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Research Progress on Antitumor Drugs Targeting BRD4

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Abstract: Bromodomain and extra-terminal structures (BET) family proteins serve as critical epigenetic "readers," among which BRD4 can recognize and bind acetylated histones, recruit transcription elongation-related complexes, and maintain high-level expression of various proto-oncogenes and superenhancer-associated genes, playing a pivotal role in the development of malignant tumors. In recent years, small-molecule inhibitors and protein degraders (PROTACs) targeting BRD4 have advanced rapidly, evolving from early dual-bromodomain (BD1/BD2) pan-BET inhibitors to BD1/BD2 selective inhibitors, BRD4 selective degraders, antibody-PROTAC conjugates, and BRD4-related dual-target drugs, demonstrating promising antitumor potential. However, limitations such as limited monotherapy efficacy, dose-limiting toxicity, and acquired resistance continue to constrain their clinical translation. This article systematically reviews the tumor biology functions of BRD4 and the theoretical foundations of its drug targeting, focusing on representative compounds of BRD4-targeting inhibitors and degraders, their antitumor mechanisms, and preclinical/clinical research progress. It also discusses novel strategies including BD2 selective inhibition, dual-target inhibition, antibody-PROTAC conjugation, and nanodelivery systems, as well as resistance mechanisms and combination therapy approaches, aiming to provide insights for further optimization of BRD4-targeted epigenetic therapies.

Keywords: BRD4; BET inhibitor; PROTAC; Protein degradation; Epigenetic therapy

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1. Overview of the relationship between BRD4 and tumor development

BRD4 is the most extensively studied member of the bromodomain and extra-terminal structures (BET) family. It stabilizes and anchors to chromatin by binding to acetylated histone tails such as H3 and H4 through its two tandem bromodomain structures (BD1 and BD2), particularly accumulating in superenhancer regions. This mechanism drives robust transcriptional activity associated with cell fate and proto-oncogenes [1]. The C-terminal extracellular domain (ET domain) of BRD4 interacts with various transcriptional and chromatin regulatory factors. Its C-terminal motif can also recruit the PTEFb complex, facilitating the resolution of promoter-proximal pauses in RNA polymerase II and maintaining the sustained expression of cell cycle-related genes and anti-apoptotic genes [2,3].

In various solid tumors and hematologic malignancies, overexpression or abnormal activity of BRD4 is closely associated with high expression of key oncogenes such as *MYC*, *BCL2*, and *CDK4/6* [4]. Meanwhile, BRD4 can promote tumor cell immune evasion and sustained proliferation through multiple mechanisms, including upregulation of PDL1,

modulation of inflammatory factors, and maintenance of telomere stability [5]. Based on these functions, BRD4 is considered a key node linking epigenetic abnormalities with oncogenic transcriptional programs. Targeting BRD4 holds promise for indirectly "pharmacologizing" transcription factors such as MYC that are difficult to directly inhibit [6].

2. Research progress on BRD4 targeted inhibitors

2.1. Early pan-BET inhibitors and the classic probe JQ1

The first batch of BET small molecule inhibitors was predominantly BD1/BD2 double-bromine domain pan-BET inhibitors, with representative examples including (+)-JQ1 and IBET series [7]. These compounds mimic acetylated lysine by entering the hydrophobic pocket of the bromine domain, competitively binding to the BD1/BD2 regions of BET proteins such as BRD4 with high affinity. This binding blocks BRD4's recognition of acetylated histones, leading to dissociation of BRD4 from superenhancers and promoter regions. Consequently, this triggers rapid transcriptional downregulation of oncogenes including *MYC*, subsequently inducing cell cycle arrest and apoptosis in various tumor cell lines [8]. However, early probes such as JQ1 were primarily used for mechanistic studies and lacked pharmacokinetic and toxicological properties suitable for clinical applications [9,10].

2.2. Clinical candidate pan-BET inhibitors

Building upon the molecular basis of JQ1, multiple pharmaceutical companies have developed pan-BET inhibitors with oral availability and clinical development potential, including OTX015 (MK8628), GSK525762, CPI0610 (pelabresib), and ABBV075 [11]. These compounds exhibited broad-spectrum antiproliferative activity against various hematologic malignancies and solid tumor cells *in vitro*, primarily through downregulation of *MYC* and its downstream driver genes, as well as induction of apoptosis or differentiation [12,13].

Early clinical trials demonstrated that BET inhibitors could achieve partial response or disease stabilization in a small subset of patients with acute leukemia and NUT cancers, but the overall objective response rate with monotherapy was limited. Dose-limiting toxicities primarily included thrombocytopenia and gastrointestinal adverse reactions [14]. These phenomena suggest that BET inhibitors possess genuine antitumor activity on one hand, while on the other hand, pan-BET inhibition and complete occupancy of the double bromide domain may lead to "epigenetic destabilization," thereby limiting tolerable doses and therapeutic windows [15].

2.3. High-efficiency novel BRD4 inhibitor NHWD870

NHWD870 is a novel-generation BET inhibitor with a structurally innovative design and enhanced selectivity for BRD4. It demonstrates superior *in vitro* inhibitory activity and superior *in vivo* antitumor efficacy compared to multiple investigational BET inhibitors (BMS986158, OTX015, GSK525762) [16]. In nine xenograft or orthotopic tumor models, NHWD870 significantly inhibited tumor growth and even induced tumor shrinkage [16].

In addition to directly inhibiting tumor cell proliferation by suppressing the BRD4MYC axis, NHWD870 can also downregulate the expression of CSF1 and HIF1α in tumor cells, thereby inhibiting tumor-associated macrophage proliferation and infiltration, exerting anti-tumor effects from both dimensions of the "tumor immune microenvironment" [16,17]. This finding suggests that BRD4-targeted inhibitors are not merely "tumor cytotoxic agents," but also epigenetic regulators capable of reshaping the tumor immune microenvironment, providing critical evidence for their combination with immune checkpoint inhibitors [16,17].

2.4. Selective inhibitors of BD1/BD2

The two bromine domains of BET proteins do not share identical functions in maintaining homeostatic transcription and inducing stress responses. The BD1/BD2 selective inhibitors obtained through structural optimization revealed that steady-state gene expression primarily relies on BD1, while inflammation-stimulated transcription requires coordinated action of

BD1 and BD2 [18].

Represented by the high-selectivity BD2 inhibitor ABBV744, it demonstrates potent antiproliferative activity in androgen receptor (AR)-positive prostate cancer and certain acute myeloid leukemia models, while maintaining strong inhibition of AR-dependent superenhancers *in vivo*. Compared to the pan-BET inhibitor ABBV075, it exhibits milder global transcriptional effects and is associated with reduced platelet and gastrointestinal toxicity [19]. This indicates that selective inhibition of BRD4/BET's BD2 domain can reduce systemic toxicity while preserving key oncogenic program suppression, potentially improving the therapeutic index [20]. In addition, the new-generation selective BET inhibitor NUV868 has demonstrated significant antitumor activity in various xenograft models of prostate cancer and pancreatic cancer, further supporting the feasibility of the BD2-targeting strategy [21].

3. Development of E3 BRD4-targeted protein degraders (PROTACs)

3.1. Theoretical advantages of PROTAC degradation of BRD4

Traditional BET inhibitors inhibit BRD4 chromatin binding solely by occupying the bromodomain, whereas PROTAC technology employs a bifunctional molecule consisting of "target protein ligand and E3 ligase ligand" to recruit BRD4 to the ubiquitin-proteasome system, inducing covalent ubiquitination and complete degradation, thereby achieving "catalytic clearance" of the full-length BRD4 protein and all its functional structural domains. Compared to inhibitors, BRD4 PROTACs exhibit the following advantages: (1) sustained degradation at low doses (event-driven rather than occupancy-driven); (2) avoidance of the common "compensatory upregulation of target proteins" observed with inhibitors [22]; (3) potential superiority over BRD4 variants with drug-resistant mutations or aberrant post-translational modifications [23].

3.2. Early BET PROTAC: MZ1 and its BRD4 selectivity

Zengerle *et al.* utilized JQ1 as a BRD4 ligand and connected it to VHL ligands to design a series of BET PROTACs. Among these, MZ1 rapidly and persistently induced BET protein degradation while demonstrating unexpected selectivity for BRD4 over BRD2/3 [24]. MZ1 can achieve significant BRD4 degradation in tumor cells at nanomolar concentrations and induce more localized transcriptional profile alterations compared to JQ1, suggesting that selective BRD4 degradation can preserve critical oncogenic pathway inhibition while reducing off-target effects. The structure of its ternary complex and the synergistic selection mechanism have been further elucidated in subsequent studies [25].

3.3. Preclinical representative drugs such as ARV825 and ARV771

ARV825, using JQ1 as the BRD4 ligand and conjugated with CRBN ligand, achieved >90% BRD4 degradation in models such as acute myeloid leukemia (AML), inducing deeper apoptosis and downregulation of proteins including MYC, CDK4/6, JAK2, and BCLXL compared to OTX015 at the same dose. It also demonstrated more significant improvements in leukemia burden and mouse survival [26].

ARV771, a BET PROTAC based on VHL ligand, demonstrates dual inhibition of AR signaling and AR levels in castration-resistant prostate cancer. It induces tumor regression in mouse xenograft models and significantly reduces BRD4 and cMYC levels [25]. This study provides the first evidence of the significant efficacy of small-molecule BET degraders in solid tumors, offering critical support for the widespread application of BRD4 PROTACs.

3.4. Ultra-efficient BET degrader QCA570

QCA570 is a PROTAC further constructed based on a novel oxazepine BET inhibitor [1,4], which efficiently degrades BRD2/3/4 at low picomolar concentrations and exhibits potent inhibition of acute leukemia cell proliferation. In the RS4;11 leukemia xenograft model, low-dose QCA570 significantly clears BRD4 and downregulates MYC *in vivo*, induces PARP cleavage and tumor cell apoptosis, ultimately achieving complete and durable tumor regression [27]. These results demonstrate that optimizing linker length, conformation, and E3 ligand selection can significantly enhance BRD4

degradation efficiency and *in vivo* antitumor efficacy, providing a feasible pathway for future drug development of BRD4 PROTACs.

3.5. Tumor/organization-specific BRD4 degradation strategy

To address the issue of insufficient tissue selectivity in PROTACs, the concept of "antibody PROTAC conjugates (AbPROTAC)" has been proposed in recent years. Using trastuzumab, an HER2 antibody, as the carrier, BRD4 PROTAC is conjugated via a cleavable linker to form HER2-dependent endocytosis-mediated AbPROTAC. This enables selective degradation of BRD4 in HER2-positive breast cancer cells while having minimal impact on HER2-negative cells [28].

Similarly, a DAC (degraderant antibody conjugate) targeting ROR1 was constructed for tumor-specific BRD4 degradation, demonstrating improved pharmacokinetic and *in vivo* antitumor activity, with further enhanced immune infiltration and antitumor effects when combined with PD1 inhibitors [29]. These studies provide novel insights for improving BRD4 PROTAC tumor targeting and expanding the therapeutic window.

4. Combination therapy of BRD4 targeting drugs and drug resistance mechanisms

4.1. Combined with chemotherapy and radiotherapy

BRD4 is involved in DNA damage repair and cell cycle regulation. Its inhibition or degradation can impair tumor cells' tolerance to DNA damage [30]. Prostate cancer studies have demonstrated that PLK1-mediated BRD4 phosphorylation and mitotic degradation can reshape BRD4 stability, thereby enhancing sensitivity to BET inhibitors. Sequential administration of docetaxel and JQ1 significantly inhibits tumor growth and overcomes BETi resistance associated with BRD4 accumulation [31].

In models such as secondary AML, the combination of ARV825 with JAK inhibitor ruxolitinib can produce synergistic lethal effects in drug-resistant or persistently residual cells, suggesting that the combination of BRD4 PROTAC with chemotherapy/targeted therapies holds promise for overcoming multidrug resistance phenotypes.

4.2. Combination with targeted therapy and immunotherapy

BET inhibitors exhibit preclinical synergy with multiple targeted agents, such as when combined with CDK4/6 inhibitors, PARP inhibitors, and BCL2 inhibitors, which can produce more profound lethal effects in models of breast cancer and leukemia. For example, BET inhibitors can reverse the resistance of ER+ breast cancer to CDK4/6 inhibitors and exhibit synergistic effects [32].

In immunotherapy, BRD4 upregulates PDL1 and promotes tumor immunosuppression, while BET inhibition or degradation can reduce PDL1 expression, suppress tumor-associated macrophages, and improve the immune microenvironment [17]. The combination of AbPROTAC and DAC with PD-1 inhibitors not only enhances tumor killing but also significantly increases the infiltration of Th1-type cytokines and effector T cells.

4.3. Drug resistance mechanisms and countermeasures

Clinical and preclinical observations have revealed that long-term BET inhibition induces enhanced transcriptional plasticity in tumor cells, leading to drug resistance through mechanisms such as enhancer reprogramming [33], bypass signal activation (e.g., WNT, MAPK) [34], and alterations in BRD4 stability (e.g., upregulation of deubiquitinating enzyme activity) [35].

Multiple post-translational modifications (PTMs) of BRD4 play a critical role in drug resistance: ubiquitination regulates BRD4 stability, while excessive deubiquitination or loss due to mutations in E3 ligases (e.g., SPOP) can lead to BRD4 accumulation, thereby inducing endogenous drug resistance [36]; phosphorylation affects BRD4 chromatin binding and cofactor interactions, such as matrix-induced Tyr97/98 phosphorylation, which enhances its chromatin binding and reduces BETi sensitivity [37].

5. New-generation BRD4 targeting strategy: Selectivity, dual-targeting, and delivery optimization

5.1. BRD4/BD2 selectivity and dual-target inhibition

Selective inhibition of BRD4 or inhibitors biased toward BD2 demonstrates advantages in reducing interference with homeostatic transcription in normal cells and toxicity. Furthermore, dual-target inhibitors combining BRD4 inhibition with other targets can leverage synthetic lethality and pathway intersection to achieve synergistic effects within a single molecule [38].

5.2. Novel delivery mode based on PROTAC

In addition to antibody PROTAC conjugates and ROR1 DAC, encapsulating BRD4 PROTAC into PLGAPEG nanoparticles can significantly improve its solubility and pharmacokinetic properties, effectively inhibiting MYC expression and tumor growth in two-dimensional and three-dimensional pancreatic cancer models. This “nano-PROTAC” approach provides a novel engineering strategy to address the drug delivery bottleneck associated with macromolecular, lipophilic PROTACs [39].

6. Conclusion and outlook

As a core member of the BET family, BRD4 plays a critical driving role in various malignant tumors by recognizing acetylated histones and activating oncogenic transcriptional networks. Drug development targeting BRD4 has established a multi-tiered pipeline encompassing pan-BET inhibitors, selective BD1/BD2 inhibitors, potent BRD4 inhibitors, PROTAC degraders, antibody-PROTAC conjugates, and nanodrug delivery systems, all of which have demonstrated significant antitumor activity in both hematologic and solid tumor models.

However, limited monotherapy efficacy, dose-limiting bone marrow and gastrointestinal toxicity, and acquired resistance remain major obstacles to the widespread clinical application of BRD4-targeted therapies. Future research should focus on the following aspects: detailed characterization of BRD4-dependent patterns and PTM regulatory networks across different tumor subtypes, identification of reliable predictive and monitoring biomarkers; further optimization of the selectivity and pharmacokinetic properties of BD2 selective inhibitors and BRD4 PROTACs, development of tumor tissue-specific delivery strategies; systematic evaluation of optimal combination regimens combining BRD4-targeted agents with chemotherapy, PARP inhibitors, CDK inhibitors, and immune checkpoint inhibitors; exploration of “second-layer” targeting strategies targeting BRD4 PTM-related enzymes and resistance pathways to delay or reverse drug resistance.

With the advancements in structural biology, chemical biology, and tumor epigenetics, BRD4-targeted drugs are poised to transition from proof-of-concept studies to more precise, safer, and personalized therapeutic strategies, emerging as a critical component of epigenetic anti-tumor therapy.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Qian H, Zhu M, Tan X, et al., 2023, Super-Enhancers and the Super-Enhancer Reader BRD4: Tumorigenic Factors and Therapeutic Targets. Cell Death Discovery, 9(1): 470.

[2] Wang N, Wu R, Tang D, et al., 2021, The BET Family in Immunity and Disease. Signal Transduction and Targeted

Therapy, 6(1): 23.

[3] Zheng B, Gold S, Iwanaszko M, et al., 2023, Distinct Layers of BRD4-PTEFb Reveal Bromodomain-Independent Function in Transcriptional Regulation. Molecular Cell, 83(16): 2896–2910.e4.

[4] Muhar M, Ebert A, Neumann T, et al., 2018, SLAM-seq Defines Direct Gene-Regulatory Functions of the BRD4-MYC Axis. Science, 360(6390): 800–805.

[5] Wang J, Xu Y, Rao X, et al., 2022, BRD4-IRF1 Axis Regulates Chemoradiotherapy-Induced PD-L1 Expression and Immune Evasion in Non-Small Cell Lung Cancer. Clinical and Translational Medicine, 12(1): e718.

[6] Delmore JE, Issa GC, Lemieux ME, et al., 2011, BET Bromodomain Inhibition as a Therapeutic Strategy to Target c-Myc. Cell, 146(6): 904–917.

[7] Filippakopoulos P, Qi J, Picaud S, et al., 2010, Selective Inhibition of BET Bromodomains. Nature, 468(7327): 1067–1073.

[8] Mertz JA, Conery AR, Bryant BM, et al., 2011, Targeting MYC Dependence in Cancer by Inhibiting BET Bromodomains. Proceedings of the National Academy of Sciences, 108(40): 16669–16674.

[9] Zuber J, Shi J, Wang E, et al., 2011, RNAi Screening Identifies Brd4 as a Therapeutic Target in Acute Myeloid Leukemia. Nature, 478(7370): 524–528.

[10] Lee DU, Katavolos P, Palanisamy G, et al., 2016, Nonselective Inhibition of the Epigenetic Transcriptional Regulator BET Induces Marked Lymphoid and Hematopoietic Toxicity in Mice. Toxicology and Applied Pharmacology, 300: 47–54.

[11] Riveiro ME, Astorgues-Xerri L, Vazquez R, et al., 2016, OTX015 (MK-8628), a Novel BET Inhibitor, Exhibits Antitumor Activity in Non-Small Cell and Small Cell Lung Cancer Models Harboring Different Oncogenic Mutations. Oncotarget, 7(51): 84675–84687.

[12] Boi M, Gaudio E, Bonetti P, et al., 2015, The BET Bromodomain Inhibitor OTX015 Affects Pathogenic Pathways in Preclinical B-cell Tumor Models and Synergizes with Targeted Drugs. Clinical Cancer Research, 21(7): 1628–1638.

[13] Ferraro E, Macri E, Zwergel C, et al., 2025, Inhibition of Bromodomain and Extra-Terminal Motif (BET) Proteins in Pediatric Sarcoma: A Systematic Review of *In Vitro* and *In Vivo* Studies. Drug Discovery Today, 30(12): 104516.

[14] Tang P, Zhang J, Liu J, et al., 2021, Targeting Bromodomain and Extraterminal Proteins for Drug Discovery: From Current Progress to Technological Development. Journal of Medicinal Chemistry, 64(5): 2419–2435.

[15] To KKW, Xing E, Larue RC, et al., 2023, BET Bromodomain Inhibitors: Novel Design Strategies and Therapeutic Applications. Molecules, 28(7): 3043.

[16] Yin M, Guo Y, Hu R, et al., 2020, A Potent BRD4 Inhibitor Suppresses Cancer Cell-Macrophage Interaction. Nature Communications, 11(1): 1833.

[17] Liao M, Long K, Dong L, et al., 2025, Targeting CLEC4E in Immunosuppressive Tumor-Associated Macrophages via BET Inhibition. Clinical and Translational Medicine, 15(10): e70505.

[18] Gilan O, Rioja I, Knezevic K, et al., 2020, Selective Targeting of BET Proteins' BD1 and BD2 in Cancer and Immunoinflammation. Science, 368(6489): 387–394.

[19] Zhang L, Cai T, Lin X, et al., 2021, Selective Inhibition of the Second Bromodomain of BET Family Proteins Results in Robust Antitumor Activity in Preclinical Models of Acute Myeloid Leukemia. Molecular Cancer Therapeutics, 20(10): 1809–1819.

[20] Kati W, 2018, Abstract DDT01-05: ABBV-744: A First-in-Class Highly BDII-Selective BET Bromodomain Inhibitor. Cancer Research, 78(13_Supplement): DDT01–05.

[21] Patel H, Hertzog J, Heller L, et al., 2023, Abstract 6264: NUV-868, a Novel BD2-Selective BET Inhibitor, in Combination with Enzalutamide or Olaparib, Inhibits the Growth of Solid Tumor Xenografts. Cancer Research, 83(7_Supplement): 6264.

[22] Lu J, Qian Y, Altieri M, et al., 2015, Hijacking the E3 Ubiquitin Ligase Cereblon to Efficiently Target BRD4. Chemistry & Biology, 22(6): 755–763.

[23] Nowak RP, DeAngelo SL, Buckley D, et al., 2018, Plasticity in Binding Confers Selectivity in Ligand-Induced Protein Degradation. Nature Chemical Biology, 14(7): 706–714.

[24] Zengerle M, Chan KH, Ciulli A, 2015, Selective Small Molecule Induced Degradation of the BET Bromodomain Protein BRD4. ACS Chemical Biology, 10(8): 1770–1777.

[25] Gadd MS, Testa A, Lucas X, et al., 2017, Structural Basis of PROTAC Cooperative Recognition for Selective Protein Degradation. Nature Chemical Biology, 13(5): 514–521.

[26] Saenz DT, Fiskus W, Qian Y, et al., 2017, Novel BET Protein Proteolysis-Targeting Chimera Exhibits Superior Lethal Activity Compared to Bromodomain Inhibitor (BETi) against Post-Myeloproliferative Neoplasms Secondary (s) AML cells. Leukemia, 31(9): 1951–1961.

[27] Qin C, Hu Y, Zhou B, et al., 2018, Discovery of QCA570 as an Exceptionally Potent and Efficacious Proteolysis Targeting Chimera (PROTAC) Degrader of Bromodomain and Extra-Terminal (BET) Proteins Capable of Inducing Complete and Durable Tumor Regression. Journal of Medicinal Chemistry, 61(15): 6685–6704.

[28] Maneiro M, Forte N, Shchepinova MM, et al., 2020, Antibody–PROTAC Conjugates Enable HER2-Dependent Targeted Protein Degradation of BRD4. ACS Chemical Biology, 15(6): 1306–1312.

[29] Wang L, Ke Y, He Q, et al., 2025, A Novel ROR1-Targeting Antibody-PROTAC Conjugate Promotes BRD4 Degradation for Solid Tumor Treatment. Theranostics, 15(4): 1238–1254.

[30] Donati B, Lorenzini E, Ciarrocchi A, 2018, BRD4 and Cancer: Going Beyond Transcriptional Regulation. Molecular Cancer, 17(1): 164.

[31] Zhang Y, Fong KW, Mao F, et al., 2024, Upregulation of PLK1 Overcomes BETi Resistance in Prostate Cancer by Triggering BRD4 Phosphorylation-Dependent Degradation During Mitosis. Cell Reports, 43(7): 114431.

[32] Liu R, Wang X, Branigan TB, et al., 2025, BET Bromodomain Inhibition Reverses CDK4/6 Inhibitor Resistance in Estrogen Receptor–Positive Breast Cancer via Induction of miR-34a-5p. Clinical Cancer Research, 31(23): 5096–5110.

[33] Pawar A, Gollavilli PN, Wang S, et al., 2018, Resistance to BET Inhibitors Leads to Alternative Therapeutic Vulnerabilities in Castration-Resistant Prostate Cancer. Cell Reports, 22(9): 2236–2245.

[34] Marr AR, Halpin M, Corbin DL, et al., 2024, The Multi-CDK Inhibitor Dinaciclib Reverses Resistance to Bromo-and Extra-Terminal Domain (BET) Inhibitors in Acute Myeloid Leukemia by Inhibiting Wnt/β-catenin Signaling. Experimental Hematology & Oncology, 13(1): 27.

[35] Jin X, Yan Y, Wang D, et al., 2018, DUB3 Promotes BET Inhibitor Resistance and Cancer Progression by Deubiquitinating BRD4. Molecular Cell, 71(4): 592–605.e4.

[36] Zhang P, Wang D, Zhao Y, et al., 2017, Intrinsic BET Inhibitor Resistance in SPOP-Mutated Prostate Cancer is Mediated by BET Protein Stabilization and AKT–mTORC1 Activation. Nature Medicine, 23(9): 1055–1062.

[37] Wang W, Tang YA, Xiao Q, et al., 2021, Stromal Induction of BRD4 Phosphorylation Results in Chromatin Remodeling and BET Inhibitor Resistance in Colorectal Cancer. Nature Communications, 12(1): 4441.

[38] Wang C, Zhang Y, Chen W, et al., 2024, Next-Generation Advanced PROTACs as Potential Therapeutic Agents in Cancer Therapy. Molecular Cancer, 23(1): 110.

[39] Minko T, 2020, Nanoformulation of BRD4-Degrading PROTAC: Improving Druggability To Target the 'Undruggable' MYC in Pancreatic Cancer. Trends in Pharmacological Sciences, 41(10): 684–686.