YALE JOURNAL OF BIOLOGY AND MEDICINE 90 (2017), pp.63-71.

REVIEW

YJBM

# A Novel Epi-drug Therapy Based on the Suppression of BET Family Epigenetic Readers

Dong-Guk Shin[a] and Dashzeveg Bayarsaihan[b,*]

[a]*The Computer Science and Engineering Department University of Connecticut, Storrs, CT;* [b]*Institute for System Genomics and Center for Regenerative Medicine and Skeletal Development, University of Connecticut Health Center, Farmington, CT*

Recent progress in epigenetic research has made a profound influence on pharmacoepigenomics, one of the fastest growing disciplines promising to provide new epi-drugs for the treatment of a broad range of diseases. Histone acetylation is among the most essential chromatin modifications underlying the dynamics of transcriptional activation. The acetylated genomic regions recruit the BET (bromodomain and extra-terminal) family of bromodomains (BRDs†), thereby serving as a molecular scaffold in establishing RNA polymerase II specificity. Over the past several years, the BET epigenetic readers have become the main targets for drug therapy. The discovery of selective small-molecule compounds with capacity to inhibit BET proteins has paved a path for developing novel strategies against cancer, cardiovascular, skeletal, and inflammatory diseases. Therefore, further research into small chemicals impeding the regulatory activity of BRDs could offer therapeutic benefits for many health problems including tumor growth, heart disease, oral, and bone disorders.

## INTRODUCTION

Histone acetylation is one of the most critical chromatin remodeling processes underlying the dynamics of open chromatin architecture and transcriptional activation [1,2]. The addition and removal of acetyl groups on lysine residues of histones and other regulatory proteins is catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs). The relaxed chromatin segments are recognized by bromodomains (BRDs) that bind to the acetylated nucleosomes, transcription factors and co-activators [3]. The binding property of BRDs could be explained by the presence of a deep, largely hydrophobic acetyl-lysine binding pocket composed of a conserved 110 amino acid domain [4].

The human proteome is comprised of 61 bromodomains, including the BET (bromodomain and extra-terminal) family possessing two tandem BRDs (BD1 and BD2) and an extra-terminal (ET) domain [5,6]. Although the BD1 of the BET family interacts with nucleosomes, the acetylated bromodomain complex is further stabilized via interactions with DNA and specific nuclear factors [7]. The ability of the ET domain to bind regulatory proteins including histone methyltransferase NSD3 has been shown to play a significant role in the positive transcription elongation factor b (p-TEFb)-independent transcriptional activation [8]. Surprisingly, the same study revealed that BRD4/NSD3 complex regulates H3K36 methylation at the BRD4-bound region.

Recent advancement in epigenetics has made a profound impact on pharmacoepigenomics, a newly grown discipline, which holds promise of providing personal-

*To whom all correspondence should be addressed: Dashzeveg Bayarsaihan, email: dashzeveg@uchc.edu, Tel: 860-679-5456.

†Abbreviations: BET, bromodomain and extra-terminal family; BRDs, bromodomains; eRNA, enhancer RNA; ESC, embryonic stem cells; HATs, histone acetyltransferases; HDACs, histone deacetylases; JAK/STAT, Janus kinase/signal transducing and activator of transcription; lncRNA, long non-coding RNA; RNAPII, RNA Polymerase II.

Keywords: bromodomains, the BET family, histone acetylation, drugs, inhibitors, epigenetics

ized therapy [9]. In the past several years, a broad spectrum of chemical compounds against DNA methyltransferases, microRNAs, and histone deacetylases has been tested to treat different disorders [10,11]. Instead of aiming at single site, a new combinatorial approach explores multi-targeted options using several epigenetic-based drugs (epi-drugs) as a possible solution to increase efficacy of drug therapy [12]. Among the epi-drug candidates, inhibitors of BRDs have demonstrated positive effects in both solid and hematologic malignancies, including brain tumors [13].

Although the BET family of epigenetic "reader" proteins (BRD2, BRD3, BRD4, and BRDT) is the primary target for small chemicals like JQ1, I-BET, and MS417, more refined analysis of chromatin recognition by the non-BET bromodomains is a necessary step toward advancing novel therapeutic strategies [14]. Several compounds interfering with BET readers are currently undergoing clinical trials for treating hematological malignancies, solid tumors, and cardiovascular, inflammatory, and autoimmune diseases [15-18]. Moreover, as pharmaceutical companies pursue a more effective therapy based on drug synergy, suppression of other BRDs including non-BET bromodomain proteins has the potential to increase the chemotherapeutic efficacy of novel epigenetic-based medications [18-21]. Here, we review and discuss different BET protein inhibitors and their applications for major diseases.

## MOLECULAR MECHANISMS UNDERLYING INHIBITION OF THE BET FAMILY

Mechanistically, BRDs recruit nuclear factors to the acetylated enhancer elements tightly linked to regulation of the lineage-specific genes [22]. The BET family is enriched at super-enhancers (SEs), the long genomic stretches composed of regular enhancer elements [23]. Although the mammalian genome contains millions of putative enhancers, a relatively small subset of SEs is engaged in transcriptional activation in any given cell type. The selection of cell-specific enhancers involves the recruitment of master transcription factors defining cell fate decisions. Additionally, the function of enhancers and SEs is influenced by high-order chromatin structure [24]. In the linear genome, the super-enhancer region is composed of a cluster of regulatory elements densely occupied by transcription factors specifying cell identity [25]. Witter et al. proposed that SEs serve as the crucial transcriptional hubs for coordinating intrinsic and extrinsic signaling pathways, and argue that decoding these control regions is an essential step toward deciphering the molecular pathways of cell fate decisions [26]. Therefore, differential distribution of BET readers across SEs could provide novel insights into lineage determination, tissue malignancy, complex diseases, and developmental disorders [27].

The collected evidence suggests that master transcription factors, p300/CBP, BRDs, as well as Mediator are enriched at SEs, a prerequisite for a coordinated regulation of lineage specification [28-30]. The crosstalk between BRD4 and Mediator is functionally implicated in transcriptional activation of genes important for the maintenance of acute myeloid leukemia [31]. BRD4 recruits Mediator and CDK9, the catalytic subunit of p-TEFb, to the regulatory regions of pluripotency factors *OCT4* and *PRDM14*, a critical intermediate phase in assisting RNA Polymerase II (RNAPII) progression through the hyperacetylated genomic regions [32]. Upon epithelial-to-mesenchymal transition, the transcription factors ETS2, HNF4A, and JUNB co-occupy SEs in an intermediate phase, facilitating an assembly of a regulatory hub that is highly sensitive to BET inhibition [33].

Interestingly, SEs are also linked to the production of enhancer RNAs (eRNAs), a subgroup of regulatory RNAs of cell fate decision [34]. As a general rule, SEs function mostly through long-range genomic interactions; for example, the *MYC* super-enhancer, enriched in BRD2, is located approximately 1.7 Mb downstream of transcription start site controlling expression of *MYC* during hematopoiesis [35]. Nagarajan et al. reported that the association of BRD4 with H3K27ac-enriched SEs is a prerequisite for the recruitment and elongation of RNAPII at enhancers producing the estrogen receptor α (ERα)-dependent eRNAs [36]. Collectively, the presented evidence indicates that BRD4 controls the ERα-associated cell proliferation and tumorigenesis by altering phosphorylation of RNAPII and histone H2B monoubiquitination. This finding is consistent with another report showing that BRD4 stimulates elongation of both protein-coding transcripts and noncoding eRNAs [37].

## BROMODOMAIN INHIBITORS

### *JQ1 Inhibitor*

BRD2 and BRD4 are involved in the regulation of antioxidant genes and therefore their inhibition could enhance antioxidant responses in lung diseases [38,39]. The impaired activation of NRF2, a transcription factor required for the control of antioxidant and cytoprotective genes, is one of the causative factors of chronic obstructive pulmonary disease associated with oxidative stress. The JQ1-specific inhibition of BRDs boosts the production of the NRF2-dependent antioxidant proteins such as heme oxygenase-1, NADPH quinone oxidoreductase 1, and glutamate-cysteine ligase catalytic subunit, thereby reducing the production of intracellular reactive oxygen species [39]. Tang et al. showed that during progressive

idiopathic pulmonary fibrosis, JQ1 attenuates the enhanced migration, proliferation, and *IL-6* release in lung fibroblasts [40]. These changes were followed by an elevation of H4K5ac marks and increased binding of BRD4 over genes linked to the profibrotic response.

A novel therapeutic strategy for treating selective proliferative diseases is based on inhibition of STAT3 mono-ubiquitination [41]. The modified form of STAT3 regulates cell cycle progression and apoptosis by recruiting BRD4 to the *SOCS3* gene, the suppressor of cytokine signaling. The functional significance of BRD4 in the STAT3-mediated transcription was validated using BET inhibitor; treatment with JQ1 attenuates *SOCS3* expression [41]. STAT5 regulates genes that are necessary for proliferation, survival, and self-renewal and participates in a broad range of leukemias and lymphomas. By attenuating the activity of BRD2, JQ1 was shown to block the STAT5-mediated regulation of target genes [42]. The proliferation of large B-cell lymphomas could also be inhibited by the initial G1 arrest followed by either apoptosis or senescence [43]. The JQ1-mediated suppression of BRD4 triggers the Caspase 3/7-initiated apoptosis and DNA damage response in the leukemia cells carrying *DNMT3A* mutation [44]. In experimental models of multiple myeloma, an antiproliferative effect of JQ1 is associated with cell-cycle arrest and cellular senescence; mechanistically, JQ1 down-regulates expression of *MYC* and its downstream target genes [45]. JQ1 inhibits transcriptional activity of STAT5 resulting in impaired maturation of human monocyte-derived dendritic cells, and therefore could be beneficial in treating T cell-mediated inflammatory diseases [46]. BET targeting of Th17 cells has been recently proposed as a potential therapeutic approach for a wide range of inflammatory and autoimmune diseases [47]. JQ1, together with another BET inhibitor I-BET151, is able to ameliorate the progression of inflammation in experimental autoimmune uveitis reducing levels of Th17 cells.

JQ1 causes significant decrease of *MYC* and *RUNX3* expression leading to apoptosis in NK/T-cell lymphoma cells [48]. JQ1 initiates tumor suppressive effects by effectively blocking the MYC-AP4 dependent pathway [49]. Hence, epi-drugs suppressing BET proteins could become a novel therapeutic strategy in treating MYC-dependent tumors. JQ1 interferes with p53 recruitment to cell death genes, which is sponsored by BRD4 in a MYC-independent fashion [50]. For instance, in medulloblastoma cells, JQ1 affects cell cycle progression by altering signaling pathway mediated by MYC and p53. In pediatric B-precursor cells, the protein stability of MYC and the progression of DNA replication are dependent on BET inhibition [51]. Additionally, JQ1 was reported to impede *MYC* transcription and acute lymphoblastic leukemia growth [52]. In multiple myeloma cells, the suppression of *MYC* by JQ1 results in down-regulation of the *IRF4* gene, a direct target of MYC/miR-125b-5p pathway [53]. The results obtained by Wang et al. suggested that JQ1 raises the effect of radiotherapy while reducing the radioresistance in non-small cell lung cancer cell lines through a *c-MYC*-independent mechanism [54]. BET interference can serve as a potential therapeutic strategy for the treatment of degenerative retinal diseases [55]. According to Zhao et al., JQ1 rescues photoreceptor degeneration by inhibiting retinal microglial activation.

JQ1 displays a synergistic effect with HDAC inhibitors SAHA and vincristine in leukemia treatment [56]. The similar research using JQ1 and the HDAC inhibitor panobinostat has revealed promising results in the treatment of acute myelogenous leukemia [57]. Both drugs can work synergistically inducing leukemia cell apoptosis, while hematopoietic progenitor cells stayed unaffected. A synergistic effect was also observed between JQ1 and venetoclax in T-cell acute lymphoblastic leukemia cell line and patient-derived xenograft models [58]. The synergy between JQ1 and the polo-like kinase 1 inhibitor volasertib augmented cell death in metastatic breast cancer cells [59]. The treatment with JQ1 causes growth retardation and induces apoptosis of myeloproliferative neoplasms [60]. The addition of ruxolitinib, a JAK1 and 2 kinase inhibitor of JAK/STAT signaling, to the JQ1 treatment facilitates a more robust apoptosis of target cells, suggesting synergistic drug response against myelofibrosis.

Type II testicular germ cell cancers, the most frequently diagnosed tumours in young men, were recently treated with BET inhibitor [61]. JQ-treated embryonal carcinoma cells xenografted *in vivo* showed tumour size reduction, proliferation rate, and angiogenesis. The combination of JQ1 and romidepsin, the HDAC inhibitor, has been shown to be more effective than a single administration of JQ1.

The occupancy of BRDs at *GLI1* and *GLI2* promoters has been implicated in Hedgehog signaling [62]. The JQ1-mediated interference with bromodomain binding is considered to be an efficient strategy for treating human defects caused by Hedgehog pathway, including atypical teratoid rhabdoid tumors, medulloblastoma, and basal cell carcinoma. The inhibition of BRD4 was suggested to protect against renal fibrosis by blocking the TGF-β-Nox4-ROS-fibrosis pathway [63]. JQ1 prevents the progression of fibrosis in rats causing decreased expression of fibrotic genes and TGFβ1-dependent *Nox4* gene involved in the generation of hydrogen peroxide.

In primary skeletal muscle cells, BRD4/SMYD3 binds to the regulatory elements of *Myostatin* and *c-Met* pausing p-TEFb binding and initiating RNAPII elongation [64]. As a consequence, JQ1 attenuates the *Myostatin* and *Atrogene* up-regulation, thus preventing skeletal

muscle atrophy. In another study, inhibition of BRDs by JQ1 was shown to activate transcription of TAZ, a key transcriptional mediator of Hippo pathway, which in turn attenuates Wnt/β-catenin activity, inducing cell cycle arrest, and preventing colon cancer cell growth [65].

According to Liu et al., BRD4 increases transcriptional elongation of pluripotency genes by dissociating p-TEFb from an inactive transcriptional complex containing HEXIM1, whereas the master regulator KLF4 works antagonistically by recruiting p-TEFb near the promoters of pluripotency genes [66]. Upon ESC differentiation, *Oct4*, *Nanog*, as well as some lineage-specific genes, are recognized by BRD4 [67]. JQ1 shifts the differentiation potential of ESCs towards the endodermal lineage by restricting BRD4 access at target loci.

7SK, a small nuclear RNA (snRNA), inhibits enhancer transcription by modulating nucleosome position [68]. In mammalian cells, the occupancy of 7SK at enhancers and SEs restricts eRNA production through a promoter pausing-independent mechanism. With the assistance of 7SK, the BAF-remodeling complex binds to enhancers, inhibiting enhancer transcription and altering local chromatin structure. It was documented that the co-occupancy of 7SK and BRD4 at SEs is sensitive to JQ1. Yokoyama et al. reported that inhibition of *ALDH1A1* expression JQ1 abrogates aldehyde dehydrogenase activity by blocking the recruitment of BRD4 to a super-enhancer and associated eRNA [69]. Collectively, this work revealed that inhibition of BRD4 with JQ1 could be a promising strategy for the treatment of epithelial ovarian cancer.

The activation of SIRT1, a member of Sirtuin family of NAD-dependent deacetylases, is linked to metabolic and inflammatory diseases [70]. JQ1 up-regulates SIRT1 and reverses the pro-inflammatory effect of SIRT1 silencing suggesting that suppression of BET proteins could become a novel strategy for the treatment of the age-related metabolic conditions. JQ1 prevents the estrogen-induced shift of RNAPII from initiation to elongation phases by pausing transcriptional machinery at the target gene promoters [71]. However, mechanistically JQ1 does not interfere with the recruitment of ERα and histone acetylation at the bound regions.

### *Other Bromodomain Inhibitors*

I-BET151 is a small molecule inhibitor of the BET family capable of inducing early cell cycle arrest and apoptosis [72]. It has also been found to possess a profound efficacy against leukemic cell lines. Similarly, the study by Dawson et al. demonstrated that transcriptional program facilitating leukemia development is sensitive to I-BET151 treatment [73]. In melanoma, I-BET151 suppresses the NF-kB signaling pathway by blocking transcription of a group of the NF-kB-dependent genes linked to inflammation and cell cycle progression [74]. In the LPS-stimulated RAW2647 cells, expression of *IL-6* is selectively inhibited with I-BET151, whereas transcription of other cytokine genes does not exhibit sensitivity to BET inhibition [75]. Although the occupancy of CBP at the *IL-6* promoter can be blocked by I-BET151, the physical and chemical properties of p65-NF-κB such as acetylation, phosphorylation, nuclear translocation, and chromatin recognition are not affected. Like JQ1, I-BET151 induces apoptosis and antiproliferation through processes associated with inhibition of p-TEFb by MYC and a general transcription regulator HEXIM [76]. I-BET151 blocks the recruitment of p-TEFb mediated by BRDs, thereby causing transcriptional repression of genes regulated by MYC. Surprisingly, the treatment of glioblastoma multiforme cells with I-BET151 can reduce levels of *HOTAIR*, the tumor-promoting lncRNA *HOX* antisense RNA [77]. BRD4 participates in the regulation of lncRNA expression by binding to the *HOTAIR* promoter. BET protein inhibition by I-BET151 is also considered effective against myeloproliferative neoplasms [78]. A constitutively expressed form of JAK2 kinase is active in erythroleukemic cells and erythroid precursors isolated from polycythemia vera patients. According to Wyspiańska et al., I-BET151 is quite effective against myeloproliferative neoplasms [78]. In glioblastoma multiforme, the most common primary brain tumor, I-BET151 disrupts BRD4 recruitment to the bound genes affecting cell cycle progression [79].

I-BET726 represents a new class of tetrahydroquinoline-based BET inhibitors, which is effective in septic shock and neuroblastoma [80]. I-BET762, another highly specific compound, is able to suppress the *MYC* expression in cancer cells [81,82]. In multiple myeloma cells, a novel inhibitor CG13250 is capable of suppressing the *MYC* transcription by impeding BRD4 binding to the *MYC* promoter [83]. The BET protein inhibitor RVX-208 mediates the antiatherogenic effect by interfering with BD1 of the BET family [84,85]. New research showed that RVX-208 contributes to the risk of cardiovascular disease by elevating the activity of the main protein component apolipoprotein A-I while suppressing pro-inflammatory, pro-atherosclerotic, and pro-thrombotic pathways [86]. The synergy between RVX-2135 and HDAC inhibition effectively reduces proliferation and induces apoptosis of lymphoma cells [87]. Conversely, RVX-297 executes its function by preferential binding to BD2 of BET proteins [88]. In diabetic kidney disease, MS417, another BET family inhibitor, hinders acetylation-mediated interaction of p65 and STAT3 with BRDs, thereby reducing proteinuria and the occurrence of kidney failure [89]. Blocking the activity of BRD4 by MS417 substantially reduces metastasis in colorectal cancer [90]. In mantle cell lymphoma, a combined treatment with CPI-

203, a BET family inhibitor, and lenalidomide, a derivative of thalidomide, has a synergistic effect on cell death induction, which is followed by the reduced expression of *MYC* and *IRF4* [91]. CPI-203 and bortezomib have been shown to display synergistic effects in drug resistant myeloma [92]. In multiple myeloma, the therapeutic activity of CPI-0610, which blocks BD1 of BET readers, works through G1 cell cycle arrest and caspase-dependent cell death associated with inhibition of *MYC*, *IKZF1* and *IRF4* [93]. Although interference of BD1 of BET proteins via small-molecule inhibitor Olinone was documented to accelerate the differential potential of mouse primary oligodendrocytes, the impediment of both bromodomains, BD1 and BD2, interferes with cell differentiation [94].

Recently, a novel strategy has been developed where a BRD inhibitor is capable of simultaneously binding to both bromodomains within a single BET protein [95]. For instance, AZD5153, possessing a bivalent binding mode, works as a selective BRD4 inhibitor [96]. The BET family inhibitor OTX015, on the other hand, has been designed to selectively bind to bromodomains 2, 3, and 4 [97]. The antiproliferative effect of OTX015 is accompanied by down-regulation of *MYC* in breast cancer cells, and this activity is synergistic with the mTOR inhibitor everolimus [98]. The treatment of anaplastic large cell lymphomas with OTX015 causes cell cycle arrest and down-regulation of *MYC*, *E2F2*, *FOS*, *JUNB*, and *ID1* [99]. A small chemical SF1126, originally developed as a PI3K inhibitor, obstructs BRD4 binding in neuroblastoma cells [100]. SF1126 can suppress the expression of *MYC* resulting in decreased neuroblastoma cell viability.

## THE BET PROTEIN INHIBITION IN ORAL HEALTH AND BONE DISEASE

A recent report by Baudhuin et al. revealed that the BET inhibition increases the trabecular bone volume and restores mechanical properties, thereby preventing bone loss during osteoporosis [101]. JQ1 attenuates osteoclast differentiation and osteoblastogenesis by inhibiting expression of NFATc1 and Runx2, the master regulators of osteoclast and osteoblast differentiation, respectively. Niu et al. demonstrated that BET inhibition has side effects on skeletal structure associated with suppression of chondrocyte differentiation and bone growth restriction [102]. In the chondrogenic cell lineage, BET inhibitors reduce the expression of *Col2a1*. Using the transgenic zebrafish line, the authors showed that I-BET151 and JQ1 influence chondrocyte differentiation and inhibit *Danio* growth. It is likely that BET inhibition abolishes the RNAPII recruitment at the *Col2a1* promoter via the BRD4-dependent mechanism. BRD4 can also initiate osteoblast differentiation by promoting lineage-specific gene expression [103]. It was demonstrated that BRD4 binds to the promoters of differentiation-induced genes. Moreover, BRD4 along with the transcription factors C/EBPb, TEAD1, FOSL2, and JUND, co-occupies the osteoblast-specific enhancers [103].

In gingival tissues affected by inflammation, JQ1 has a significant effect on the expression of lipopolysaccharide-stimulated inflammatory cytokine genes *IL-1β*, *IL-6*, and *TNF-α*, and the osteoclast markers *c-Fos*, *NFATc1*, *TRAP*, and *cathepsin K* [104]. Therefore, JQ1 is considered to be a promising epi-drug for treating periodontitis. JQ1 suppresses transcription of *TLR2/4* and impedes NF-κB phosphorylation and nuclear translocation [104]. The authors proposed that JQ1 prevents the enrichment of BRD4 at the promoters of *NF-κB*, *TNF-α*, *c-Fos*, and *NFATc1*. Remarkably, in murine periodontal tissues, alveolar bone loss caused by reduced osteoclasts could be alleviated after JQ1 treatment [104].

JQ1 specifically affects growth of mesenchymal stem cells by inhibiting Wnt signaling causing down-regulation of genes involved in self-renewal, cell cycle, DNA replication, and mitosis [105]. Although JQ1 facilitates cell cycle arrest in G1 phase, it does not induce apoptosis or senescence. In osteosarcoma cells, JQ1 attenuates cell viability and attenuates osteoblast differentiation [106]. The release of BRD4 from acetylated chromatin by JQ1 triggers silencing of *MYC* and *RUNX2* transcription reducing differentiation of osteoclasts.

## CONCLUSION AND OUTLOOK

In recent years, inhibition of the BET family of epigenetic readers has gained a lot of attention due to specific and efficient targeting of BRD4 and other BET proteins involved in transcriptional activation. A range of chemical compounds specific to BET activity is currently being tested in clinical trials and the development of novel chemicals against specific epigenetic marks has the potential to offer effective therapies in the near future [107]. However, among existing small molecules, none exhibits a selective effect on a single BET protein; the known chemical agents do not specifically distinguish between BRD4 and other BET proteins, which possess partially overlapping functions but not redundant with BRD4 [108]. Although a number of clinical trials showed encouraging preliminary findings, there are concerns of toxicity caused by BET inhibition, as well as the development of resistance.

In the context of erythroid cells, in-depth investigation of BRDs has helped delineate distinct and overlapping roles of BET readers [109]. It is well documented that BET inhibition reduces proliferation of multiple myeloma, leukemia, and NUT midline carcinoma (NMC), a rare aggressive subtype of squamous cell cancer [110]. In NMC, BRD3 and BRD4 are fused to the NUT protein

thus acting as dominant oncoproteins. It was proposed that BRD4-NUT recruits p300/CBP to initiate chromatin hyperacetylation to attract additional BRD4 supporting transcriptional upregulation [111]. This is in contradiction with another observation showing that p300 sequestration into the BRD4-NUT-rich loci creates inactive hyperacetylated chromatin leading to p53 inactivation [112]. Therefore, additional research dissecting distinct steps in chromatin recognition by BET family members will shed light on context-dependent differences in transcriptional responses.

In summary, a dynamic interplay between the genome and bromodomains underlies cell type-specific enhancer activation and RNAPII elongation and therefore, the efficacy and safety of epigenetic therapy, at least in part, is dependent on the functional relationship between BET proteins and other key epigenetic factors.

## REFERENCES


1. Dutta A, Abmayr SM, Workman JL. Diverse Activities of Histone Acylations Connect Metabolism to Chromatin Function. Mol Cell. 2016;63(4):547-52.
2. Bayarsaihan D. Deciphering the Epigenetic Code in Embryonic and Dental Pulp Stem Cells. Yale J Biol Med. 2016;89(4):539-563.
3. Fu LL, Tian M, Li X, Li JJ, Huang J, Ouyang L, et al. Inhibition of BET bromodomains as a therapeutic strategy for cancer drug discovery. Oncotarget. 2015;6(8):5501-16.
4. Fujisawa T, Filippakopoulos P. Functions of bromodomain-containing proteins and their roles in homeostasis and cancer. Nat Rev Mol Cell Biol. 2017. in press.
5. Taniguchi Y. The Bromodomain and Extra-Terminal Domain (BET) Family: Functional Anatomy of BET Paralogous Proteins. Int J Mol Sci. 2016;17(11).
6. Ferri E, Petosa C, McKenna CE. Bromodomains: Structure, function and pharmacology of inhibition. Biochem Pharmacol. 2016;106:1-18.
7. Miller TC, Simon B, Rybin V, Grötsch H, Curtet S, Khochbin S, et al. A bromodomain-DNA interaction facilitates acetylation-dependent bivalent nucleosome recognition by the BET protein BRDT. Nat Commun. 2016;7:13855.
8. Rahman S, Sowa ME, Ottinger M, Smith JA, Shi Y, Harper JW, et al. The Brd4 extraterminal domain confers transcription activation independent of pTEFb by recruiting multiple proteins, including NSD3. Mol Cell Biol. 2011;31(13):2641-52.
9. Majchrzak-Celińska A, Baer-Dubowska W. Pharmacoepigenetics: an element of personalized therapy? Expert Opin Drug Metab Toxicol. 2016;28:1-12.
10. Chistiakov DA, Myasoedova VA, Orekhov AN, Bobryshev YV. Epigenetically active drugs inhibiting DNA methylation and histone deacetylation. Curr Pharm Des. 2016; in press
11. Salarinia R, Sahebkar A, Peyvandi M, Mirzaei HR, Jaafari MR, Riahi MM, et al. Epi-Drugs and Epi-miRs: Moving Beyond Current Cancer Therapies. Curr Cancer Drug Targets 2016;16(9):773-788.
12. Benedetti R, Conte M, Iside C, Altucci L. Epigenetic-based therapy: From single- to multi-target approaches. Int J Biochem Cell Biol. 2015;69:121-31.
13. Wadhwa E, Nicolaides T. Bromodomain Inhibitor Review: Bromodomain and Extra-terminal Family Protein Inhibitors as a Potential New Therapy in Central Nervous System Tumors. Cureus. 2016;8(5):e620.
14. Chiang CM. Phospho-BRD4: transcription plasticity and drug targeting. Drug Discov Today Technol. 2016;19:17-22.
15. Ghoshal A, Yugandhar D, Srivastava AK. BET inhibitors in cancer therapeutics: a patent review. Expert Opin Ther Pat. 2016;26(4):505-22.
16. Noguchi-Yachide T. BET Bromodomain as a Target of Epigenetic Therapy. Chem Pharm Bull. (Tokyo). 2016;64(6):540-7.
17. Shu S, Polyak K. BET Bromodomain Proteins as Cancer Therapeutic Targets. Cold Spring Harb Symp Quant Biol. 2017; in press
18. Suarez-Álvarez B, Rodríguez RM, Ruiz-Ortega M, López-Larrea C. Bet proteins: an approach to future therapies in transplantation. Am J Transplant. 2017; in press.
19. Smith SG, Zhou MM. The Bromodomain: A New Target in Emerging Epigenetic Medicine. ACS Chem Biol. 2016;11(3):598-608.
20. Romero FA, Taylor AM, Crawford TD, Tsui V, Côté A, Magnuson S. Disrupting Acetyl-Lysine Recognition: Progress in the Development of Bromodomain Inhibitors. J Med Chem. 2016;59(4):1271-98.
21. Padmanabhan B, Mathur S, Manjula R, Tripathi S. Bromodomain and extra-terminal (BET) family proteins: New therapeutic targets in major diseases. J Biosci. 2016;41(2):295-311.
22. Shi J, Vakoc CR. The mechanisms behind the therapeutic activity of BET bromodomain inhibition. Mol Cell. 2014;54(5):728-36.
23. Blinka S, Reimer MH Jr, Pulakanti K, Rao S. Super-Enhancers at the Nanog Locus Differentially Regulate Neighboring Pluripotency-Associated Genes. Cell Rep. 2016;17(1):19-28.
24. Heinz S, Romanoski CE, Benner C, Glass CK. The selection and function of cell type-specific enhancers. Nat Rev Mol Cell Biol. 2015;16(3):144-54.
25. Pott S, Lieb JD. What are super-enhancers? Nat Genet. 2015;47(1):8-12.
26. Witte S, O'Shea JJ, Vahedi G. Super-enhancers: Asset management in immune cell genomes. Trends Immunol. 2015;36(9):519-26.
27. Niederriter AR, Varshney A, Parker SC, Martin DM. Super Enhancers in Cancers, Complex Disease, and Developmental Disorders. Genes (Basel). 2015;6(4):1183-200.
28. Whyte WA, Orlando DA, Hnisz D, Abraham BJ, Lin CY, Kagey MH, Rahl PB, Lee TI, Young RA. Master transcription factors and mediator establish super-enhancers at key cell identity genes. Cell. 2013;153(2):307-19.
29. Yin JW, Wang G. The Mediator complex: a master coordinator of transcription and cell lineage development. Development. 2014;141(5):977-87.
30. Lovén J, Hoke HA, Lin CY, Lau A, Orlando DA, Vakoc CR, Bradner JE, Lee TI, Young RA. Selective inhibition of tumor oncogenes by disruption of super-enhancers. Cell.

2013;153(2):320-34.
31. Bhagwat AS, Roe JS, Mok BY, Hohmann AF, Shi J, Vakoc CR. BET Bromodomain Inhibition Releases the Mediator Complex from Select cis-Regulatory Elements. Cell Rep. 2016;15(3):519-30.
32. Di Micco R, Fontanals-Cirera B, Low V, Ntziachristos P, Yuen SK, Lovell CD, Dolgalev I, Yonekubo Y, Zhang G, et al. Control of embryonic stem cell identity by BRD4-dependent transcriptional elongation of super-enhancer-associated pluripotency genes. Cell Rep. 2014;9(1):234-47.
33. Chang H, Liu Y, Xue M, Liu H, Du S, Zhang L, et al. Synergistic action of master transcription factors controls epithelial-to-mesenchymal transition. Nucleic Acids Res. 2016;44(6):2514-27.
34. Hah N, Benner C, Chong LW, Yu RT, Downes M, Evans RM. Inflammation-sensitive super enhancers form domains of coordinately regulated enhancer RNAs. Proc Natl Acad Sci U S A. 2015;112(3):E297-302.
35. Pinz S, Unser S, Rascle A. Signal transducer and activator of transcription STAT5 is recruited to c-Myc super-enhancer. BMC Mol Biol. 2016;17:10.
36. Nagarajan S, Hossan T, Alawi M, Najafova Z, Indenbirken D, Bedi U, Taipaleenmäki H, Ben-Batalla I, Scheller M, et al. Bromodomain protein BRD4 is required for estrogen receptor-dependent enhancer activation and gene transcription. Cell Rep. 2014;8(2):460-9.
37. Kanno T, Kanno Y, LeRoy G, Campos E, Sun HW, Brooks SR, Vahedi G, Heightman TD, Garcia BA, et al. BRD4 assists elongation of both coding and enhancer RNAs by interacting with acetylated histones. Nat Struct Mol Biol. 2014;21(12):1047-57.
38. Michaeloudes C, Mercado N, Clarke C, Bhavsar PK, Adcock IM, Barnes PJ, et al. Bromodomain and extraterminal proteins suppress NF-E2-related factor 2-mediated antioxidant gene expression. J Immunol. 2014;192(10):4913-20
39. Hussong M, Börno ST, Kerick M, Wunderlich A, Franz A, Sültmann H, et al. The bromodomain protein BRD4 regulates the KEAP1/NRF2-dependent oxidative stress response. Cell Death Dis. 2014;5:e1195.
40. Tang X, Peng R, Phillips JE, Deguzman J, Ren Y, Apparsundaram S, et al. Assessment of Brd4 inhibition in idiopathic pulmonary fibrosis lung fibroblasts and in vivo models of lung fibrosis. Am J Pathol. 2013;183(2):470-9.
41. Ray S, Zhao Y, Jamaluddin M, Edeh CB, Lee C, Brasier AR. Inducible STAT3 NH2 terminal mono-ubiquitination promotes BRD4 complex formation to regulate apoptosis. Cell Signal. 2014;26(7):1445-55.
42. Liu S, Walker SR, Nelson EA, Cerulli R, Xiang M, Toniolo PA, et al. Targeting STAT5 in hematologic malignancies through inhibition of the bromodomain and extra-terminal (BET) bromodomain protein BRD2. Mol Cancer Ther. 2014;13(5):1194-205.
43. Trabucco SE, Gerstein RM, Evens AM, Bradner JE, Shultz LD, Greiner DL, et al. Inhibition of bromodomain proteins for the treatment of human diffuse large B-cell lymphoma. Clin Cancer Res. 2015;21(1):113-22.
44. Stewart HJ, Horne GA, Bastow S, Chevassut TJ. BRD4 associates with p53 in DNMT3A-mutated leukemia cells and is implicated in apoptosis by the bromodomain inhibitor JQ1. Cancer Med. 2013;2(6):826-35.
45. Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell. 2011;146(6):904-17.
46. Toniolo PA, Liu S, Yeh JE, Moraes-Vieira PM, Walker SR, Vafaizadeh V, et al. Inhibiting STAT5 by the BET bromodomain inhibitor JQ1 disrupts human dendritic cell maturation. J Immunol. 2015;194(7):3180-90.
47. Eskandarpour M, Alexander R, Adamson P, Calder VL. Pharmacological Inhibition of Bromodomain Proteins Suppresses Retinal Inflammatory Disease and Downregulates Retinal Th17 Cells. J Immunol. 2017;198(3):1093-1103.
48. Selvarajan V, Osato M, Nah GS, Yan J, Tae-Hoon C, Voon DC, et al. RUNX3 is oncogenic in natural killer/T-cell lymphoma and is transcriptionally regulated by MYC. Leukemia. 2017
49. Choi SK, Hong SH, Kim HS, Shin CY, Nam SW, Choi WS, et al. JQ1, an inhibitor of the epigenetic reader BRD4, suppresses the bidirectional MYC-AP4 axis via multiple mechanisms. Oncol Rep. 2016;35(2):1186-94.
50. Henssen A, Thor T, Odersky A, Heukamp L, El-Hindy N, Beckers A, et al. BET bromodomain protein inhibition is a therapeutic option for medulloblastoma. Oncotarget. 2013;4(11):2080-95.
51. Da Costa D, Agathanggelou A, Perry T, Weston V, Petermann E, Zlatanou A, et al. BET inhibition as a single or combined therapeutic approach in primary paediatric B-precursor acute lymphoblastic leukaemia. Blood Cancer J. 2013;3:e126.
52. Roderick JE, Tesell J, Shultz LD, Brehm MA, Greiner DL, Harris MH, et al. c-Myc inhibition prevents leukemia initiation in mice and impairs the growth of relapsed and induction failure pediatric T-ALL cells. Blood. 2014;123(7):1040-50.
53. Abruzzese MP, Bilotta MT, Fionda C, Zingoni A, Soriani A, Vulpis E, et al. Inhibition of bromodomain and extra-terminal (BET) proteins increases NKG2D ligand MICA expression and sensitivity to NK cell-mediated cytotoxicity in multiple myeloma cells: role of cMYC-IRF4-miR-125b interplay. J Hematol Oncol. 2016;9(1):134.
54. Wang J, Wang Y, Mei H, Yin Z, Geng Y, Zhang T, et al. The BET bromodomain inhibitor JQ1 radiosensitizes non-small cell lung cancer cells by upregulating p21. Cancer Lett. 2017;391:141-151.
55. Zhao L, Li J, Fu Y, Zhang M, Wang B, Ouellette J, et al. Photoreceptor protection via blockade of BET epigenetic readers in a murine model of inherited retinal degeneration. J Neuroinflammation. 2017;14(1):14.
56. Loosveld M, Castellano R, Gon S, Goubard A, Crouzet T, Pouyet L, et al. Therapeutic targeting of c-Myc in T-cell acute lymphoblastic leukemia, T-ALL. Oncotarget. 2014;5(10):3168-72.
57. Fiskus W, Sharma S, Qi J, Valenta JA, Schaub LJ, Shah B, et al. Highly active combination of BRD4 antagonist and histone deacetylase inhibitor against human acute myelogenous leukemia cells. Mol Cancer Ther. 2014;13:1142-54.
58. Peirs S, Frismantas V, Matthijssens F, Van Loocke W, Pieters T, et al. Targeting BET proteins improves the therapeutic efficacy of BCL-2 inhibition in T-cell acute lymphoblastic leukemia. Leukemia. 2017; in press
59. Nieto-Jiménez C, Alcaraz-Sanabria A, Pérez-Peña J, Corrales-Sánchez V, Serrano-Heras G, Galán-Moya EM, et al.

Targeting basal-like breast tumors with bromodomain and extraterminal domain (BET) and polo-like kinase inhibitors. Oncotarget. 2017; in press
60. Saenz DT, Fiskus W, Manshouri T, Rajapakshe K, Krieger S, Sun B, et al. BET protein bromodomain inhibitor-based combinations are highly active against post-myeloproliferative neoplasm secondary AML cells. Leukemia. 2016; in press.
61. Jostes S, Nettersheim D, Fellermeyer M, Schneider S, Hafezi F, Honecker F, et al. The bromodomain inhibitor JQ1 triggers growth arrest and apoptosis in testicular germ cell tumours in vitro and in vivo. J Cell Mol Med. 2016; in press.
62. Tang Y, Gholamin S, Schubert S, Willardson MI, Lee A, Bandopadhayay P, et al. Epigenetic targeting of Hedgehog pathway transcriptional output through BET bromodomain inhibition. Nat Med. 2014;20(7):732-40.
63. Zhou B, Mu J, Gong Y, Lu C, Zhao Y, He T, et al. Brd4 inhibition attenuates unilateral ureteral obstruction-induced fibrosis by blocking TGF-β-mediated Nox4 expression. Redox Biol. 2016;11:390-402.
64. Proserpio V, Fittipaldi R, Ryall JG, Sartorelli V, Caretti G. The methyltransferase SMYD3 mediates the recruitment of transcriptional cofactors at the myostatin and c-Met genes and regulates skeletal muscle atrophy. Genes Dev. 2013;27(11):1299-312.
65. Duan Q, Xiao Y, Zhu L, Liu Z, Mao X, Zhou Z, et al. BET bromodomain is a novel regulator of TAZ and its activity. Biochim Biophys Acta. 2016;1859(12):1527-1537.
66. Liu L, Xu Y, He M, Zhang M, Cui F, Lu L, et al. Transcriptional pause release is a rate-limiting step for somatic cell reprogramming. Cell Stem Cell. 2014;15(5):574-88.
67. Gonzales-Cope M, Sidoli S, Bhanu NV, Won KJ, Garcia BA. Histone H4 acetylation and the epigenetic reader Brd4 are critical regulators of pluripotency in embryonic stem cells. BMC Genomics. 2016;17:95.
68. Flynn RA, Do BT, Rubin AJ, Calo E, Lee B, Kuchelmeister H, et al. 7SK-BAF axis controls pervasive transcription at enhancers. Nat Struct Mol Biol. 2016;23(3):231-8.
69. Yokoyama Y, Zhu H, Lee JH, Kossenkov AV, Wu SY, Wickramasinghe JM, et al. BET Inhibitors Suppress ALDH Activity by Targeting ALDH1A1 Super-Enhancer in Ovarian Cancer. Cancer Res. 2016;76(21):6320-6330.
70. Kokkola T, Suuronen T, Pesonen M, Filippakopoulos P, Salminen A, Jarho EM, et al. BET Inhibition Upregulates SIRT1 and Alleviates Inflammatory Responses. Chembiochem. 2015;16(14):1997-2001.
71. Sengupta S, Biarnes MC, Clarke R, Jordan VC. Inhibition of BET proteins impairs estrogen-mediated growth and transcription in breast cancers by pausing RNA polymerase advancement. Breast Cancer Res Treat. 2015;150(2):265-78.
72. Dawson MA, Prinjha RK, Dittmann A, Giotopoulos G, Bantscheff M, Chan WI, et al. Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. Nature. 2011;478(7370):529-33.
73. Dawson MA, Gudgin EJ, Horton SJ, Giotopoulos G, Meduri E, Robson S, et al. Recurrent mutations, including NPM1c, activate a BRD4-dependent core transcriptional program in acute myeloid leukemia. Leukemia. 2014;28(2):311-20.
74. Gallagher SJ, Mijatov B, Gunatilake D, Gowrishankar K, Tiffen J, James W, et al. Control of NF-kB activity in human melanoma by bromodomain and extra-terminal protein inhibitor I-BET151. Pigment Cell Melanoma Res. 2014;27(6):1126-37.
75. Barrett E, Brothers S, Wahlestedt C, Beurel E. I-BET151 selectively regulates IL-6 production. Biochim Biophys Acta. 2014;1842(9):1549-55.
76. Chaidos A, Caputo V, Gouvedenou K, Liu B, Marigo I, Chaudhry MS, et al. Potent antimyeloma activity of the novel bromodomain inhibitors I-BET151 and I-BET762. Blood. 2014;123(5):697-705.
77. Pastori C, Kapranov P, Penas C, Peschansky V, Volmar CH, Sarkaria JN, et al. The Bromodomain protein BRD4 controls HOTAIR, a long noncoding RNA essential for glioblastoma proliferation. Proc Natl Acad Sci U S A. 2015;112(27):8326-31.
78. Wyspiańska BS, Bannister AJ, Barbieri I, Nangalia J, Godfrey A, Calero-Nieto FJ, et al. BET protein inhibition shows efficacy against JAK2V617F-driven neoplasms. Leukemia. 2014;28(1):88-97.
79. Pastori C, Daniel M, Penas C, Volmar CH, Johnstone AL, Brothers SP, et al. BET bromodomain proteins are required for glioblastoma cell proliferation. Epigenetics. 2014;9(4):611-20.
80. Gosmini R, Nguyen VL, Toum J, Simon C, Brusq JM, Krysa G, et al. The discovery of I-BET726 (GSK1324726A), a potent tetrahydroquinoline ApoA1 up-regulator and selective BET bromodomain inhibitor. J Med Chem. 2014;57(19):8111-31.
81. Wyce A, Ganji G, Smitheman KN, Chung CW, Korenchuk S, Bai Y, et al. BET inhibition silences expression of MYCN and BCL2 and induces cytotoxicity in neuroblastoma tumor models. PLoS One. 2013;8(8):e72967.
82. Zhao Y, Yang CY, Wang S. The making of I-BET762, a BET bromodomain inhibitor now in clinical development. J Med Chem. 2013;56(19):7498-500.
83. Imayoshi N, Yoshioka M, Chauhan J, Nakata S, Toda Y, Fletcher S, et al. CG13250, a novel bromodomain inhibitor, suppresses proliferation of multiple myeloma cells in an orthotopic mouse model. Biochem Biophys Res Commun. 2017; 484(2):262-268.
84. Picaud S, Wells C, Felletar I, Brotherton D, Martin S, Savitsky P, et al. RVX-208, an inhibitor of BET transcriptional regulators with selectivity for the second bromodomain. Proc Natl Acad Sci U S A. 2013;110(49):19754-9.
85. Jahagirdar R, Zhang H, Azhar S, Tobin J, Attwell S, Yu R, et al. A novel BET bromodomain inhibitor, RVX-208, shows reduction of atherosclerosis in hyperlipidemic ApoE deficient mice. Atherosclerosis. 2014;236(1):91-100.
86. Gilham D, Wasiak S, Tsujikawa LM, Halliday C, Norek K, Patel RG, et al. RVX-208, a BET-inhibitor for treating atherosclerotic cardiovascular disease, raises ApoA-I/HDL and represses pathways that contribute to cardiovascular disease. Atherosclerosis. 2016;247:48-57.
87. Bhadury J, Nilsson LM, Muralidharan SV, Green LC, Li Z, Gesner EM, et al. BET and HDAC inhibitors induce similar genes and biological effects and synergize to kill in Myc-induced murine lymphoma. Proc Natl Acad Sci U S A. 2014;111(26):E2721-30.
88. Kharenko OA, Gesner EM, Patel RG, Norek K, White A, Fontano E, et al. RVX-297- a novel BD2 selective inhibitor

of BET bromodomains. Biochem Biophys Res Commun. 2016;477(1):62-7.
89. Liu R, Zhong Y, Li X, Chen H, Jim B, Zhou MM, Chuang PY, He JC. Role of transcription factor acetylation in diabetic kidney disease. Diabetes. 2014;63(7):2440-53.
90. Hu Y, Zhou J, Ye F, Xiong H, Peng L, Zheng Z, et al. BRD4 inhibitor inhibits colorectal cancer growth and metastasis. Int J Mol Sci. 2015;16(1):1928-48.
91. Moros A, Rodríguez V, Saborit-Villarroya I, Montraveta A, Balsas P, Sandy P, et al. Synergistic antitumor activity of lenalidomide with the BET bromodomain inhibitor CPI203 in bortezomib-resistant mantle cell lymphoma. Leukemia. 2014;28(10):2049-59.
92. Siegel MB, Liu SQ, Davare MA, Spurgeon SE, Loriaux MM, Druker BJ, et al. Small molecule inhibitor screen identifies synergistic activity of the bromodomain inhibitor CPI203 and bortezomib in drug resistant myeloma. Oncotarget. 2015;6(22):18921-32.
93. Siu KT, Ramachandran J, Yee AJ, Eda H, Santo L, Panaroni C, et al. Preclinical activity of CPI-0610, a novel small molecule bromodomain and extra-terminal protein inhibitor in the therapy of multiple myeloma. Leukemia. 2016; in press.
94. Gacias M, Gerona-Navarro G, Plotnikov AN, Zhang G, Zeng L, Kaur J, et al. Selective chemical modulation of gene transcription favors oligodendrocyte lineage progression. Chem Biol. 2014;21(7):841-54.
95. Waring MJ, Chen H, Rabow AA, Walker G, Bobby R, Boiko S, et al. Potent and selective bivalent inhibitors of BET bromodomains. Nat Chem Biol. 2016;12(12):1097-1104.
96. Rhyasen GW, Hattersley MM, Yao Y, Dulak A, Wang W, Petteruti P, et al. AZD5153: A Novel Bivalent BET Bromodomain Inhibitor Highly Active against Hematologic Malignancies. Mol Cancer Ther. 2016;15(11):2563-2574.
97. Riveiro ME, Astorgues-Xerri L, Vazquez R, Frapolli R, Kwee I, Rinaldi A, et al. 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. 2016;7(51):84675-84687.
98. Vázquez R, Riveiro ME, Astorgues-Xerri L, Odore E, Rezai K, Erba E, et al. The bromodomain inhibitor OTX015 (MK-8628) exerts anti-tumor activity in triple-negative breast cancer models as single agent and in combination with everolimus. Oncotarget. 2017;8(5):7598-7613.
99. Boi M, Todaro M, Vurchio V, Yang SN, Moon J, Kwee I, et al. Therapeutic efficacy of the bromodomain inhibitor OTX015/MK-8628 in ALK-positive anaplastic large cell lymphoma: an alternative modality to overcome resistant phenotypes. Oncotarget. 2016;7(48):79637-79653.
100. Erdreich-Epstein A, Singh AR, Joshi S, Vega FM, Guo P, Xu J, et al. Association of high microvessel αvβ3 and low PTEN with poor outcome in stage 3 neuroblastoma: rationale for using first in class dual PI3K/BRD4 inhibitor, SF1126. Oncotarget. 2016; in press
101. Baud'huin M, Lamoureux F, Jacques C, Rodriguez Calleja L, Quillard T, Charrier C, et al. Inhibition of BET proteins and epigenetic signaling as a potential treatment for osteoporosis. Bone. 2017;94:10-21.
102. Niu N, Shao R, Yan G, Zou W. Bromodomain and Extra-terminal Proteins (BET) Inhibitors Suppress Chondrocyte Differentiation and Restrain Bone Growth. J Biol Chem. 2016;291(52):26647-57.
103. Najafova Z, Tirado-Magallanes R, Subramaniam M, Hossan T, Schmidt G, Nagarajan S, et al. BRD4 localization to lineage-specific enhancers is associated with a distinct transcription factor repertoire. Nucleic Acids Res. 2016;45(1):127-141.
104. Meng S, Zhang L, Tang Y, Tu Q, Zheng L, Yu L, et al. BET Inhibitor JQ1 Blocks Inflammation and Bone Destruction. J Dent Res. 2014;93(7):657-62.
105. Alghamdi S, Khan I, Beeravolu N, McKee C, Thibodeau B, Wilson G, et al. BET protein inhibitor JQ1 inhibits growth and modulates WNT signaling in mesenchymal stem cells. Stem Cell Res Ther. 2016;7:22.
106. Lamoureux F, Baud'huin M, Rodriguez Calleja L, Jacques C, Berreur M, et al. Selective inhibition of BET bromodomain epigenetic signalling interferes with the bone-associated tumour vicious cycle. Nat Commun. 2014;5:3511.
107. Gelato KA, Shaikhibrahim Z, Ocker M, Haendler B. Targeting epigenetic regulators for cancer therapy: modulation of bromodomain proteins, methyltransferases, demethylases, and microRNAs. Expert Opin Ther Targets. 2016;20(7):783-99.
108. Andrieu G, Belkina AC, Denis GV. Clinical trials for BET inhibitors run ahead of the science. Drug Discov Today Technol. 2016;19:45-50.
109. Stonestrom AJ, Hsu SC, Werner MT, Blobel GA. Erythropoiesis provides a BRD's eye view of BET protein function. Drug Discov Today Technol. 2016;19:23-28.
110. French CA. Small-Molecule Targeting of BET Proteins in Cancer. Adv Cancer Res. 2016;131:21-58.
111. Wang R, You J. Mechanistic analysis of the role of bromodomain-containing protein 4 (BRD4) in BRD4-NUT oncoprotein-induced transcriptional activation. J Biol Chem. 2015;290(5):2744-58.
112. Reynoird N, Schwartz BE, Delvecchio M, Sadoul K, Meyers D, Mukherjee C, et al. Oncogenesis by sequestration of CBP/p300 in transcriptionally inactive hyperacetylated chromatin domains. EMBO J. 2010;29(17):2943-52.