Bromodomain and extra-terminal inhibitors emerge as potential therapeutic avenues for gastrointestinal cancers

Hui-Yan Sun, Song-Tao Du, Ya-Yun Li, Guang-Tong Deng, Fu-Rong Zeng

ORCID number: Hui-Yan Sun 0000-0002-5697-933X; Song-Tao Du 0000-0001-5536-3632; Ya-Yun Li 0000-0002-4799-663X; Guang-Tong Deng 0000-0002-4424-9727; Fu-Rong Zeng 0000-0001-6621-8131.

Author contributions: Zeng FR, Deng GT and Sun HY designed the study; Sun HY and Deng GT wrote the manuscript; Du ST, Li YY helped to revise the manuscript; all the authors supported the study.

Conflict-of-interest statement: No conflict of interest.

Supported by: Fellowship of the China Postdoctoral Science Foundation, No. 2020M682594, and No. 2021T140748.

Country/Territory of origin: China

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an

Hui-Yan Sun, Song-Tao Du, Ya-Yun Li, Guang-Tong Deng, Fu-Rong Zeng, Department of Dermatology, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Hui-Yan Sun, Fu-Rong Zeng, Department of Oncology, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Hui-Yan Sun, Song-Tao Du, Ya-Yun Li, Guang-Tong Deng, Fu-Rong Zeng, Hunan Engineering Research Center of Skin Health and Disease, Hunan Key Laboratory of Skin Cancer and Psoriasis, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Hui-Yan Sun, Song-Tao Du, Ya-Yun Li, Guang-Tong Deng, Fu-Rong Zeng, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Song-Tao Du, Department of Colorectal Surgical Oncology, Harbin Medical University Cancer Hospital, Harbin 150081, Heilongjiang Province, China

Corresponding author: Fu-Rong Zeng, MD, Doctor, Department of Oncology, Xiangya Hospital, Central South University, No. 87 Xiangya Road, Changsha 410008, Hunan Province, China. zengflorachn@hotmail.com

Abstract
Gastrointestinal (GI) cancers, including colorectal cancer, pancreatic cancer, liver cancer and gastric cancer, are severe social burdens due to high incidence and mortality rates. Bromodomain and extra-terminal (BET) proteins are epigenetic readers consisting of four conserved members (BRD2, BRD3, BRD4 and BRDT). BET family perform pivotal roles in tumorigenesis through transcriptional regulation, thereby emerging as potential therapeutic targets. BET inhibitors, disrupting the interaction between BET proteins and acetylated lysines, have been reported to suppress tumor initiation and progression in most of GI cancers. In this review, we will demonstrate how BET proteins participate in the GI cancers progression and highlight the therapeutic potential of targeting BET proteins for GI cancers treatment.

Key Words: Gastrointestinal cancer; Bromodomain and extra-terminal proteins; Bromodomain and extra-terminal inhibitors; Acetylated lysines
BET proteins: Structure and inhibition mechanism

BET family proteins include four subtypes: BRD2 (also known as FSRG1, RING3, RNFL3, FSH, or D6S113E), BRD3 (also known as ORFX or RING3L), BRD4 (also known as MCAP or HUNK1) and BRDT (also known as BRD6, CT9, or SPGF21)[13,14]. Each of the BET proteins has a highly conserved structure including two tandem -110 amino acid bromodomains (BD1 and BD2) with direct specificity for acetylated lysines, as well as an N-terminal (NTD) domain, which facilitates tumor initiation and progression. Down-regulation of BET proteins expression and inactivation of their function represent a possible mechanism of anti-tumor effect of BET inhibitors. Therefore, BET inhibitors present to be a rational strategy for the sake of GI cancers treatment. Several BET inhibitors targeting the BET bromodomains (BD) are currently under clinical investigations and preclinical data provides rationale for the use of BET inhibitors in treating GI cancers.

In this review, we will briefly describe the structure and inhibition mechanism of BET proteins and illustrate the role of BET proteins in the initiation and progression of human GI cancers. Then, we will identify whether targeting BET proteins, alone or in combination with other therapies, exhibits potential benefits in GI cancers through preclinical evidence. Finally, we will speculate the outlook of the translation of BET inhibitors into clinic.
BET proteins have two BDs with the acetylated lysine binding pocket. Compared with acetylated histones, BDs have a higher affinity for small molecules, which provide new possibilities for the development of inhibitors\[18\]. By occupying the BD pockets, BET inhibitors, such as JQ-1, mimic the binding mode and competitively inhibit binding between acetylated lysines and BDs, resulting in disrupting oncogenic rearrangement and inhibiting the development of some aggressive types of cancer (Figure 2).

**BET PROTEINS IN GI CANCERS**

Oncogenic roles of BET proteins family were firstly revealed in the NUT carcinoma. BRD4 and BRD3 are involved in the chromosomal rearrangements of NUT carcinoma by forming BET-NUT fusion protein\[19\]. The inspirational discovery that BET proteins serve as potential cancer therapeutic targets encourages researchers to look for possible functions of BET proteins in other cancers, including GI cancers. Strikingly, BET proteins (BRD2, BRD4) are overexpressed in GI cancers and have been reported to promote GI cancers progression via multiple mechanisms.

BRD2 was firstly defined as a non-canonical protein kinase\[20\], which could promote the GI cancers progression by recruiting transcriptional factors and initiating transcriptional regulation. Recent studies demonstrated that BRD2 promoted the progression of CRC, pancreatic ductal adenocarcinoma (PDAC) and GC\[21\]. Specifically, BRD2 forms a complex with transcription factor ELK4 by recognizing its K125 acetyl-lysine, and then activates transcription of LAMB3 in CRC, leading to tumor growth and metastasis\[22\]. Moreover, BRD2 drives a fibroinflammatory stromal reaction in PDAC by initiating the transcription of oncogene cellular-myelocytomatosis (c-MYC) and other stroma-inducible genes\[23\]. Huang et al\[24\] illustrated a different pathway that BRD2 could activate the transcriptional factor GLI, which regulated the pancreatic cancer microenvironment. These findings suggest that BRD2 is a poor prognostic predictor of GI cancers.

BRD3 was rarely studied in GI cancers. However, recently, some frameshift mutations of BRD3 have been found in GC\[25\]. Also, Tan et al\[26\] found that BRD3 was among the top six driver genes for familial aggregation of PDAC through whole-genome sequencing. That means unlike BRD2/4, BRD3 may function in GI cancer through a different mechanism.

BRD4 is the most extensively studied BET proteins in GI cancers which is highly expressed in cancer tissues and cell lines, including CRC\[27\], pancreatic cancer\[28\], liver cancer\[29\], and GC\[30\]. The overexpression of BRD4 promotes GI cancer cell growth, differentiation and metastasis, and correlates with poor outcome of GI cancers patients\[31,32\]. On one hand, BRD4 could directly bind to the promoter region of
Upon Bromodomain and extra-terminal (BET) inhibitors binding to Bromodomains, BET proteins are displaced from chromatin. Lacking domains directly interacting with chromatin, BET proteins fail to activate oncogenes, and thus BET inhibitors exert cytotoxic effects on cancer cells. BET: Bromodomain and extra-terminal.

BRD4 could recognize acetylated lysines on epithelial-to-mesenchymal transition (EMT)-activating transcriptional factors like Twist or Snail, the activation of which facilitated the differentiation and survival of EMT cells and promoted metastatic growth in GI cancers. Additionally, BRD4 was reported to be recruited to senescence-activated super-enhancers to mediate cellular senescence. The senescent cancer cells induced the secretion of various cytokines and increased CRC cells migration and invasion abilities. In addition to the direct induction of tumorigenesis, BRD4 was also involved in the crosstalk between cancer and cancer-associated fibroblasts. Inhibiting the BRD4 protein changed both transcription and structure of matrisome in PDAC and resulted in better patients’ survival. Moreover, Yasukawa et al. also described that BRD4 played an important role in cancer associated fibroblasts in GC. These oncogenic functions suggest that BRD4 is an important molecular target for GI cancers.

**BET INHIBITORS IN GI CANCERS**

Given that BET proteins are important regulators in GI cancer, targeting BET proteins will be a good therapeutic strategy for GI cancers treatment. A series of compounds have been reported as potential therapeutic avenues for GI cancers by targeting BET proteins (Table 1). BET inhibitors share the similar mechanism by displacing BET proteins from chromatin and regulating transcriptional factors. By mediating cell cycle arrest, facilitating apoptosis, and inducing senescence, BET inhibitors functionally inhibit cell proliferation, invasion and migration in most GI cancers including CRC, pancreatic cancer, liver cancer and GC. Mechanically, BET inhibitors exert anti-tumor activity in c-MYC dependent, as well as c-MYC independent manners. BET inhibitors have been widely used in preclinical models, but BET inhibitors alone exhibit limited-single agent activity confronting drug resistance. Combinational therapy with chemotherapy, immunotherapy or other small molecule inhibitors may amplify the clinical outcomes in GI cancers. Herein, we review the application of BET inhibitors in GI cancers.

**CRC**

Preclinical data demonstrated that BET inhibitors alone had exhibited efficacy against CRC by inhibiting tumor growth and inducing apoptosis in vivo and vitro. However, resistance to BET inhibitors was the major obstacle to CRC treatment. Wang et al. raised one possible mechanism that the interaction of STAT3 through BRD4 phosphorylation might result in the resistance of BET inhibitors in CRC. Combining BET inhibitors and other targeted therapies could help to overcome resistance and
## Table 1 Preclinical models of Bromodomain and extra-terminal inhibitors in gastrointestinal cancers

| GI cancers models          | BET inhibitors | Combination with | Targets                  | Pathway/mechanism                          | Ref. |
|----------------------------|----------------|-----------------|--------------------------|--------------------------------------------|------|
| CRC                        | JQ-1           | 5-FU            | DR5                      | Apoptosis                                  | [49] |
|                            | JQ-1           | Bortezomib      | MYC, FOXM1               | G2/M arrest                                | [47] |
|                            | JQ-1           | -               | HGF, MET                 | Cancer-associated fibroblasts              | [98] |
|                            | Apabetalone    | -               | APOA1                    | Intracellular cholesterol metabolism       | [99] |
|                            | JQ-1           | BEZ235 (PI3K/mTOR inhibitor) | RTKs                      | Overcome resistance to PI3K/mTOR inhibition | [40] |
|                            | JQ-1           | Sulforaphane (HDAC3 inhibitor) | ERCC2                     | Nucleotide excision repair pathway         | [48] |
|                            | 1-BET151, bromoporine | -               | BRD4, SNAIL, SLUG         | EMT                                        | [100]|
| SMAD4-deficient CRC        | OTX-015        | -               | MYC                      | MYC-p21 axis, G1 cell cycle arrest         | [54] |
| Colon cancer               | JQ-1           | -               | Nkd2, β-catenin, miR-21  | Wnt/β-catenin signaling, apoptosis         | [45] |
| Gastric and colon cancer   | JQ-1           | Arsenic sulfide | NFATs, c-MYC             | Mitochondrial pathway induced cell apoptosis | [51] |
| PDAC                       | JQ-1           | -               | HMGA2                    | Block growth of chemoresistant cells       | [55] |
|                            | JQ-1           | Olaparib (PARP inhibitor) | BRD2/4, Ku80, RAD51     | DNA damage                                 | [60] |
|                            | JQ-1           | SAHA (HDAC inhibitor) | p57                      | Cell death                                 | [61] |
|                            | JQ-1           | Gemcitabine     | HMGC52, APOC1            | DNA damage and apoptosis                   | [62] |
| CPT203                     | -              | MYC, GLI, SHH   | SHH-GLI signaling pathway, cell cycle progression | [24] |
| Pancreatic cancer          | JQ-1, OTX-015  | Quercetin       | BRD4(JQ-1) and hnRNP/A1(Quercetin) | Apoptosis                                 | [63] |
| KDM6A null pancreatic cancer | JQ-1           | -               | MYC, p63, RUNX3          | Reverse squamous differentiation           | [100, 102] |
| Liver cancer               | JQ-1           | -               | BRD4, E2F2               | BRD4-E2F2-cell cycle regulation axis,      | [34] |
|                            | JQ-1           | -               | PD-L1, PD-L2             | PD-1/PD-L1 signaling                       | [71] |
| HCC                        | JQ-1, I-BET762 | Anti-PD-L1 Ab   | BRD4, C/Eββ1, p300       | Suppress M-MDSCs, enhance PD-L1 blockade efficacy | [73] |
|                            | JQ-1           | -               | MYC                      | Impair mitochondrial respiration and glycolysis, induce apoptosis | [66] |
|                            | Hjp-6-171      | GSK3β inhibitor (CHIR-98014) | β-catenin, NOTUM        | WNT pathway                               | [68] |
|                            | SF1126 (P’an PI3K/BRD4 Inhibitor) | Sorafenib         | BRD4, c-MYC              | Ras/Raf/MAPK, PI3K/akt/mTOR pathways       | [90] |
|                            | JQ-1           | -               | PESI                     | Cell proliferation, glycolysis             | [35] |
|                            | JQ-1           | Flavopiridol    | Mcl-1                    | Apoptosis                                  | [67] |
|                            | JQ-1, OTX-015  | -               | SMARCA4                  | Down-regulate migration related genes      | [65] |
| CCA2                       | JQ-1           | PI3K/mTOR inhibitors | c-Myc, YAP               | Overcome resistance to PI3K/mTOR inhibition | [64] |
| Gastric cancer             | JQ-1           | -               | BRD4, E2F                | E2F/miR-106b-5p/p21 axis, cellular senescence | [32] |
|                            | JQ-1           | -               | RUNX2                    | RUNX2/NID1 signaling, site-specific chromatinremodeling | [75] |
|                            | JQ1, PNZ5      | -               | c-MYC                    | Apoptosis                                  | [33, 74] |
Sun HY et al. BET inhibitors for gastrointestinal cancers treatment

| iBET-151 | Paclitaxel | RTK | G1 cell cycle arrest |
|-----------|------------|-----|---------------------|
| AZD5153   | -          | Sirt5, Mus81 | Sirt5/Mus81/ZEB1 axis, inhibit metastasis |
| GAC       | JQ-1       | CA3 (YAP inhibitor) | Gal3/RalA/YAP1/c-MYC axis |

CRC: Colorectal cancer; PDAC: Pancreatic ductal adenocarcinoma; HCC: Hepatocellular carcinoma; CCA: Cholangiocarcinoma; GAC: Gastric adenocarcinoma; 5-FU: 5-Fluorouracil; c-MYC: Cellular-myelocytomatosis.

render CRC more sensitive to BET inhibitors. For example, nuclear factor-kappa B inhibitors[47], PD3K/mTOR inhibitors[40], HDAC3 inhibitor[48] have been reported to sensitize GI cancers to BET inhibitors, and finally achieve synergistic effects.

Moreover, BET inhibition could be used in combination with chemotherapy to enhance chemotherapy effect via increasing the apoptosis induction[49]. For example, BET inhibitors could increase the sensitivity of CRC cells to 5-fluorouracil[50] and Arsenic sulfide[51,52] (Figure 3). More importantly, this combination therapy could decrease the side effect of chemotherapeutic drugs[53]. Moreover, BET inhibitors conferred a synthetic lethality with loss of SMAD4 in CRC cells by restoring the loss of c-MYC repression[54], suggesting that BET inhibitors were essential for the treatment of SMAD4-deficient CRC.

**Pancreatic cancer**

BET inhibitors not only effectively inhibited PDAC cell growth in three-dimensional collagen partly by repressing c-MYC expression, but also conducted its efficacy in a MYC-independent way by repressing the expression of FOSL1[55]. However, clinical studies suggested that BET inhibitors monotherapies were not effective revenues for PDAC treatment[56]. Drug resistance assumed the major responsibility for treatment failure. The main mechanism of resistance was associated with either up-regulating or stabilizing c-MYC expression. Loss of FBP1[57], aberrant expression of ADAR1[58], high levels of GLI[24] and overexpression of PES1[59] could explain the up-regulation of c-MYC in pancreatic cancer.

To improve the efficacy of BET inhibitor on PDAC, several studies evaluated the efficiency of BET inhibitors in combination with other agents. Encouragingly, BET inhibitors could synergize with other target therapy in preclinical PDAC models. For example, BET inhibitor attenuated the DNA repair through decreasing Ku80 and RAD51 proteins, and sensitized the PDAC to PARP inhibitors[60]. Another team also illustrated that BET inhibitors synergizing with HDAC inhibitors enhanced the efficacy of inducing cell death via de-repressing p57[61]. In addition to being combined with target therapies, BET augmented the efficiency of chemotherapeutic drugs like Gemcitabine by increasing DNA damage and apoptosis[62]. Besides, BET inhibitors combined with Quercetin suppress hnRNPA1 leading to better therapeutic effect compared with monotherapy[63].

**Liver cancer**

BET inhibitors exhibit anti-tumorigenic effects on both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), but in different manners. JQ-1 inhibited CCA growth in a MYC-dependent way[64], while JQ-1 played its anti-tumor role in HCC by suppressing E2F2-cell cycle regulation circuit[34] or the expression of SMARCA4[65]. Notably, Yin et al[66] stated that JQ-1 exerted more cytotoxicity on MYC-positive HCC cells than sorafenib (first-line drug for advanced HCC) by inducing more apoptosis. This team further demonstrated that EGFR signaling contributed to the JQ1 resistance by stabilizing MYC. Zhang et al[67] arrived at a different resistance mechanism that upregulation of Mcl-1 was a major contributor to the resistance to BET inhibitor in HCC cells. They further found that BET inhibitors, in combination with other drugs capable of down-regulating Mcl-1 had a synergic effect in human HCC. Liu et al[68] reported another resistance mechanism and the reactivation of WNT pathway in liver cancer cells could increase the sensitivity of HCC to BET inhibitor[68].

BET inhibitor were also reported to impact the immunotherapy efficacy in HCC (Figure 4). Several studies had shown that BET inhibition could enhance anti-tumor immunity via modulating programmed cell death-ligand 1 (PD-L1) expression[69,70]. Liu et al[71] demonstrated that JQ-1 could decrease the total mRNA and protein levels of PD-L1 in liver cancer cell lines. However, Liu et al[72] reported that JQ1 upregulated the expression of PD-L1 on the plasma membrane in vivo and in vitro, but did not change the total levels of PD-L1 mRNA and protein. Another study conducted by Cheng and his colleague[73] reported that I-BET762, exerted a synergistic effect with...
Bromodomain and extra-terminal (BET) inhibitors and arsenic sulfide exert synergistic cytotoxicity via down-regulating c-MYC and induce cell apoptosis in an intrinsic (mitochondrial) pathway; while BET inhibitors in combination with 5-Fluorouracil mediate apoptosis in a death receptor 5-dependent manner which is regulated in extrinsic (death receptor) pathway. BET: Bromodomain and extra-terminal; AS: Arsenic sulfide; 5-FU: 5-fluorouracil; DR5: Death receptor 5; c-MYC: Cellular-myelocytomatosis.

Bromodomain and extra-terminal (BET) inhibitors treatment impacts programmed death-1-ligand-1 (PD-L1) expression, resulting in sensitizing the liver response to anti-PD-L1 blockade. Also, the co-inhibition can inhibit liver-infiltrating monocytic myeloid-derived suppressor cells and enhance tumor-infiltrating CD8+ T cells, which contributes to the elimination of drug resistance. BET: Bromodomain and extra-terminal; HCC: Hepatocellular carcinoma; M-MDSCs: Monocytic myeloid-derived suppressor cells; PD-L1: Programmed death-1-ligand-1.

JQ-1 exerts an anti-cancer effect on GC as well. Interestingly, JQ-1 has race specificity on GC that Asians rendered more resistance to BET inhibitors than Brazilians[74]. Recently, Zhou et al[75] noted that JQ-1 suppressed proliferation, migration and invasion of GC cells via targeting RUNX2/NID1 axis, while BET inhibitor AZD5153 inhibited GC metastasis by regulating Mus81 at both RNA and protein levels[76]. Kim et al[77] revealed new BRD4 inhibitor that showed efficiency in l-BET762 resistant GC cell lines[77]. Additionally, through blocking the expression of c-MYC and YAP1, JQ-1 reduced gastric adenocarcinoma cell growth induced by Gal-3, and the anti-cancer activity could be improved in combination with YAP inhibitors[78]. Other combination strategies with chemotherapy drugs have also been reported. The combination of...
BET inhibitors, including I-BET762 (NCT01587703), INCB057643 (NCT02711137), INCB054329 (NCT02431260), AZD5153 (NCT03205176) and OTX-015 (NCT02698176) have entered Clinical Trial for diverse cancers[86], but the majority of them remain in the Phase I/II. Here, we are concentrating on the trials of BET inhibitors alone or in combination with other inhibitors in GI cancers (Table 2).

I-BET762 (Molibresib) is a pan-BET inhibitor that remarkably inhibits the PDAC cell proliferation by down-regulating c-MYC and reducing protein levels of ERK1/2. Remarkably, the anti-tumor effect can be enhanced combined with gemcitabine[87]. NCT03925428 is a phase I clinical trial that tests the side effects and best dose of I-BET 762 combined with entinostat in solid tumors or lymphomas advanced or refractory, including PDAC. However, the study was withdrawn because other protocol moved to disapprove.

INCB054329 and INCB057643 are two small-molecule BET inhibitors which exhibit anti-cancer activity by reducing the expression level of c-MYC[88,89]. Phase I/II dose-escalation, safety and tolerability studies of INCB054329 and INCB057643 were conducted in subjects with advanced malignancies including GI cancers. INCB054329 was terminated due to an unfavorable clinical Pharmacokinetic (PK) profile (NCT02431260). INCB057643 compared with INCB054329 has a longer half-life and a shorter PK variability. However, patients received INCB057643 resulted in treatment discontinuance or dose interruption or dose reduction due to TRAEs and the study ultimately terminated in 2020 (NCT02711137).

AZD5153 is a novel BRD4 inhibitor, effecting Mus81 down-regulation and suppressing tumor migration in GC[76]. A Phase I study was initiated to evaluate the safety, pharmacokinetics, and pharmacodynamics of AZD5253 alone or in combination with Olaparib in patients with malignant solid tumors, including pancreatic cancer. The recruiting status of this study remains active, not recruiting (NCT-03205176).

Dual PI3K/BRD4 Inhibitor SF1126 blocks both the Ras/Raf/MAPK and PI3K/AKT/mTOR pathways and disrupts c-MYC expression as well[90]. And a Phase I clinical trial of SF1126 has completed in humans with well toleration and efficacy in...
Table 2 Clinical trials of Bromodomain and extra-terminal inhibitors in gastrointestinal cancers (Trial ID on www.clinicaltrials.gov)

| Drug             | Combination with                | Condition                                                                 | Status                        | Clinical phase | Trial ID            |
|------------------|---------------------------------|---------------------------------------------------------------------------|-------------------------------|----------------|---------------------|
| INCBO54329       |                                 | Solid Tumors and Hematologic Malignancy (CRPC, BC, HGSC, CRC, Ewing sarcoma, Pancreatic adenocarcinoma, AML, MDS, MF, MM) | Terminated due to PK variability | Phase I/II     | NCT02431260        |
| INCBO57643       | Gemcitabine; Paclitaxel;        | Solid Tumors (CRPC, BC, HGSC, CRC, Glioblastoma multiforme, Ewing sarcoma, Pancreatic adenocarcinoma, AML, MDS) | Terminated due to safety issues | Phase I/II     | NCT02711137        |
| AZD5153          | Olaparib                        | Malignant Solid Tumors, Lymphoma, Ovarian Cancer, Breast Cancer, Pancreatic Cancer, Prostate Cancer | Active, not recruiting        | Phase I        | NCT03205176        |
| I-BET762         | Entinostat                      | Solid tumors (Advanced Malignant Solid Neoplasm, Refractory Malignant Solid Neoplasm, Refractory Pancreatic Carcinoma, Stage II/IIA/IIB/III/IV Pancreatic cancer AJCC v8, Unresectable Pancreatic Carcinoma) or Lymphomas | Withdrawn (Other-Protocol moved to Disapprove) | Phase I        | NCT03925428        |
| SF1126           |                                 | Advanced Hepatocellular Carcinoma                                         | Active, not recruiting        | Phase I        | NCT03059147        |

Figure 5 Schematic of new Bromodomain and extra-terminal molecules targeting Bromodomain-containing protein 4 using PROTACs technology. The bifunctional molecules contain two binders with one (usually bromodomain and extra-terminal inhibitors like JQ-1 or OTX015) targeting Bromodomain-containing protein 4 (BRD4) and the other binding E3 Ligase, which triggers the ubiquitination and degradation of BRD4. BRD4: Bromodomain-containing protein 4.

solid tumor including CRC\[91\]. Recently, SF1126 is being tested in combination with Nivolumab in patients with advanced HCC and this study is expected to be completed by October 2022 (NCT03059147).

With high bioavailability and biosafety, SF1126 has completed a Phase I clinical study and steps into a Phase II study in advanced HCC. And AZD5153 shows an optimistic preclinical result in GC treatment. All these evidences demonstrate that BET inhibitors constitute a promising field of clinical research in GI cancers. Continued progresses are required especially in exploring rational combinations to open new possibilities for BET inhibitors as anti-GI cancers agents.

CONCLUSION

BET inhibitors have emerged as a new possible strategy for the treatment of GI cancers in recent years. However, either nondurable cytotoxic effects, such as thrombocytopenia and GI disorders\[92\] or drug resistance make BET inhibitors fail to be adminis-
trated as single agents by far. To achieve better selectivity and reduce unwanted toxicities, BET inhibitors continue to be updated, increasing their potential in cancer treatment.

The first-generation pan-BET inhibitors have been identified to suppress GI cancer in preclinical results, however, the inevitable side effects limit their clinical applications. Hence, drug discovery efforts concentrate on selectively inhibiting BET proteins[93]. Selective BD inhibitors achieved almost equally efficacy in cancer to the pan-BET inhibitors[94] and showed less toxicity[95]. A set of selective BD inhibitors help to understand the role of BD in cancers and further focusing on specific BD perturbations may provide more efficiency and tolerability in GI cancers treatment.

Another approach to acquire selective inhibition is to target each BET family members. Since BRD4 is the predominant BET protein that mediates the development of GI cancers, selective BRD4 inhibition may have a better outlook. New BRD4 degraders ARV-825 and A1874 that have already shown their antitumor efficiency in preclinical results support further clinical development of BET inhibitors in GI cancers.

Other strategy to improve the efficacy and pharmacokinetic property of BET inhibitors is via modulating their structure. After modification, these major clinical BET inhibitors continue to be updated, increasing their potential in cancer treatment.

Additionally, synergistic inhibition provides an optimistic prospect for increasing the efficacy of BET inhibitors. The preclinical and clinical results verify high potential in combinational therapy. The resistance to BET inhibitors will be overcome if the efficacy of BET inhibitors. The preclinical and clinical results verify high potential in multiple solid tumors[96]. The optimistic preclinical result makes it possible to treat GI cancer with single agents.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jamal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
2. Stoica AF, Chang CH, Pauklin S. Molecular Therapeutics of Pancreatic Ductal Adenocarcinoma: Targeted Pathways and the Role of Cancer Stem Cells. Trends Pharmacol Sci 2020; 41: 977-993 [PMID: 33092892 DOI: 10.1016/j.tips.2020.09.005]
3. Moertel CG. Chemotherapy of gastrointestinal cancer. N Engl J Med 1978; 299: 1049-1052 [PMID: 660664 DOI: 10.1056/NEJM197811092991906]
4. Chen X, Zeh HJ, Kang R, Kroemer G, Tang D. Cell death in pancreatic cancer: from pathogenesis to therapy. Nat Rev Gastroenterol Hepatol 2021; 18: 804-825 [PMID: 33431036 DOI: 10.1038/s41575-021-00486-6]
5. Debenham BJ, Hu KS, Harrison LB. Present status and future directions of intraoperative radiotherapy. Lancet Oncol 2013; 14: e457-e464 [PMID: 24079873 DOI: 10.1016/S1470-2045(13)70270-5]
6. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. CA Cancer J Clin 2021; 71: 264-279 [PMID: 33592120 DOI: 10.3322/caac.21657]
7. Long J, Lin J, Wang A, Wu L, Zheng Y, Yang X, Wan X, Xu H, Chen S, Zhao H. PD-1/PD-L blockade in gastrointestinal cancers: lessons learned and the road toward precision immunotherapy. J Hematol Oncol 2017; 10: 146 [PMID: 28774337 DOI: 10.1186/s13045-017-0511-2]
8. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, Park JO, Hochhauser D, Arnold D, Oh DY, Reinacher-Schick A, Tortora G, Algül H, O'Reilly EM, McGuinness D, Cui KY, Schlenger K, Locker GY, Kindler HL. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med 2019; 381: 317-327 [PMID: 31157963 DOI: 10.1056/NEJMoa1903387]
9. Duan C, Hong W, Gibbs P, Ackland S, Sjoquist K, Tebbutt NC, Price T, Burge M. Personalizing First-Line Systemic Therapy in Metastatic Colorectal Cancer: Is There a Role for Initial Low-Intensity Therapy in 2021 and Beyond? Clin Colorectal Cancer 2021; 20: 245-255 [PMID: 34103264 DOI: 10.1016/j.ccc.2021.05.001]
10. Zhang N, Ng AS, Cai S, Li Q, Yang L, Kerr D. Novel therapeutic strategies: targeting epithelial-mesenchymal transition in colorectal cancer. Lancet Oncol 2021; 22: e358-e368 [PMID: 34339656 DOI: 10.1016/S1470-2045(21)00343-0]
11. Nussbaum YI, Manjunath Y, Suvilesh KN, Warren WC, Shyu CR, Kaifi JT, Corbia MA, Mitchell JB. Current and Prospective Methods for Assessing Anti-Tumor Immunity in Colorectal Cancer. Int J Mol Sci 2021; 22 [PMID: 33946558 DOI: 10.3390/ijms22094802]
12. Doroshow BD, Eder JP, LoRusso PM. BET inhibitors: a novel epigenetic approach. Ann Oncol 2017; 28: 1776-1787 [PMID: 28838216 DOI: 10.1093/annonc/mdx157]
Fan P, Cancer. Signal Transduct Target Ther 2021; 6: 23 [PMID: 33462181 DOI: 10.1038/s41392-020-00384-4]

Dhaluin C, Carlson JE, Zeng L, He C, Aggarwal AK, Zhou MM. Structure and ligand of a histone acetyltransferase bromodomain. Nature 1999; 399: 491-496 [PMID: 10365964 DOI: 10.1038/20974]

Itzen F, Greifenberg AK, Böskën CA, Geyer M. Brd4 activates P-TETfs for RNA polymerase II CTD phosphorylation. Nucleic Acids Res 2014; 42: 7577-7590 [PMID: 24860166 DOI: 10.1093/nar/gku449]

Wu SY, Chang CM. The double bromodomain-containing chromatin adaptor Brd4 and transcriptional regulation. J Biol Chem 2007; 282: 13141-13145 [PMID: 17329240 DOI: 10.1074/jbc.R70001200]

Filippakopoulos P, Knapp S. Targeting bromodomains: epigenetic readers of lysine acetylation. Nat Rev Drug Discov 2014; 13: 337-356 [PMID: 24751816 DOI: 10.1038/nrd4286]

Statthis A, Bertonì F. BET Proteins as Targets for Anticancer Treatment. Cancer Discov 2018; 8: 24-36 [PMID: 29263030 DOI: 10.1158/2159-8290.CD-17-0065]

Belkina AC, Denis GV. BET domain co-regulators in obesity, inflammation and cancer. Nat Rev Cancer 2012; 12: 465-477 [PMID: 22722403 DOI: 10.1038/nrc3256]

Chen Z, Li Z, Souto M, Wang W, Piazuelo MB, Zha S, Guo Y, Maturana MJ, Corvalán AH, Chen X, Xu Z, El-Rifai WM. Integrated Analysis of Mouse and Human Gastrointestinal Neoplasms Identifies Conserved microRNA Networks in Gastric Carcinogenesis. Gastroenterology 2019; 156: 1127-1139.e8 [PMID: 30502323 DOI: 10.1053/j.gastro.2018.11.052]

Zhu Z, Song J, Guo Y, Huang Z, Chen X, Dang X, Huang Y, Yang Y, Ou W, Yang Y, Wu W, Liu CY, Cui LV, LAMB3 promotes tumour progression through the AKT-FOXO3A axis and is transcriptionally regulated by the BRD2/acetylated ELK4 complex in colorectal cancer. Oncogene 2020; 39: 4666-4680 [PMID: 32398865 DOI: 10.1038/s41388-020-1321-5]

Sherman MH, Yu RT, Tseng TW, Sousa CM, Liu S, Truitt ML, He N, Ding N, Liddle C, Atkins AR, Leblanc M, Collisson EA, Asara JM, Kimmelman AC, Downes M, Evans RM. Stromal cues regulate the pancreatic cancer epigenome and metabolome. Proc Natl Acad Sci U S A 2017; 114: 1129-1134 [PMID: 28096419 DOI: 10.1073/pnas.1620164114]

Huang Y, Nahar S, Nakahara A, Fernandez-Barrena MG, Mertz JA, Bryant BM, Adams CE, Mino-Kenudson M, Von Alt KN, Chang K, Conery AR, Hatton C, Sims RJ 3rd, Fernandez-Zapico ME, Dhalluin C, Greifenberg AK, Bösken CA, Geyer M. Brd4 activates P-TEFb for RNA polymerase II CTD phosphorylation. J Biol Chem 2014; 289: 10394-10407 [PMID: 24582595 DOI: 10.1074/jbc.R114.543032]

Yu RT, Tseng TW, Sousa CM, Liu S, Truitt ML, He N, Ding N, Liddle C, Atkins AR, Leblanc M, Collisson EA, Asara JM, Kimmelman AC, Downes M, Evans RM. Stromal cues regulate the pancreatic cancer epigenome and metabolome. Proc Natl Acad Sci U S A 2017; 114: 1129-1134 [PMID: 28096419 DOI: 10.1073/pnas.1620164114]

Tao Y, Chen CY, Cui L. LAMB3 promotes tumour progression through the AKT-FOXO3/4 axis and is transcriptionally regulated by the BRD2/acetylated ELK4 complex in colorectal cancer. Oncogene 2020; 39: 4666-4680 [PMID: 32398865 DOI: 10.1038/s41388-020-1321-5]

Chen Z, Li Z, Souto M, Wang W, Piazuelo MB, Zha S, Guo Y, Maturana MJ, Corvalán AH, Chen X, Xu Z, El-Rifai WM. Integrated Analysis of Mouse and Human Gastrointestinal Neoplasms Identifies Conserved microRNA Networks in Gastric Carcinogenesis. Gastroenterology 2019; 156: 1127-1139.e8 [PMID: 30502323 DOI: 10.1053/j.gastro.2018.11.052]

Zhu Z, Song J, Guo Y, Huang Z, Chen X, Dang X, Huang Y, Yang Y, Ou W, Yang Y, Wu W, Liu CY, Cui LV, LAMB3 promotes tumour progression through the AKT-FOXO3A axis and is transcriptionally regulated by the BRD2/acetylated ELK4 complex in colorectal cancer. Oncogene 2020; 39: 4666-4680 [PMID: 32398865 DOI: 10.1038/s41388-020-1321-5]

Sherman MH, Yu RT, Tseng TW, Sousa CM, Liu S, Truitt ML, He N, Ding N, Liddle C, Atkins AR, Leblanc M, Collisson EA, Asara JM, Kimmelman AC, Downes M, Evans RM. Stromal cues regulate the pancreatic cancer epigenome and metabolome. Proc Natl Acad Sci U S A 2017; 114: 1129-1134 [PMID: 28096419 DOI: 10.1073/pnas.1620164114]

Huang Y, Nahar S, Nakahara A, Fernandez-Barrena MG, Mertz JA, Bryant BM, Adams CE, Mino-Kenudson M, Von Alt KN, Chang K, Conery AR, Hatton C, Sims RJ 3rd, Fernandez-Zapico ME, Dhalluin C, Greifenberg AK, Bösken CA, Geyer M. Brd4 activates P-TEFb for RNA polymerase II CTD phosphorylation. J Biol Chem 2014; 289: 10394-10407 [PMID: 24582595 DOI: 10.1074/jbc.R114.543032]

Yu RT, Tseng TW, Sousa CM, Liu S, Truitt ML, He N, Ding N, Liddle C, Atkins AR, Leblanc M, Collisson EA, Asara JM, Kimmelman AC, Downes M, Evans RM. Stromal cues regulate the pancreatic cancer epigenome and metabolome. Proc Natl Acad Sci U S A 2017; 114: 1129-1134 [PMID: 28096419 DOI: 10.1073/pnas.1620164114]
cell proliferation and glycolysis in hepatocellular carcinoma. *Int J Biochem Cell Biol* 2018; 104: 1-8 [PMID: 30172011 DOI: 10.1016/j.biocel.2018.08.014]

36 **Zhao J**, Meng Z, Xie C, Yang C, Liu Z, Wu S, Wang B, Fan P, Jin X, Wu H. B7-H3 is regulated by BRD4 and promotes TL1R4 expression in pancreatic ductal adenocarcinoma. *Int J Biochem Cell Biol* 2019; 108: 84-91 [PMID: 30664982 DOI: 10.1016/j.biocel.2019.01.011]

37 **Wang LT**, Wang SN, Chiu SS, Liu KY, Chai CY, Chiang CM, Huang SK, Yokoyama KK, Hsu SH. TIP60-dependent acetylation of the SPZ1-TWIST complex promotes epithelial-mesenchymal transition and metastasis in liver cancer. *Oncogene* 2019; 38: 518-532 [PMID: 30154425 DOI: 10.1038/s41388-018-0457-2]

38 **Qin ZY**, Wang T, Su S, Shen LT, Zhu GX, Liu Q, Zhang L, Liu KW, Zhang Y, Zhou ZH, Zhang XN, Wen LZ, Yao YL, Sun WJ, Guo Y, Liu KJ, Liu L, Wang XW, Wei YL, Wang J, Xiao HL, Liu P, Bian XW, Chen DF, Wang B. BRD4 Promotes Gastric Cancer Progression and Metastasis through Acetylation-Dependent Stabilization of Snail. *Cancer Res* 2019; 79: 4869-4881 [PMID: 31311807 DOI: 10.1158/0008-5472.CAN-19-0442]

39 **Tasdemin N**, Banito A, Roe JS, Alonso-Curbelo D, Camiolo M, Tschaharganeh DF, Huang CH, Aksoy O, Bolden JE, Chen CC, Fennell M, Thapar V, Chicas A, Vakoc CR, Lowe SW. BRD4 Connects Enhancer Remodeling to Senescence Immune Surveillance. *Cancer Discov* 2016; 6: 612-629 [PMID: 27099234 DOI: 10.1158/2159-8290.CD-16-0217]

40 **Lee HS**, Lee S, Cho KH. Cotargeting BET proteins overcomes resistance arising from PI3K/mTOR blockade-induced protumorigenic senescence in colorectal cancer. *Int J Cancer* 2020; 147: 2824-2837 [PMID: 32599660 DOI: 10.1002/ijc.333047]

41 **Housselman KC**, Finetti P, Birnbaum DJ, Monsalve CS, Wellner UF, Begg SKS, Nakagawa A, Hank T, Li A, Goldsworthy MA, Sharma H, Bertucci F, Birnbaum D, Tani E, Ligorio MA, Ting DT, Schilling O, Biniossek ML, Bronsert P, Ferrone CR, Keek T, Mino-Kenudson M, Lillenseen KD, Wardshaw AL, Fernández-Del Castillo C, Liss AS. Neoepitope-Strontium Cell Cross-talk Regulates Matrisome Expression in Pancreatic Cancer. *Mutat Cancer Res* 2020; 18: 1889-1902 [PMID: 32873625 DOI: 10.1158/1541-7786.MCR-20-0439]

42 **Yasukawa Y**, Hattori N, Iida N, Takeshima H, Maeda M, Kiyono T, Sekine S, Seto Y, Ushijima T. SAAS1 is upregulated in gastric cancer-associated fibroblasts possibly by its enhancer activation. *Carcinogenesis* 2021; 42: 180-189 [PMID: 33284950 DOI: 10.1092/carcin/bga31]

43 **Filippakopoulos P**, Qi J, Piccard S, Shen Y, Smith WB, Fedorov O, Morse EM, Keates T, Hickman TT, Felletar I, Phippott M, Munro S, McKeown MR, Wang Y, Christie AL, West N, Cameron MJ, Schwartz B, Heightman TD, La Thangue N, French CA, Wiest O, Kung AL, Knapp S, Bradner JE. Selective inhibition of BET bromodomains. *Nature* 2010; 468: 1067-1073 [PMID: 20871596 DOI: 10.1038/nature09594]

44 **Delmore JE**, Issa GC, Lemieux ME, Rahil PB, Shi J, Jacobs HM, Kastritsis E, Gilpatrick T, Paranal RM, Qi J, Chness M, Schinzel AC, McKeown MR, Heffermann TP, Vakoc CR, Bergsagel PL, Ghobrial IM, Richardson PG, Young RA, Hahn WC, Anderson KC, Kung AL, Bradner JE, Mistiades CS. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell* 2011; 146: 904-917 [PMID: 21889194 DOI: 10.1016/j.cell.2011.08.017]

45 **Zhang Y**, Tian S, Xiong J, Zhou Y, Song H, Liu C. JQ1 Inhibits Colon Cancer Proliferation via Suppressing Wnt/β-Catenin Signaling and miR-21. *Chem Res Toxicol* 2018; 31: 302-307 [PMID: 29660711 DOI: 10.1021/acs.chemrestox.7b00346]

46 **Wang W**, Tang YA, Xiao Q, Lee WC, Cheng B, Niu Z, Ouguz G, Feng M, Lee PL, Li B, Yang ZH, Chen YF, Lan P, Wu XJ, Yu Q. Stromal induction of BRD4 phosphorylation Results in Chromatin Remodeling and BET inhibitor Resistance in Colorectal Cancer. *Nat Commun* 2021; 12: 4441 [PMID: 34290255 DOI: 10.1038/s41467-021-24687-4]

47 **Wu T**, Wang G, Chen W, Zhu Z, Liu Y, Huang Z, Huang Y, Du P, Yang Y, Liu CY, Cui L. Co-inhibition of BET proteins and NF-κB as a potential therapy for colorectal cancer through synergetic inhibiting MYC and FOXM1 expressions. *Cell Death Dis* 2018; 9: 315 [PMID: 29472532 DOI: 10.1038/s41419-018-0354-y]

48 **Kappoor S**, Gustafson T, Zhang M, Chen YS, Li J, Nguyen P, Perez JET, Dashwood WM, Rajendran P, Dashwood RH. Deacetylase Plus Bromodomain Inhibition Downregulates ERCC2 and Suppresses the Growth of Metastatic Colon Cancer Cells. *Cancers (Basel)* 2021; 13 [PMID: 33809839 DOI: 10.3390/cancers13061438]

49 **Tan X**, Tong J, Wang YJ, Fletcher R, Schoen RE, Yu J, Shen L, Zhang L. BET Inhibitors Potentiate Chemotherapy and Killing of SPOP-Mutant Colon Cancer Cells via Induction of DR5. *Cancer Res* 2019; 79: 1191-1203 [PMID: 30674532 DOI: 10.1158/0008-5472.CAN-18-3223]

50 **Cheng X**, Huang Z, Long D, Jin W. BET inhibitor bromosporine enhances 5-FU effect in colorectal cancer cells. *Biochem Biophys Res Commun* 2020; 521: 840-845 [PMID: 31708100 DOI: 10.1016/j.bbrc.2019.11.009]

51 **Tan Z**, Zhang X, Kang T, Zhang L, Chen S. Arsenic sulfide amplifies JQ1 toxicity via mitochondrial pathway in gastric and colon cancer cells. *Drug Des Devel Ther* 2018; 12: 3913-3927 [PMID: 30532520 DOI: 10.2147/DDDT.S180976]

52 **Zhang L**, Tong Y, Zhang X, Pan M, Chen S. Arsenic sulfide combined with JQ1, chemotherapy agents, or celecoxib inhibit gastric and colon cancer cell growth. *Drug Des Devel Ther* 2015; 9: 5851-5862 [PMID: 26586936 DOI: 10.2147/DDDT.S92943]

53 **Lei L**, Xie X, He L, Chen K, Lv Z, Zhou B, Li Y, Hu W, Zhou Z. The bromodomain and extraternal domain inhibitor JQ1 synergistically sensitizes human colorectal cancer cells to
topoisomerase 1 inhibitors through repression of Mre11-mediated DNA repair pathway. *Invest New Drugs* 2021; 39: 362-376 [PMID: 32981006 DOI: 10.1007/s10637-020-01014-0]

54 Shi C, Yang EJ, Liu Y, Mou PK, Ren G, Shim JS. Bromodomain and extra-terminal motif (BET) inhibition is synthetic lethal with loss of SMAD4 in colorectal cancer cells via restoring the loss of MYC repression. *Oncogene* 2021; 40: 937-950 [PMID: 33293694 DOI: 10.1080/s1438-8201-01500-w]

55 Sahai V, Kumar K, Knab LM, Chow CR, Raza SS, Bentrem D, Ebine K, Munshi HG. BET bromodomain inhibitors block growth of pancreatic cancer cells in three-dimensional collagen. *Mol Cancer Ther* 2014; 13: 1907-1917 [PMID: 24807963 DOI: 10.1186/1555-7163-MCT-13-6925]

56 Hessmann E, Johnsen SA, Siveke JT, Ellenrieder V. Epigenetic treatment of pancreatic cancer: is there a therapeutic perspective on the horizon? *Gut* 2017; 66: 168-179 [PMID: 27811314 DOI: 10.1136/gutjnl-2016-312539]

57 Wang B, Fan P, Zhao J, Wu H, Jin X. FBP1 Loss contributes to BET inhibitors resistance by underlying c-Myc expression in pancreatic ductal adenocarcinoma. *J Exp Clin Cancer Res* 2018; 37: 224 [PMID: 30201002 DOI: 10.1186/s13046-018-0888-y]

58 Sun Y, Fan J, Wang B, Meng Z, Ren D, Zhao J, Liu Z, Li D, Jin X, Wu H. The aberrant expression of ADAR1 promotes resistance to BET inhibitors in pancreatic cancer by stabilizing c-Myc. *Am J Cancer Res* 2020; 10: 148-163 [PMID: 32064158]

59 Jin X, Fang R, Fan P, Zeng L, Zhang B, Lu X, Liu T. PES1 promotes BET inhibitors resistance and cells proliferation through increasing c-Myc expression in pancreatic cancer. *J Exp Clin Cancer Res* 2019; 38: 463 [PMID: 31718704 DOI: 10.1186/s13046-019-1466-7]

60 Miller AL, Fehling SC, Garcia PL, Gamblin TL, Council LN, van Waardenburg RCAM, Yang ES, Bradner JE, Yoon KJ. The BET inhibitor JQ1 attenuates double-strand break repair and sensitizes models of pancreatic ductal adenocarcinoma to PARP inhibitors. *Ebiomedicine* 2019; 44: 419-430 [PMID: 31126889 DOI: 10.1016/j.ebiom.2019.05.035]

61 Mazur PK, Herner A, Mello SS, Wirth M, Hausmann S, Sánchez-Rivera FJ, Loefgren SM, Kuschma T, Hahn SA, Vangala D, Trajkovic-Arici M, Gupta A, Heid I, Noël PB, Braren R, Erkan M, Kleeff J, Sipos B, Sayles LC, Heikens MA, Heinitzer E, Ellenrieder V, Esposito I, Jacks T, Bradner JE, Khatri P, Sweet-Cordero EA, Attardi LD, Schmid RM, Schneider G, Sage J, Siveke JT. Combined inhibition of BET family proteins and histone deacetylases as a potential epigenetics-based therapy for pancreatic ductal adenocarcinoma. *Nat Med* 2015; 21: 1163-1171 [PMID: 26390243 DOI: 10.1038/nm.3952]

62 Miller AL, Garcia PL, Fehling SC, Gamblin TL, Vance RB, Council LN, Chen D, Yang ES, van Waardenburg RCAM, Yoon KJ. The BET Inhibitor JQ1 Augments the Antitumor Efficacy of Gemcitabine in Preclinical Models of Pancreatic Cancer. *Cancers (Basel)* 2021; 13 [PMID: 34928864 DOI: 10.3390/cancers13143470]

63 Pham TN, Dostert P, Poulopoulos N, Lengauer C, Markert R, Mattison N, Keck M, Orsulic S, Korbelik M, Haber D. Myc-induced bypass of p53 checkpoint and sensitivity to BET inhibition in breast cancer. *Oncogene* 2021; 40: 1924-1936 [PMID: 34104417 DOI: 10.1080/09507992.2021.1884766]

64 Zhen HP, Li GQ, Zhang Y, Guo WZ, Zhang JK, Li J, Lv JF, Zhang SJ. Upregulation of M-cl1 inhibits JQ1-triggered anticancer activity in colorectal cancer cell lines. *Biochem Biophys Res Commun* 2020; 495: 2456-2461 [PMID: 29287727 DOI: 10.1016/j.bbrc.2017.12.153]

65 Liu Y, Xue M, Cao D, Qin L, Wang Y, Miao Z, Wang P, Hu X, Shen J, Xiong B. Multi-omics characterization of Wnt pathway reactivation to ameliorate BET inhibitor resistance in liver cancer cells. *Genomics* 2021; 113: 1057-1069 [PMID: 33667649 DOI: 10.1016/j.ygeno.2020.02.017]

66 Zhu H, Bensghf F, Svoronos N, Rutkowski MR, Billet BG, Allegrezza MJ, Kokkovan Y, Kossenkov AV, Bradner JE, Conne-Garcia JR, Zhang R. BET Bromodomain Inhibition Promotes Anti-tumor Immunity by Suppressing PD-L1 Expression. *Cell Rep* 2016; 16: 2829-2837 [PMID: 27266654 DOI: 10.1016/j.celrep.2016.08.032]

67 Hogg SJ, Vervoort SJ, Deswal S, Ott CJ, Li J, Cluse LA, Beavis PA, Darcy PK, Martin BP, Spencer A, Traunbauer AK, Sadowin I, Bauer K, Valenti P, Bradner JE, Zuber J, Shortt J, Johnstone RW. BET-Bromodomain Inhibitors Engage the Host Immune System and Regulate Expression of the Immune Checkpoint Ligand PD-L1. *Cell Rep* 2017; 18: 2162-2174 [PMID: 28249162 DOI: 10.1016/j.celrep.2017.02.011]

68 Liu K, Zhou Z, Gao H, Yang F, Qian Y, Jin H, Guo Y, Liu Y, Li H, Zhang C, Guo J, Wan Y, Chen R. JQ1, a BET-bromodomain inhibitor, inhibits human cancer growth and suppresses PD-L1 expression. *Cell Biol Int* 2019; 43: 642-650 [PMID: 30958600 DOI: 10.1002/cbin.11139]

69 Liu C, Miao X, Wang Y, Wen L, Cheng X, Kong D, Zhao P, Song D, Wang X, Ding X, Xia H,
Wang W, Sun Q, Gong W. Bromo- and extraterminal domain protein inhibition improves immunotherapy efficacy in hepatocellular carcinoma. *Cancer Sci* 2020; **111**: 3503-3515 [PMID: 32726482 DOI: 10.1111/cas.14588]

73 Liu M, Zhou J, Liu X, Feng Y, Yang W, Wu F, Cheung OK, Sun H, Zeng X, Tang W, Mok MTS, Wong J, Yeung PC, Lai PBS, Chen Z, Jin H, Chen J, Chan SL, Chan AWH, To KF, Sung JJY, Chen M, Cheng AS. Targeting monocyte-intrinsic enhancer reprogramming improves immunotherapy efficacy in hepatocellular carcinoma. *Gut* 2020; **69**: 365-379 [PMID: 31076403 DOI: 10.1136/gutjnl-2018-317257]

74 Montenegro RC, Clark PG, Howarth A, Wan X, Cerone A, Siejka P, Nunez-Alonso GA, Monteiro O, Rogers C, Gamble V, Burbano R, Brennan PE, Tallant C, Ebner D, Fedorov O, O'Neill E, Knapp S, Dixon D, Müller S. BET inhibition as a new strategy for the treatment of gastric cancer. *Oncotarget* 2016; **7**: 43997-44012 [PMID: 27259267 DOI: 10.18632/oncotarget.9766]

75 Zhou S, Zhang S, Wang L, Huang S, Yuan Y, Yang J, Wang H, Li X, Wang P, Zhou L, Xu Y, Gao H, Zhang Y, Lv Y, Zou S. BET protein inhibitor JQ1 downregulates chromatin accessibility and suppresses metastasis of gastric cancer via inactivating RUNX2/NID1 signaling. *Onco genesis* 2020; **9**: 33 [PMID: 32157097 DOI: 10.3843/s41389-020-0218-z]

76 Yin Y, Liu W, Shen Q, Zhang P, Wang L, Tao R, Li H, Ma X, Zeng X, Cheong JH, Song S, Ajani JA, Mills GB, Tao K, Peng G. The DNA Endonuclease Mus81 Regulates ZEB1 Expression and Serves as a Target of BET4 Inhibitors in Gastric Cancer. *Mol Cancer Ther* 2019; **18**: 1439-1450 [PMID: 31142662 DOI: 10.1158/1535-7163.MCT-18-0833]

77 Kim YH, Kim M, Kim JE, Yoo M, Lee HK, Lee CO, Jung KY, Kim Y, Choi SU, Park CH. Novel bromodomain and extraterminal domain protein inhibitors with a unique scaffold exhibit antitumor effects. *Oncol Lett* 2021; **21**: 473 [PMID: 33907583 DOI: 10.3892/ol.2021.12734]

78 Ajani JA, Estrella JS, Chen Q, Correa AM, Ma L, Scott AW, Jin J, Liu B, Xie M, Sudo K, Shiozaki H, Badgwell B, Weston B, Lee JH, Bhutani MS, Onodera H, Suzuki K, Suzuki A, Ding S, Hofstetter WL, Johnson RL, Bresalier RS, Song S. Galectin-3 expression is prognostic in diffuse type gastric adenocarcinoma, confers aggressive phenotype, and can be targeted by YAP1/BET inhibitors. *Br J Cancer* 2018; **118**: 52-61 [PMID: 29136404 DOI: 10.1038/bjc.2017.388]

79 Kang SK, Bae HJ, Kwon WS, Che J, Kim TS, Chung HC, Rha SY. Transcriptome analysis of iBET-151, a BET inhibitor alone and in combination with paclitaxel in gastric cancer cell lines. *Genomics Inform* 2020; **18**: e37 [PMID: 33412753 DOI: 10.5088/GI.2020.18.4.e37]

80 Zengerle M, Chan KH, Ciulli A. Selective Small Molecule Induced Degradation of the BET Bromodomain Protein BRD4. *ACS Chem Biol* 2015; **10**: 1770-1777 [PMID: 26035625 DOI: 10.1021/acschembio.5b00216]

81 Lu Q, Ding X, Huang T, Zhang S, Li Y, Xu L, Chen G, Ying Y, Wang Y, Feng Z, Wang L, Zou X. BRD4 degrader ARV-825 produces long-lasting loss of BRD4 protein and exhibits potent efficacy against cholangiocarcinoma cells. *Am J Transl Res* 2019; **11**: 5728-5739 [PMID: 31632543]

82 Minko T. Nanoformulation of BRD4-Degrading PROTAC: Improving Drugability To Target the ‘Undruggable’ MYC in Pancreatic Cancer. *Trends Pharmacol Sci* 2020; **41**: 688-686 [PMID: 32893006 DOI: 10.1016/j.tips.2020.08.009]

83 Qin AC, Jin H, Song Y, Gao Y, Chen YF, Zhou LN, Wang SS, Lu XS. The therapeutic effect of the BRD4-degrading PROTAC A1874 in human colon cancer cells. *Cell Death Dis* 2020; **11**: 805 [PMID: 33404602 DOI: 10.1038/s41419-020-03015-6]

84 Shirasaki R, Matthews GM, Gandolfi S, de Matos Simoes R, Buckley DL, Raja Vora J, Sievers QL, Brüggenthies JB, Dashevsky O, Pourhesh M, Harb W, Pelegurco J, Smith DC, Piha-Paul SA, Szmulwitz R, Noél MS, Yeleswarapu S, Liu P, Switzky J, Zhou G, Zheng F, Mehta A. Development of 2 Bromodomain and Extraterminal Inhibitors With Distinct Pharmacokinetic and Pharmacodynamic Profiles for the Treatment of Advanced Malignancies. *Cancer Res* 2020; **80**: 1247-1257 [PMID: 31527168 DOI: 10.1158/1078-0432.CCR-18-4071]

85 Ott E, Schmidt S, Kastner C, Denk S, Kettler J, Müller N, Gerner CT, Wolf E, Gallant P, Wiegerson A. Targeting bromodomain-containing protein 4 (BRD4) inhibits MYC expression in colorectal cancer cells. *Neoplasia* 2019; **21**: 1110-1120 [PMID: 31734632 DOI: 10.1016/j.neo.2019.10.003]

86 Alqahtani A, Choucar A, Ashraf M, Hammouda DM, Alloghbi A, Khan T, Senzer N, Nemunaitis J. Bromodomain and extra-terminal motif inhibitors: a review of preclinical and clinical advances in cancer therapy. *Future Sci OA* 2019; **5**: FSO372 [PMID: 30906568 DOI: 10.4155/fsoa-2018-0115]

87 Xie F, Huang M, Lin X, Liu C, Liu Z, Meng F, Wang C, Huang Q. The BET inhibitor I-BET762 inhibits pancreatic ductal adenocarcinoma cell proliferation and enhances the therapeutic effect of gemcitabine. *Sci Rep* 2018; **8**: 8102 [PMID: 29802402 DOI: 10.1038/s41598-018-26496-0]

88 Falchook G, Rosen S, LoRusso P, Watts J, Gupta S, Coombs CC, Talpaz M, Kurzrock R, Mita M, Cassaday R, Harb W, Pequero J, Smith DC, Piha-Paul SA, Szmulwitz R, Noél MS, Yeleswarapu S, Liu P, Switzky J, Zhou G, Zheng F, Mehta A. Development of 2 Bromodomain and Extraterminal Inhibitors With Distinct Pharmacokinetic and Pharmacodynamic Profiles for the Treatment of Advanced Malignancies. *Clin Cancer Res* 2020; **26**: 1247-1257 [PMID: 31527168 DOI: 10.1158/1078-0432.CCR-18-4071]

89 Leaf AS, Liu P, Krieger-Burke T, Ruggeri B, Liby KT. The Bromodomain Inhibitor, INCB057643, Targets Both Cancer Cells and the Tumor Microenvironment in Two Preclinical Models of
Cholangiocarcinoma. DNA Damage and Apoptosis, and Inhibits Tumor Growth in a Patient-Derived Xenograft Model of Richardson JH, Cui X, van Waardenburg RCAM, Bradner JE, Yang ES, Yoon KJ. JQ1 Induces Sensitivity to BET Inhibitors. Super-Enhancers to Induce Gender-Specific Squamous-like Pancreatic Cancer and Confers Andricovich J DOI: 10.1126/science.aaz8455

SLUG-induced side population phenotype of HCT116 human colorectal cancer cells and its effects can be ameliorated using the BET inhibitor apabetalone. colorectal cancer prognosis by facilitating tumour growth and caveolin-1-dependent invasiveness, and these effects can be ameliorated using the BET inhibitor apabetalone. Kato Y, Kondo S, Itakura T, Tokunaga M, Hatayama S, Katayama K, Sugimoto Y. SNAIL- and AURK-A Activates Super-Enhancers to Induce Gender-Specific Squamous-like Pancreatic Cancer and Confers Sensitivity to BET Inhibitors. Cancer Cell 2018; 33: 512-526.e8 DOI: 10.1016/j.ccell.2018.02.003

Garcia PL, Miller AL, Gamblin TL, Council LN, Christein JD, Arnoletti JP, Heslin MJ, Reddy S, Richardson JD, Xi X, van Waardenburg RCAM, Bradner JE, Yang ES, Yoon KJ. JQ1 Induces DNA Damage and Apoptosis, and Inhibits Tumor Growth in a Patient-Derived Xenograft Model of Cholangiocarcinoma. Mol Cancer Ther 2018; 17: 107-118 DOI: 10.1158/1535-7163.MCT-16-0922
