

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72 S. Khemaissa, S. Sagan and A. Walrant, *Crystals*, 2021, **11**, 1032.
73 W. Zhou, B. You, X. Zhao, S. Si, Y. Li and J. Zhang, *SLAS Discov.*, 2024, **29**, 100153.
74 H. Qayoom and M. A. Mir, *Biomed. Pharmacother.*, 2024, **179**, 117351.
75 S. Guha, J. Ghimire, E. Wu and W. C. Wimley, *Chem. Rev.*, 2019, **119**, 6040–6085.
76 S. G. Patel, E. J. Sayers, L. He, R. Narayan, T. L. Williams, E. M. Mills, R. K. Allemann, L. Y. P. Luk, A. T. Jones and Y.-H. Tsai, *Sci. Rep.*, 2019, **9**, 6298.
77 L. Gentilucci, R. De Marco and L. Cerisoli, *Curr. Pharm. Des.*, 2010, **16**, 3185–3203.
78 J. Cheng, J. Zhou, L. Kong, H. Wang, Y. Zhang, X. Wang, G. Liu and Q. Chu, *RSC Med. Chem.*, 2023, **14**, 2496–2508.
79 A. Ray, S. Rana, D. Banerjee, A. Mitra, R. Datta, S. Naskar and S. Sarkar, *Toxicol. Appl. Pharmacol.*, 2016, **290**, 54–65.
80 D. Paris, K. Townsend, A. Quadros, J. Humphrey, J. Sun, S. Brem, M. Wotoczek-Obadia, A. DelleDonne, N. Patel, D. F. Obregon, R. Crescentini, L. Abdullah, D. Coppola, A. M. Rojiani, F. Crawford, S. M. Sebti and M. Mullan, *Angiogenesis*, 2004, **7**, 75–85.
81 T. Teesalu, K. N. Sugahara and E. Ruoslahti, *Front. Oncol.*, 2013, **3**, DOI: **10.3389/fonc.2013.00216**.
82 L. Diao and B. Meibohm, *Clin. Pharmacokinet.*, 2013, **52**, 855–868.
83 P. Tyagi, S. Pechenov and J. Anand Subramony, *J. Controlled Release*, 2018, **287**, 167–176.
84 Y. Han, Z. Gao, L. Chen, L. Kang, W. Huang, M. Jin, Q. Wang and Y. H. Bae, *Acta Pharm. Sin. B*, 2019, **9**, 902–922.
85 S.-j. Cao, S. Xu, H.-m. Wang, Y. Ling, J. Dong, R.-d. Xia and X.-h. Sun, *AAPS PharmSciTech*, 2019, **20**, 190.
86 A. Accardo, A. Luigi, A. Michela, M. Giancarlo and D. and Tesauro, *Int. J. Nanomed.*, 2014, **9**, 1537–1557.
87 J. M. Harris, N. E. Martin and M. Modi, *Clin. Pharmacokinet.*, 2001, **40**, 539–551.
88 H. Wu and J. Huang, *Protein Pept. Lett.*, 2018, **25**, 514–521.
89 F. M. Veronese and A. Mero, *BioDrugs*, 2008, **22**, 315–329.
90 V. Ejigah, O. Owoseni, P. Bataille-Backer, O. D. Ogundipe, F. A. Fisusi and S. K. Adesina, *Polymers*, 2022, **14**, 2601.
91 N. Matougui, L. Boge, A.-C. Groo, A. Umerska, L. Ringstad, H. Bysell and P. Saulnier, *Int. J. Pharm.*, 2016, **502**, 80–97.
92 M. F. Lee and C. L. Poh, *Pharm. Res.*, 2023, **40**, 617–632.
93 M. K. Riaz, M. A. Riaz, X. Zhang, C. Lin, K. H. Wong, X. Chen, G. Zhang, A. Lu and Z. Yang, *Int. J. Mol. Sci.*, 2018, **19**, 195.
94 D. Tsvetkova and S. Ivanova, *Molecules*, 2022, **27**, 2466.
95 S. A. Patel and A. J. Minn, *Immunity*, 2018, **48**, 417–433.
96 S. C. Wei, C. R. Duffy and J. P. Allison, *Cancer Discov.*, 2018, **8**, 1069–1086.
97 H. He, X. Shao, Y. Li, R. Gihu, H. Xie, J. Zhou and H. Yan, *Front. Pharmacol*, 2021, **12**, DOI: **10.3389/fphar.2021.675675**.
98 H. Y. K. Yip and A. Papa, *Cells*, 2021, **10**, 659.
99 A. Vinukonda, K. Rapolu, R. K. Jadi and V. R. Devadasu, *Int. J. Pept. Res. Ther.*, 2025, **31**, 51.
100 Z. Yang, H. Xu and X. Zhao, *Adv. Sci.*, 2020, **7**, 1903718.
101 H. Qin, Y. Ding, A. Mujeeb, Y. Zhao and G. Nie, *Mol. Pharmacol.*, 2017, **92**, 219–231.
102 C. Sohrabi, A. Foster and A. Tavassoli, *Nat. Rev. Chem.*, 2020, **4**, 90–101.
103 A. A. Vinogradov, Y. Yin and H. Suga, *J. Am. Chem. Soc.*, 2019, **141**, 4167–4181.
104 Y. Tasdemiroglu, R. G. Gourdie and J.-Q. He, *Eur. J. Pharmacol.*, 2022, **932**, 175192.
105 M. Bhattacharya, A. R. Sharma, P. Ghosh, P. Patra, B. Mallick, B. C. Patra, S.-S. Lee and C. Chakraborty, *Infect. Genet. Evol.*, 2022, **99**, 105245.
106 D. Liu, L. Liu, X. Li, S. Wang, G. Wu and X. Che, *Vaccines*, 2024, **12**, 950.
107 A. P. Davenport, C. C. G. Scully, C. de Graaf, A. J. H. Brown and J. J. Maguire, *Nat. Rev. Drug Discovery*, 2020, **19**, 389–413.
108 X. Sui, X. Niu, X. Zhou and Y. Gao, *Cancer Biol. Med.*, 2024, **21**, 198.
109 R. He, B. Finan, J. P. Mayer and R. D. DiMarchi, *Molecules*, 2019, **24**, 1855.
110 S. Lee, J. Xie and X. Chen, *Biochemistry*, 2010, **49**, 1364–1376.
111 X. Zhang, Y. Wu, J. Lin, S. Lu, X. Lu, A. Cheng, H. Chen, W. Zhang and X. Luan, *Acta Pharm. Sin. B*, 2024, **14**, 3818–3833.
112 N. K. Wolf, D. U. Kissiov and D. H. Raulet, *Nat. Rev. Immunol.*, 2023, **23**, 90–105.
113 B. Seliger, *Front. Immunol.*, 2019, **10**, DOI: **10.3389/fimmu.2019.02043**.
114 C. Lamers, *Future Drug Discov.*, 2022, **4**, FDD75.
115 D. S. Nielsen, N. E. Shepherd, W. Xu, A. J. Lucke, M. J. Stoermer and D. P. Fairlie, *Chem. Rev.*, 2017, **117**, 8094–8128.
116 P. Milla, F. Dosio and L. Cattel, *Curr. Drug Metab.*, 2012, **13**, 105–119.
117 B. Yang, G. D. S. Ana, P. Sanyogitta, B. Annette and L. and Zhou, *Expet Opin. Drug Deliv.*, 2022, **19**, 1233–1245.
118 M. Vanneman and G. Dranoff, *Nat. Rev. Cancer*, 2012, **12**, 237–251.
119 Y. Song, L. Lei, X. Cai, H. Wei and C.-Y. Yu, *Adv. Healthcare Mater.*, 2025, **14**, 2400512.
120 S. A. Moschos, *Bioanalysis*, 2012, **4**, 2499–2511.
121 E. M. Kamel, F. F. Aba Alkhayl, H. A. Alqhtani, M. Bin-Jumah and A. M. Lamsabhi, *Int. J. Biol. Macromol.*, 2024, **282**, 136982.
122 E. M. Kamel, S. I. Othman, F. F. Aba Alkhayl, H. A. Rudayni, A. A. Allam and A. M. Lamsabhi, *Int. J. Biol. Macromol.*, 2025, **302**, 140609.
123 M. Lorscheider, G. Alice, N. Jessica, V. Kadi-Liis, R. Joël and C. Chassaing, *Ther. Deliv.*, 2021, **12**, 55–76.
124 J. Li, Y. Bing, G. Shenghua, L. Xinyong and P. Zhan, *Expet Opin. Drug Discov.*, 2024, **19**, 1439–1456.
125 A. Kaushik, S. Parashar, R. K. Ambasta and P. Kumar, *Ageing Res. Rev.*, 2024, **96**, 102279.
126 N. Parrott, N. Manevski and A. Olivares-Morales, *Mol. Pharm.*, 2022, **19**, 3858–3868.
127 S. Reissmann, *J. Pept. Sci.*, 2014, **20**, 760–784.

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128 Y. Zhang, L. Jiang, S. Huang, C. Lian, H. Liang, Y. Xing, J. Liu, X. Tian, Z. Liu, R. Wang, Y. An, F. Lu, Y. Pan, W. Han, Z. Li and F. Yin, *Adv. Sci.*, 2024, **11**, 2307754.
129 O. Al Musaimi, L. Lombardi, D. R. Williams and F. Albericio, *Pharmaceuticals*, 2022, **15**, 1283.
130 J. Huang and K. Xiao, *Pharmaceutics*, 2022, **14**, 1586.
131 G. A. Guillén-Meléndez, R. A. Pérez-Hernández, A. Chávez-Montes, U. Castillo-Velázquez, M. de Jesús Loera-Arias, C. R. Montes-de-Oca-Saucedo, H. Rodríguez-Rocha, F. F. Contreras-Torres, O. Saucedo-Cárdenas and A. Soto-Domínguez, *Toxicon*, 2024, **244**, 107753.
132 R. Mahato, W. Tai and K. Cheng, *Adv. Drug Del. Rev.*, 2011, **63**, 659–670.
133 L. Yang, Y. Tian, W. S. Leong, H. Song, W. Yang, M. Wang, X. Wang, J. Kong, B. Shan and Z. Song, *Breast Cancer Res.*, 2018, **20**, 113.
134 H. He, L. Sun, J. Ye, E. Liu, S. Chen, Q. Liang, M. C. Shin and V. C. Yang, *J. Controlled Release*, 2016, **240**, 67–76.
135 M. T. Manzari, Y. Shamay, H. Kiguchi, N. Rosen, M. Scaltriti and D. A. Heller, *Nat. Rev. Mater.*, 2021, **6**, 351–370.
136 Q. Hu, W. Sun, C. Wang and Z. Gu, *Adv. Drug Del. Rev.*, 2016, **98**, 19–34.
137 Q. Jiang and K. Ganesh, *Nat. Cancer*, 2022, **3**, 6–8.
138 B. Cheng, X. Fei, Z. Ding, X. Peng, Z. Su, W. Pan and J. Chen, *J. Med. Chem.*, 2024, **67**, 6906–6921.
139 A. Vikal, R. Maurya, B. B. Patel, R. Sharma, P. Patel, U. K. Patil and B. Das Kurmi, *Drug Deliv. Transl. Res.*, 2025, **15**, 1801–1827.
140 K. Desale, K. Kuche and S. Jain, *Biomater. Sci.*, 2021, **9**, 1153–1188.
141 L. Liu, L. Yu, Y. Wang, L. Zhou, Y. Liu, X. Pan and J. Huang, *Pharmacol. Res.*, 2024, **207**, 107305.
142 P. O. Adero, H. Amarasekara, P. Wen, L. Bohé and D. Crich, *Chem. Rev.*, 2018, **118**, 8242–8284.
143 D. Lin, L. Shen, M. Luo, K. Zhang, J. Li, Q. Yang, F. Zhu, D. Zhou, S. Zheng, Y. Chen and J. Zhou, *Signal Transduct. Targeted Ther.*, 2021, **6**, 404.
144 H. Chen, J. Liu, H. Ü. Kaniskan, W. Wei and J. Jin, *J. Med. Chem.*, 2021, **64**, 12273–12285.
145 Y. Zhao, Y.-Y. Guan, F. Zhao, T. Yu, S.-J. Zhang, Y.-Z. Zhang, Y.-C. Duan and X.-L. Zhou, *Eur. J. Med. Chem.*, 2022, **231**, 114144.
146 Y. Cen, L. Chen, Z. Liu, Q. Lin, X. Fang, H. Yao and C. Gong, *Cell Death Discov.*, 2023, **9**, 52.
147 L. Yang, M. Han, X. Zhao, L. Zheng, F. Kong, S. Zhang, L. Jia, X. Li and M. Wang, *Oncol. Lett.*, 2024, **28**, 349.
148 Y. He, M. M. Sun, G. G. Zhang, J. Yang, K. S. Chen, W. W. Xu and B. Li, *Signal Transduct. Targeted Ther.*, 2021, **6**, 425.
149 N. D. Germain, W. K. Chung and P. D. Sarmiere, *Mol. Aspects Med.*, 2023, **91**, 101148.
150 M. Esposito, S. Ganesan and Y. Kang, *Nat. Cancer*, 2021, **2**, 258–270.
151 H. Guo, X. Xu, J. Zhang, Y. Du, X. Yang, Z. He, L. Zhao, T. Liang and L. Guo, *Pharmaceuticals*, 2024, **17**, 1048.
152 R. A. Ward, S. Fawell, N. Floc'h, V. Flemington, D. McKerrecher and P. D. Smith, *Chem. Rev.*, 2021, **121**, 3297–3351.

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