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BRD4 as Breast Cancer Target Protein: A Comprehensive Review on Therapeutic Approaches

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ABSTRACT

Approximately one-half of all women will be diagnosed with breast cancer at some time in their life, according to current estimates. This complex illness is distinguished by an abnormal arrangement of gene expression as well as epigenetic changes. Changes to a cell's DNA that do not alter the nucleotide sequence and are not connected with illness are known as epigenetic alterations. These proteins function as "readers" of chromatin, attracting transcriptional regulators to gene target promoters and regulating transcriptional elongation. BET proteins, also known as bromodomain and extra terminal domain proteins, are a kind of epigenetic molecule that regulates the expression of several cancer-related genes. Bromodomains (*BRDs*) are epigenetic reader domains that are specifically designed to recognize acetylated lysine residues arranged histone protein splicing factor tails and only protein sequencing modules that are capable of precisely targeting acetylated lysine residues inside the structure of a protein. Under the BET gene family, BRD4 is a transcriptional regulator of gene expression (*Bromodomain Containing 4*) and is involved in RNA polymerase II transcriptional regulation. It has been linked to many ailments, according to research. The purpose of this review is to explore how BRD4 inhibitors support breast cancer patients who get tailored therapy by inhibiting cancer cell proliferation, invasion, and migration, as well as the broad therapeutic use of BRD4 inhibitors. Additionally, effective combinations of BRD4 inhibitors with various chemo- and immunotherapeutic agents are highlighted, as is the possibility for future research in this field.

INTRODUCTION

Breast carcinoma remains the utmost prevalent kind of cancer among females and the second greatest reason for cancer mortality in females. Breast cancer is 100 times more common in women than in men. It is the second most frequent non-skin cancer in women globally (after lung cancer) and the fifth largest cause of cancer mortality in women, contributing about 10.4 percent of all cancer cases.[1]Based on well-established molecular markers, these tumours are presently categorized into four molecular subgroups such as oestrogen (ER) and progesterone (PR) receptor-positive, HER2 receptor status, and the Ki67 proliferation index. The majority of breast cancer is characterized either as luminal A, luminal B, basal-like, and HER2 overexpression. It is based on many well-known biomarkers, such as the expression of said estrogen receptor (ER) and the progesterone receptor (PR). [2], [3] In fewer than 14% of instances, Luminal A represents HER2-negative, ER-positive through/deprived of PR positivity, and Ki67-negative. Luminal B is classified as HER2-positive or HER2-negative, including those with ER-positive and/or PR-positive hormone state and a Ki67 concentration of more than 14%. HER2 overexpression happens in tumours that are positive for HER2, negative for ER and PR, and contain a tolerable quantity of Ki67. In basal-like, it possesses triple negative receptors along with variable levels of Ki67. TNBC, which remains ER/PR and HER2 negative owing to the absence of a receptor in such tumours, is the utmost violent type of breast cancer. [4]

Epigenetic modifications are reversible, heritable changes to a cell's DNA that do not result in changes in nucleotide sequence. [5]Several epigenetic changes occur during cancer, including abnormal acetylation and methylation patterns. Dysregulated gene expression and aberrant cell proliferation are the results of these changes. The post-translational processes are acetylation of histone lysine residues, which regulates chromatin shape and makes it accessible to DNA and RNA polymerases as well as transcription factors.[6], [7]Acetylation of histone tail lysine residues is a critical epigenetic modification. Bromodomain containing proteins is a kind of protein that acts as a chromatin "reader" and recruits chromatin transforming enzymes towards gene aimed promoters.[5], [8]

Bromodomains (BRD) are classified as the first protein-binding domain that precisely recognizes the acetylated lysine mark on histone N-terminal tails. Because of their specific identification of acetylated lysine, BRDs show a vital part in the genetic transcription in

chromatin (KAc). [9] Every human genome contains 61 BRDs in 46 proteins, which can be divided into eight categories centered upon structure and purpose similarity.[10]

BRD4 is a member of the BET family, which along with BRD4involves BRD2, BRD3, and bromodomain testis-specific protein (BRDT). [9]– [11]BRD4 remains a transcriptional as well as an epigenetic regulator that is required for embryogenesis and breast cancer development. [12]BRD4 is the sole affiliate of the BET family that interacts directly with RNA polymerase II to form the P-TEFb (Positive transcription elongation factor B) complex. [5], [13]BRD4 acts as an epigenetic reader, encouraging the creation of large transcription regulatory complexes that control DNA replication and repair, transcription, and chromatin reconfiguration.[9]

The existence of two successive bromodomains identifies BRD4 (BD1, BD2). Because of their enhanced affinity for proteins with multiple acetylated residues, BRD4 and the other BET proteins engage with hyper-acetylated histone regions along chromatin, accruing on transcriptionally active regulatory regions and helping to promote gene transcription together around the initiation and elongation phases.[14], [15] According to recent research, BRD4 may stimulate the aberrant appearance of oncogenes such as c-Myc, NF-B, Aurora B, and Bcl-2 via recruiting positive transcription elongation factor (p-TEFb). [9]

BRD4 inhibitors control gene transcription by preventing BET proteins from binding to chromosomes.[12]According to a recent study, inhibiting BET proteins decreased PD-1/PD-L1 signaling in TNBC. [16]Furthermore, one study revealed that inhibiting BRD4 lowered PD-L1 transcription happening in TNBC cells, suggesting thus BRD4 inhibition could be beneficial for TNBC therapy.[17] Several current trials are assessing the effectiveness of BRD4 inhibitors for TNBC, suggesting BRD4 may be a promising target for TNBC therapy. [18]Furthermore, it's been shown that BRD4 isoforms have opposing activities in breast cancer, giving a new paradigm for developing successfully targeted therapeutics for the disease.[19] From the above statements, it has been found that BRD4 inhibition is now considered to be one of the most promising strategies for eliminating the growth of breast cancer cells.

All preclinical and clinical information on BRD4 inhibitors is reviewed in this article to assess their anticancer effects on breast cancer.

1.0 Transversal functions of BRD4

The transversal purpose of BRD4 in maintaining genomic constancy will be discussed in this review, which will provide fresh insights into breast cancer cells.

2.0.1 Regulation of Transcription

Initially, BRD4 was sustained by either a cell cycle regulating protein that binds to chromosomes during mitosis to identify genes that need the rapid transcription in G1 to facilitate cell cycle advancement. [12], [20]BRD4 transcriptional activity is required for cell identity determination and embryogenesis. By modulating or working with Embryonic Stem Cells (ESCs) transcriptional factors in the initial phases of embryogenesis, BRD4 is essential for sustainedESC self-renewal and pluripotency.[21]Later in development, BRD4 is necessary for the determination of cell identity by preferentially regulating lineage-specific genes. [22]BRD4 is a transcription activator, but the fact that it has been dispersed suggests that it might also operate as a transcriptional repressor. [15], [23]BRD4 acts as a nucleation center again for the creation of large protein complexes that boost RNA-Polymerase II activity, which drives transcription onset and elongation, by acting as just a histone logic analyzer on hyperacetylated as well as transcriptionally effective chromatin sites (both promoters and ENHs). Although not fully dependent on BRD4 BDs and their capacity to detect acetyl-proteins, this function is heavily reliant on them.[11], [12]

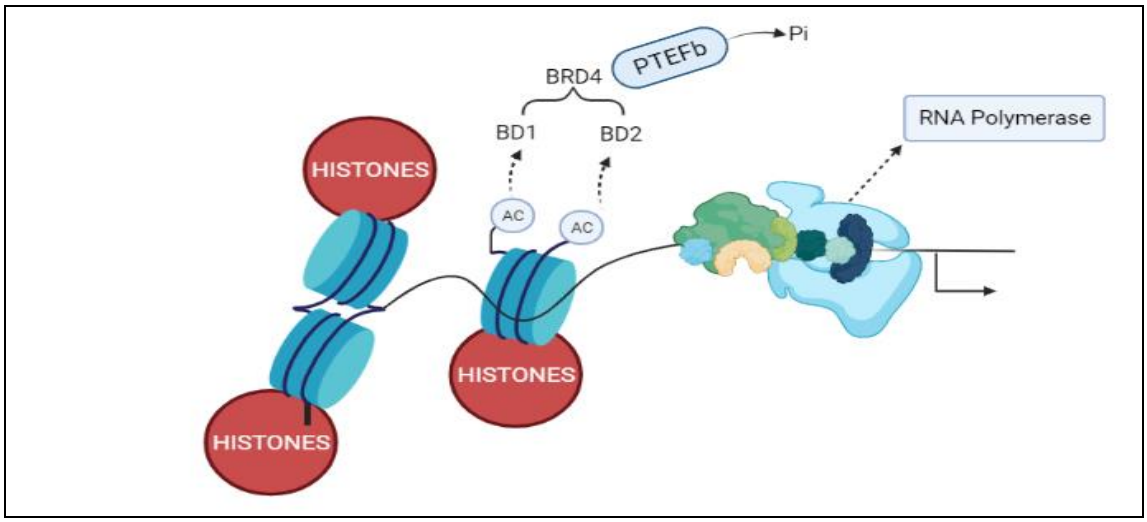

Figure 1: Transcriptional control by BRD4. Accumulation of P–TEFb in the nucleus is enabled by BET proteins binding to histones through acetylated lysines. Transcription is solitarily conceivable when the carboxyl-terminal domain of RNA polymerase is phosphorylated on serine 2 by PTEFb.

2.0.2 Transcription Initiation and Elongation

The initial stage in transcription initiation is the enrolment of RNA-Polymerase II towards the preinitiation complex (PIC) on the gene promoter, accompanied by phosphorylation of RNA-Polymerase II in addition to upkeep of the RNA-Polymerase II promoter contacts. As TFs as well as other transcription regulatory proteins control PIC assembly, ENHs have an enormous influence. Mediator (Transducer) of RNA-Polymerase II transcription receives signals from TFs and activators at ENHs, stretches the synthesis of PICs, and initiates transcription. Tumour cell development is the first stage in the genesis of a tumour in addition to the mechanism through which regular cells become malignant. According to research, breast cancer is more prevalent in individuals with diabetes patients with type 2(T2D), following the survival of inflammatory cells in the neoplastic microenvironment, patients with breast cancer have a shorter disease-free survival rate. [24]Inflammation of the visceral adipose tissue (VAT), which is frequent in T2D patients, causes inflammatory alterations in the breast adipose tissue and the release of pro-inflammatory cytokines such as Tumor necrosis, TNF, IL-17A, and IL-22, all of which may promote cancer start. [25]When RORC relative binding protein gets generated and BRD4 attaches to the RORC promoter, the synthesis of both IL-17 and IL-22 transcripts increases, which may be reversed by blocking BRD4. This shows that BRD4 may be involved in the epigenetic control of RORC, and as a result, the synthesis of pro-inflammatory cytokines is regulated. [26], [27]

The c-MYC oncogene regulates MYC, a transcription factor implicated through cellular progression, apoptosis, and also the development and maintenance of pluripotency. [28]MYC expression, as well as function alterations, remain mutual in both the inflammatory and malignant circumstances, indicating that MYC controls serious cellular and molecular pathways linking systemic inflammation just before cancer. [29]According to in vivo investigations, VAT enhanced MYC nuclear activity and fibroblast growth factor 2 (FGF2) circulation levels, both of which promote epithelial cell transition. [30]VAT volume, FGF2 release, and epithelial cell neoplasia are reduced by inhibiting BRD4, in part by preventing MYC-dependent transcription.[31]

Senescence is a defense mechanism that protects cellular homeostasis, inhibits premalignant cell advancement, and stops the cell cycle in injured cells. While the majority of senescent cells possess closed chromatin, cancer cells may display a unique secretory-associated senescent phenotype (SASP), in which oncogene-induced senescence modifies the enhancer

landscape and recruits BRD4. [32]As a consequence, BRD4 significantly induced the release of SASP proteins such as IL-1, IL-1, IL8, BMP2, and INHBA. Hindering BRD4 using BET inhibitors reduces SASP factor production that causes senescence in cancer cells, allowing NK cells and M1-oriented macrophages to more efficiently identify and phagocytize cancer cells.[32], [33]

2.0.3 Inflammation and Progression of tumour cell

Tumour formation within a neoplastic cell population is characterized by the acquisition of phenotypic traits such as increased cell proliferation as well as intrusiveness.[34]Increased inflammation and activation of pro-inflammatory signaling pathways in the tumour microenvironment have been linked to the transcription factors NF-kB and Cox-2 as well as the transcription factors MYC and cyclin D1 and CD47. All of these factors are known to promote tumour development. [35]NF-kB has two distinct roles when it comes to triple-negative breast cancer. It is associated with the initiation of the host's inherent immune reactions. Still, constitutive NF-kB activation is prevalent in many malignancies, and this signalling stimulates the production of pro-tumorigenic and pro-inflammatory cytokines which include the IL-6 and TNF-∝. [36]

The BET family of proteins have been demonstrated to control the production of inflammatory mediators, which have previously been associated with the development and progression of these breast cancer cells. As shown across TNBC cell lines, BRD4 regulates the activity of nuclear factor-kB (NF-kB), demonstrating that bromodomain-containing proteins have a conserved role in activating the NF-kB signaling pathway. By suppressing NF-kB activation with BET inhibitors against the protein related to NF-kB, p50, and its precursor, p105, activation of NF-kB is gradually decreased. [37], [38]By altering NF-B-dependent signaling and reducing the production of NF-B target genes, BRD4 inhibition decreases the growth of TNBC cells. Therapeutic outreach of BRD4 hinders its binding to the c-MYC promoter, thus further restricting the expression of MYC-dependent target genes for both malignant cells and inflammatory cell communities found in the tumour microenvironment, implying that therapeutic targeting of BET proteins may represent a novel approach for inhibiting the BRD4-mediated pathway.[5], [37]

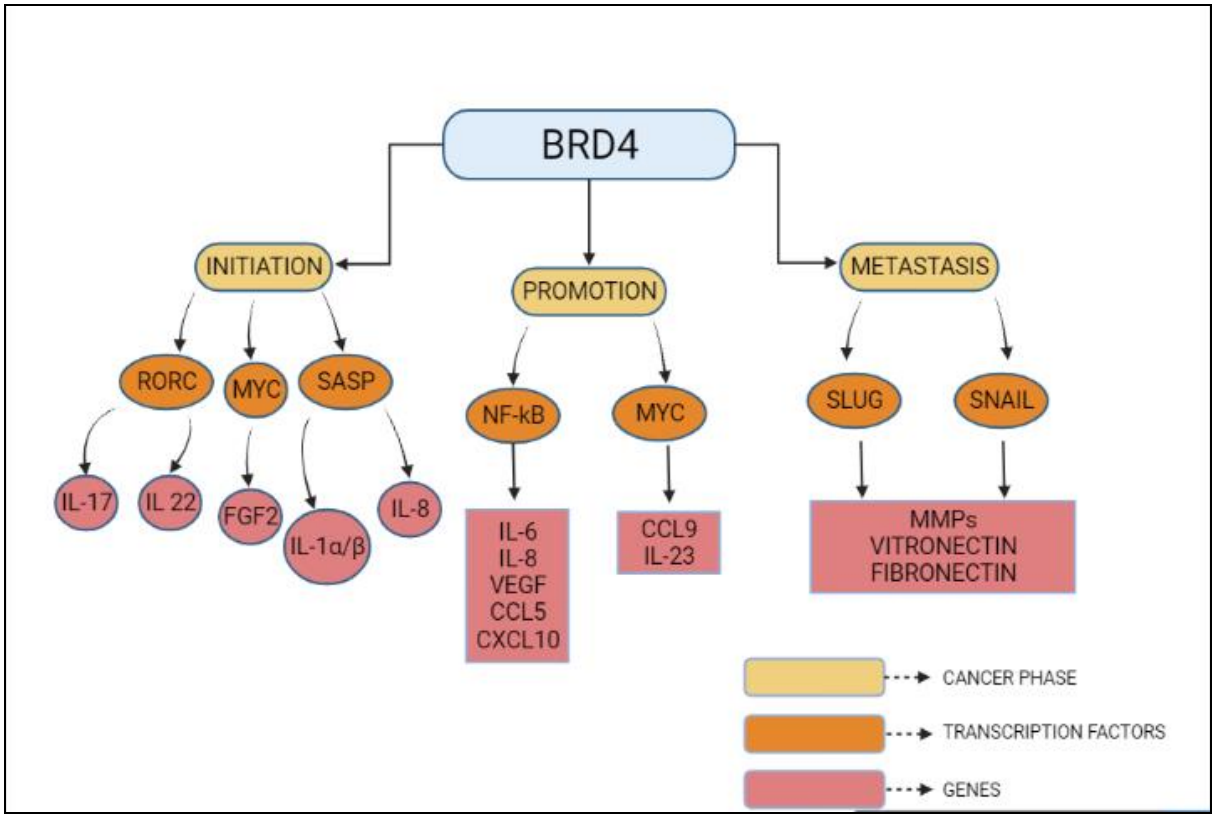

Figure 2: Cancer initiation, progression, and metastasis are all enhanced by BRD4 deregulation. BRD4 is a transcription factor and gene that affects all elements of cancer when it is overexpressed.

3.0 Dysregulation of BRD4 in breast cancer: mechanism and consequences

BET proteins were first identified as critical epigenetic controllers involved in inflammation and inflammatory conditions, but it is currently well-known that they remain often dysregulated in cancer, resulting in unregulated chromatin remodeling and gene transcription which promotes carcinogenesis. [39]Numerous human malignancies, particularly breast cancer, have been linked to rearrangements or mutations in the BRD4 gene, involving missense and nonsense alterations. [40] Rearrangements or mutations in the BRD4 gene have been linked to several types of human cancers, including breast cancer.

On the other hand, in vitro, abnormal BET protein expression, notably BRD4, has been shown to accelerate the cell cycle, invasion, and metastasis of these cancer cell lines. [41]Amino acid changes inside the two edges helices B and C, as well as the area around the acetyl-lysine binding site, boost BRD4's carcinogenic potential. [42]Protein stability at elevated temperature was exposed to be harmed by amino acid changes in the BET protein family's convinced sections, as revealed by Lori et al.These results put forward those genetic

proceedings influencing BET family members may have an influence on protein structure as well as interactions of protein-protein or else protein–DNA, which are involved in the regulation of biological processes. [43]

4.0 BRD4 dysregulation improves the metastasis of breast cancer cells

The materialized mechanism by which malignant cells travel from the main tumour location towards nearby organs via the lymphatic or circulatory system is known as metastasis. Resistance to chemotherapy is a crucial characteristic of malignant, metastatic cancer cells, and it has a considerable effect on cancer treatment outcomes. Cancer cells drop their polarity, cell–cell linkages, and aggressive capabilities even during epithelial to mesenchymal transition (EMT), which commences the metastatic cascade.[5]

In breast cancer cells, signaling over the Jagged1/Notch1 pathway would stimulate the EMT and improves the tumour's ability to invade the surrounding tissue. Jagged1 interacts with the Notch receptor, which is subsequently sliced and translocated near the nucleus, in which it interacts with CBF1, suppressor of Hairless, Lag-1 (CSL), and Coenzyme A (CoAs) could increase the production of transcription factors involved in EMT, such as Snail and Slug. [44]

According to the study's results, BRD4 enhances a breast cancer cell line’s migratory capability through Notch1-induced signaling. Breast cancer cells may be affected by tumor-associated inflammation mediators that modify the epigenetic levels of BRD4 in breast cancer cells via the activation of the Jagged1 promoter region, according to the results of a series of studies on IL-6.In TNBC cell lines, JQ1, a BRD4 inhibitor, has been found to impede cellular attack and relocation as well as IL-6-mediated signaling via the Jagged1/Notch1 pathway. [26], [45]

5.0 Therapeutic approaches in targeting bet bromodomain proteins

Dysregulation of these BET family proteins has indeed remained to a variety of biological functions, together with inflammation and cancer cell genesis, proliferation, and metastatic tendency.[46] Breast cancer and triple-negative breast cancer cells, among others, depend on epigenetic dysregulation to maintain their malignant phenotype, according to a new study. Epigenetic proteins might be therapeutic targets because they relied on epigenetic proteins. [47] Therefore, medicines aimed at lowering BET protein function while also targeting epigenetic regulators may provide a novel therapeutic strategy for breast cancer. Based on their anti-tumor actions in vitro, numerous small chemical BET protein inhibitors have been

found and tested. Novel BRD4 inhibitors cause little and reversible clinical damage in patients with breast cancer, according to phase I clinical trials that evaluated their safety and effectiveness in these patients.[48], [49] even though BET inhibitors have exhibited target inhibition and possible therapeutic benefits in vitro and animal studies, no significant therapeutic benefit has been reported in Phase I trials in cancer patients, indicating that BET suppression as a single agent treatment may be restricted. [5], [49]

6.0 BRD4 inhibitors in breast cancer

Inhibiting BRD4 is a feasible and promising treatment strategy for breast cancer. Its knockdown, whether chemical or genetic, efficiently stops cell cycle regulation and triggers apoptosis, which leads to cell death. [50] Significant effort has been expended in recent years to discover BRD4 inhibitors utilizing a mix of wet-lab and dry-lab approaches.[51]

BRD4 inhibition may be used to limit breast cancer cell proliferation and cause apoptosis. BRD4's function in cancer metastasis is mostly unclear.[52]A recent study suggests that BRD4 regulates cell motility via altering the Jagged1/Notch1 signal transduction pathway as well as interacting with the EMT transcription factor (EMT-TF) Twist.[45] EMT is the method through which epithelial cells acquire a mesenchymal character and become migratory and invasive.[53] Twist, Snail, and Zeb1 are all EMT-TFs that may initiate EMT and increase cancer metastasis.[54]Histone methyltransferases, like lysine-specific demethylase 1 (LSD1) and Suv39H1 histone methyltransferases, regulate the transcriptional regulator Snail (encoded by SNAI1), which is essential for the synthesis of E-cadherin during EMT.[55] The second bromodomain of BRD4 may be activated by diacetylated EMT-TF Twist. Because BRD4 function is very context-dependent, it is employed to ascertain the functions of BRD4 and its regulatory effects on Breast Cancer (BC) cell spread. [56], [57]

One of the earliest and most thoroughly scrutinised BET inhibitors is JQ1 (A Thienotriazolodiazepine). By crystallizing JQ1 with BRD4, we have discovered the physicalroot for its inhibitory action. This class of compounds includes isoxazoles, quinolinones, naphthyridine analogues and acetylated BRD 4 analogues. JQ1 be able to prevent the actions of both BD1 and BD2 of BRD4.[10], [58]

Herein, our overview of BRD4 inhibitors provides an up-to-date look at their potential therapeutic applications as shown in Table 1.

Table 1: Various BRD4 inhibitors along with their therapeutic applications

BRD4 Inhibitors	Therapeutic application	References
Azeplines	A famous Pharmaceutical Company has revealed a variety of thienodiazepines molecules as inhibitors of BRD4 in the year 2009. JQ1 is the first BET protein family inhibitor to be publicly reported. Breast cancer cells' growth is significantly slowed by JQ1-induced apoptosis. MDA-MB-23 and HT-29 breast cancer cells demonstrate substantial pharmacological action when grown on the triazobenzene scaffold.	[10], [59]
Quinoline and its derivatives	The BET inhibitors quinoline and quinazoline improve anticancer efficacy in vitro and in vivo. Pfizer revealed the development of new pyrido [2, 3-b] pyrazinone BRD4 inhibitors. Similar to the above-mentioned inhibition, these compounds have the potential to suppress the activation of the downstream c-Myc gene. To modulate signaling pathways and carry out specialised actions, new dihydroazolinone molecules successfully bind to BRD4.	[9], [60]
N-methyl pyridinone and its derivatives	Compound 6 (ABBV-075) does have a substantial inhibitory impact on BRD4 BD1 and BRD4 BD2, which explains why Abbvie's researchers were able to significantly reduce MX-1 cell proliferation. MX-1 cells may be effectively targeted by polycyclic drugs, which inhibit BRD4. These compounds were tested for their capacity to suppress BRD4 proliferation, and the results showed that they were effective against breast cancer cell multiplication.	[61]
Pyrroles	According to Abbvie, pyrrole derivatives (compounds 78–80) are effective BRD4 inhibitors. At a dose of 38 nM, compound 78 inhibits BRD4 BD1 and at 225 nM, inhibits BRD4 BD2. Additionally, the inhibitory activity on MX-1 breasts cancer cell lines appeared promising.	[9], [62]
Isoxazoles	Hewing et al. established the first isoxazole-based BET-selective inhibitors. I-BET151 is one of the derivatives which has been shown in vivo and in vitro to hinder the development	[9], [63]

	of cancer cell lines and persuade cell death. Clinical investigations indicate that it may activate JAK2 and inhibit cancer cell proliferation in individuals with severe breast cancer, hence improving survival.	
PROTAC-based BRD4 inhibitors	Aside from developing BRD4 small molecule inhibitors to combat cancer, researchers are also working hard to develop new chemical biology techniques to combat BRD4. Proteolysis targeting chimeric (PROTAC) compounds are an exciting new family of drugs that aim proteolysis by attracting an enzyme known as ubiquitin-ligase to destroy the target protein. Proteasome degradation of the target occurs in breast malignancies like TNBC when BRD4-targeting drugs, such as BET-PROTAC MZ1, are used.	[64]–[67]

7.0 Advances in BRD4 inhibitors

In the literature, small-molecule blockers of such BRD4 protein have indeed been described, which include (+)-JQ1, OTX-015, and I-BET762. In 2020, High-throughput screening (HTS) and fragment-based drug discovery approaches were used to identify five putative BRD4 inhibitors.(30B-30Q, 139 31B-31Z, 140 32B-32J, 141 33B-33U, 142 and 34B-34M 143). Compound 30i (R47) has been the most specific BD2 inhibitor within the study. 30b-30q (1000-fold). It must have the correct pharmacokinetic and physical characteristics to be employed in animals. R47 S-isomer also enables BRD4 inhibitors to approach the BD2 bromodomain quite efficiently.[68]

In a study done by Liu's team, IC50 values of BRD4 (BD1) of 2.15 M and 4.36 M, correspondingly, were discovered for chemical 32g R51 (ethynyl) (BD2).In the same way (+)-JQ1 did, compound 32g inhibited BRD4 and improved the protein's stability in the process. Docking tests showed that Asn140 may create a hydrogen bond with Asn140, and so occupies the center of the acetyl-lysine binding cavity. Only a tiny effect on inhibitory activity was seen when R51 was added to the scaffold's core[70]. Apoptosis and enhanced PARP and caspase-3/7 expression were also observed in THP-1 cell lines after BRD4 protein inhibition with compound 32g. [2], [69]

8.0 Combinational strategies

While BET inhibitors have shown limited therapeutic value when used alone, a number of studies have indicated that when combined with other small molecule inhibitors or immunotherapies, BRD4 inhibitors have synergistic anti-tumour efficacy.[70] This section will concentrate on innovative anti-cancer combination tactics utilizing small molecule inhibitors of BRD4 proteins and immunomodulatory medicines.

The combination of BRD4 inhibitors and mTOR inhibitors may have a major impact on breast cancer therapy. The most potent inhibitor OTX-015 in conjunction well with BRD4 inhibitor arrests the cell cycle and downregulates c-Myc.When employed with further anticancer medications (mTOR inhibitors, PI3K inhibitors, BTK or HDAC inhibitors, for example), JQ1 and other thienotriazolodiazepine compounds have an improved therapeutic effect when compared with BRD4 inhibitors alone. [71], [72]

According to studies analyzing the impact of lenalidomide, a strong immunomodulatory drug (IMiD) in primary effusion lymphoma (PEL), the medication increases interferon-, interferon-, and interferon-expression in PEL cells and has been found to be cytotoxic to PEL cells. BRD4 and BRD4 inhibitors may greatly enhance the anti-proliferative action of lenalidomide on cancer cells.[72] Multiple studies have shown how a combination of a BRD4 inhibitor and lenalidomide can reduce tumour burden while also increasing overall survival times. Immunomodulatory medications' cytotoxic effects and suppression of BRD4-dependent MYC expression are suggested to be contributing factor (IMiDs). [73]

Gene expression is lowered in breast cancer cells when BET proteins and Bruton’s tyrosine kinase (BTK) are targeted together. Due to this, gene-dependent signaling is less likely to activate NF-B and JAK/STAT pathways.[71]To regulate T cell immune checkpoint activation, PD-L1 is essential. Numerous human malignancies overexpress PD-L1, and clinical trials are underway to establish if immune checkpoint inhibitors, alone or in conjunction with other medications, are safe and effective in the treatment of cancer. According to Zhu et al., BRD4 is an important controller of PD-L1 expression in breast cancer cells.[74]The CD274 gene encodes PD-L1, and BRD4 interacts directly to the gene's promoter to activate transcription. When mice were administered with the BET inhibitor JQ1, anti-tumor T-cell effectiveness was related to lower PDL1 levels in cancerous cells as well as cancer-associated immune cells.[75] In c-MYC-driven cancer cells, when compared to either

treatment alone, the combination of JQ1 and PD-1 antibody-based dramatically reduced tumour burden and extended overall survival.[74], [76]

Adoptive immunotherapeutic techniques in cancer therapy, which includes tumor-specific chimeric antigen receptor (CAR)-expressing T cells, are nowadays becoming popular. Antigen-specific toxicities, such as potentially lethal upregulation syndromes, have delayed the development of CAR-T cell therapies. To avoid cancer recurrence in mind, the use of CAR-T cells along with other adjuvant therapies are being studied as a reasonable strategy.[77]JQ1, a pan BET family inhibitor, is frequently used to regulate patient-derived CD8+ T cells formerly to selective transfer. In contrast to effector memory T cells, CD8+ T cells treated with JQ1 retain stem cell-like (TsC) as well as central memory (TsCm) properties and exhibit enhanced antitumor activity (Tem). JQ1 treatment, which inhibits T effector cell development, also inhibits BRD4 interaction to the BATF gene promoter. This suggests that pre-treatment with BRD4 inhibitors may improve T cell immunotherapy adherence. [78]

A final technique has been attempted in MYC-driven breast cancers, and it entails concurrent PI3K and BRD4 signalling pathway inhibition. The PI3K pathway regulates MYC protein degradation, on the other hand;MYC gene transcription is regulated by BRD4, a very well-proclaimed genetic regulator.[79]Morpholinothienopyrane has been demonstrated to exhibit biological activity when PI3K and BRD4 inhibitors are used (SF2523). Since SF2523 reduces MYC expression and stimulation, combining PI3K and BRD4 inhibition may be an alternate method for the up regulated treatment response in MYC-positive breast tumours. It has been shown to decrease tumour volume and the burden of metastatic disease. [5], [79]

9.0 CONCLUSION AND FUTURE PERSPECTIVES

According to the Agency for Research on cancer, it is estimated that breast cancer kills more women than any other kind of cancer, and it is the second most common disease globally. Breast cancer therapies include chemotherapy, immunotherapy, hormonal therapy, surgical methods, in addition to radiation therapy.In breast cancer therapy, BET inhibitors represent a new age of epigenetic medicines. BRD2, BRD3 and BRD4 are the three members of the BET family that are expressed in all mammals. Because of their toxicity, BET inhibitors should be carefully monitored in breast cancer cell lines and xenograft models. BET inhibitors must be well tolerated to optimize clinical effectiveness while avoiding exceeding the toxicity threshold, as seen by these concerns. One of the key players in the onset and progression of

many serious diseases is bromodomain (BRD) readers, which modify gene regulatory networks by reading histone acetylation. About eukaryotic transcriptional development and metastasis, BRD4 is a particularly well-studied member of the family, since it may be able to recruit the P-TEFb complex (positive transcription elongation factor complex).

Epigenetic readers, writers, and erasers together have alleged to possess an important role in the etiology of inflammatory disorders and cancer.An axis of BRD4 signalling in breast cancer cells demonstrates that BRD4 can modulate gene expression and pathway signalling to control breast cancer migration. In this review, we looked at the biological impact of targeting BRD4 on breast cancer development. We observed that siRNA for BRD4 or a particular BET family protein inhibitor inhibits BC cell migration and EMT.

BRD4 has emerged as a master regulator of genome activity and stability, exhibiting a consistent mechanism of action across a wide range of functions. BRD4 detects hyper-acetylated chromatin regions and accumulates there, promoting the recruitment and stability of functional multiprotein complexes. When proteins fix to chromatin at high densities, they change the structure and produce new functional domains that improve protein function and interaction.

It is becoming clear that BRD4 has a role in a wide range of cancer-supporting activities, and these findings suggest a wide range of potential cytotoxic uses in breast cancer. Breast cancer cell lines and mice models were made more sensitive to BRD4 inhibitors, which resulted in a decrease in tumour development. To degrade BRD4, the BET PROTACS bind BRD4 and activate the proteasome. PROTACs connect BRD4 to the E3 ubiquitin ligase, resulting in a faster breakdown process. In human breast cancer patients, new BRD4 protein inhibitors have a limited efficiency even if they have low clinical toxicity. The combination of BRD4 inhibitors with immunomodulatory medicines benefits both tumours and the tumour microenvironment. Efficient further research will evaluate the function of BET proteins in modulating genes that promote inflammation and neoplastic development in individuals with breast cancer.

Because of this, BRD4 inhibitors should be used to boost the effectiveness of current chemotherapy and molecular treatments. The heterogeneity of BRD4 inhibitors in breast cancer provides a great therapeutic challenge that must be addressed by novel treatment alternatives. Overall, these BRD4 inhibitors represent a promising clinical search sector. There is still a lot of work to be done to see whether BRD4 inhibition can do this.

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CONFLICT OF INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication.

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ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

INFORMED CONSENT

Since the work does not contain any studies with human participants, no consents are required.

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