

Review

Targeting SWI/SNF Complexes in Cancer: Pharmacological Approaches and Implications

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Abstract: SWI/SNF enzymes are heterogeneous multi-subunit complexes that utilize the energy from ATP hydrolysis to remodel chromatin structure, facilitating transcription, DNA replication, and repair. In mammalian cells, distinct sub-complexes, including cBAF, ncBAF, and PBAF exhibit varying subunit compositions and have different genomic functions. Alterations in the SWI/SNF complex and sub-complex functions are a prominent feature in cancer, making them attractive targets for therapeutic intervention. Current strategies in cancer therapeutics involve the use of pharmacological agents designed to bind and disrupt the activity of SWI/SNF complexes or specific sub-complexes. Inhibitors targeting the catalytic subunits, SMARCA4/2, and small molecules binding SWI/SNF bromodomains are the primary approaches for suppressing SWI/SNF function. Proteolysis-targeting chimeras (PROTACs) were generated by the covalent linkage of the bromodomain or ATPase-binding ligand to an E3 ligase-binding moiety. This engineered connection promotes the degradation of specific SWI/SNF subunits, enhancing and extending the impact of this pharmacological intervention in some cases. Extensive preclinical studies have underscored the therapeutic potential of these drugs across diverse cancer types. Encouragingly, some of these agents have progressed from preclinical research to clinical trials, indicating a promising stride toward the development of effective cancer therapeutics targeting SWI/SNF complex and sub-complex functions.

Keywords: SWI/SNF chromatin-remodeling complexes; cancer; allosteric ATPase inhibitors; bromodomain inhibitors; PROTACs; epigenetics; transcription; DNA damage



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1. SWI/SNF Structure and Function

SWI/SNF chromatin-remodeling enzymes are multi-subunit complexes, conserved across different eukaryotes, including fungi, plants, and animals [1]. Mammalian SWI/SNF is composed of a central catalytic subunit with ATPase activity that is either SMARCA4 (BRG1) or SMARCA2 (BRM) and 8–15 associated subunits (BAFs) [2]. Distinct SWI/SNF complexes have been purified from mammalian cells and designated as canonical (c)BAF, non-canonical (nc) BAF, or PBAF depending on the identity of the catalytic subunit and BAF composition [3–9] (Figure 1). In addition, mammalian complexes can vary in composition and in a cell-specific manner [10,11].

SWI/SNF remodels chromatin structures by using the energy from ATP hydrolysis. This results in DNA translocation around the nucleosome, making nucleosomal DNA accessible to nuclear factors [12–14]. SWI/SNF can slide or evict nucleosomes and disrupt the association of transcription factors from chromatin [15,16]. In vitro, either ATPase, SMARCA4, or SMARCA2, is capable of remodeling nucleosomes, and this remodeling activity is enhanced by a core complex containing SMARCB1 (INI1, BAF47), SMARCC1 (BAF155), and SMARCC2 (BAF170) [17]. The C-terminus of SMARCB1 interacts with an acidic patch of the nucleosome, securing SWI/SNF to the nucleosome, thereby promoting optimum chromatin-remodeling activity [18–20], while SMARCC1/2 assemble as dimers to provide a scaffold needed for proper SWI/SNF assembly [21].

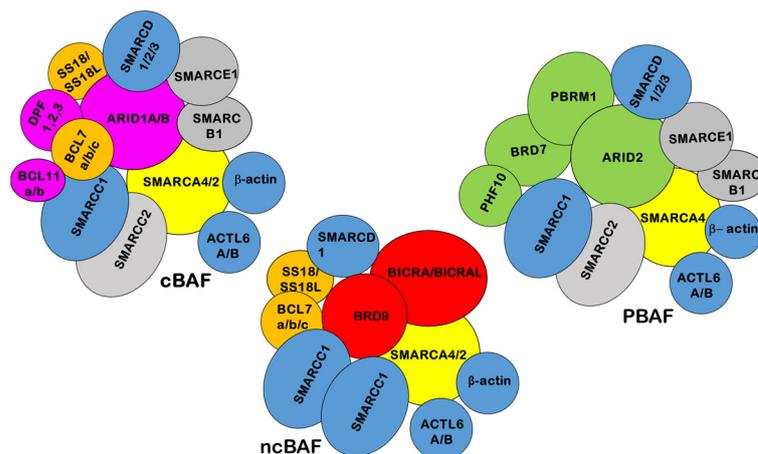


Figure 1. SWI/SNF Chromatin-Remodeling Complexes. Different SWI/SNF complexes exist in the form of cBAF, PBAF, and ncBAF. Yellow: SMARCA4 and SMARCA2 catalytic subunits. Purple: cBAF specific subunits. Green: PBAF specific subunits. Red: ncBAF specific subunits. Blue: subunits that assemble into all three complexes. Grey: subunits that assemble into cBAF and PBAF. Orange: subunits that assemble into cBAF and ncBAF.

Additional subunits provide features for optimal chromatin remodeling and impart structural specificity to the different SWI/SNF complexes. Both cBAF and PBAF complexes have a modular structure such that multiple subunits work together to interact with chromatin [6,20,22,23]. The largest subunit of cBAF complexes, ARID1A (and likely its paralog, ARID1B), serves as an assembly center for other BAF subunits and enhances nucleosome sliding activity *in vitro* [20]. ARID2 acts as a scaffold for the assembly of PBAF unique subunits, imparting architectural features that are distinct from BAF complexes as well as unique contacts with histone tails and nucleosomal DNA [22,23]. Actin-related proteins stabilize SWI/SNF complex formation and couple DNA translocation with ATP hydrolysis [24,25]. PBRM1, BRD7, and BRD9, as well as the catalytic subunits, SMARCA4 and SMARCA2, have bromodomains which bind acetylated histones, anchoring SWI/SNF to acetylated genomic sites [26–29]. Other BAFs such as SMARCD1, 2, and 3, and SMARCE1 are important for mediating interactions with a diversity of nuclear factors that recruit SWI/SNF to specific genomic sites [30–38]. Due to the distinctive and shared composition of BAFs, the various SWI/SNF complexes not only shape chromatin in a highly regulated manner, but also exhibit specialized functions *in vivo*. This high level of SWI/SNF regulation is frequently disrupted in cancer by mutations, altered subunit expression, activity, or aberrant SWI/SNF recruitment to genomic sites.

All three major SWI/SNF complexes play a critical role in the regulation of gene expression. cBAF, PBAF, and ncBAF are required for transcription, especially for the activation and repression of gene expression, during embryonic development and cellular differentiation, and in response to a plethora of external stimuli [8,39–45]. The various SWI/SNF complexes are targeted to different genomic regions to regulate overlapping and distinct genes and can compensate or have antagonistic roles. For example, SMARCA4 and SMARCA2 are paralogous subunits that exist in different SWI/SNF complexes and can compensate for each other in RB signaling but have antagonistic roles in p53 signaling [46,47]. ARID1B can partially compensate for ARID1A loss in the regulation of enhancer architecture in colorectal cancer cells [48]. The PBAF and cBAF complexes have divergent roles in the regulation of exhausted T cell differentiation; PBAF preserves stemness, while cBAF promotes differentiation to effector T cells [49]. Deficiency of the PBAF subunit, PBRM1, constricts T cell exhaustion and has been associated with an improved response to immunotherapy in melanoma and clear cell renal cell carcinoma [50–52]. Some of the distinct functions of the various complexes arise as a result of the genomic locations they occupy. cBAF complex occupancy is concentrated at gene enhancers [53,54], PBAF complexes at gene promoters [55], and ncBAF complexes at promoters and CTCF sites, which

define topologically associated domain (TAD) boundaries [5]. Despite differential genome localization, there appears to be cross talk between the different complexes that is relevant in cancer. For example, the loss of PBAF results in the genomic re-distribution of cBAF complexes in melanoma cells, and the loss of cBAF disturbs the genomic occupancy of PBAF in transformed epithelial cells [55,56]. There is also the de-stabilization of cBAF complexes by the loss of SMARCE1 deficiency in clear cell meningioma which increases ncBAF activity [57]. SWI/SNF plays critical roles in transcription by regulating access to the transcriptional machinery, maintaining chromatin architecture in order to establish enhancer–promoter contacts [58]. Blocking SWI/SNF activity can have immediate consequences on genome-wide chromatin accessibility, transcription factor binding, and gene expression, indicating that SWI/SNF activity is continuously required to maintain proper chromatin architecture [59–61]. Because of its critical role in transcription, perturbations in the SWI/SNF complex structures and functions result in widespread gene expression alterations that promote tumorigenesis.

SWI/SNF complexes play an important role in the maintenance of genome integrity and cellular survival from DNA damage. In response to double-strand breaks (DSBs), SWI/SNF complexes silence transcriptionally active genomic sites to facilitate efficient repair by either homologous recombination (HR) or non-homologous end joining (NHEJ). In HR, the PBAF and ncBAF complexes evict RNA polymerase II near the sites of DNA damage to rapidly silence transcription, while the cBAF complex maintains transcriptional silencing and promotes recruitment of the repair proteins, RNaseH1 and RAD52, to facilitate R loop resolution [62]. The BRD9 component of ncBAF also binds to an acetylated lysine on RAD54 and promotes RAD54 and RAD51 interactions [63]. PBAF also mediates transcriptional silencing and cBAF allows for recruitment of repair proteins during NHEJ [64,65]. SWI/SNF complexes have also been implicated in nucleotide excision repair (NER) through both the transcription-coupled repair (TCR) pathway and global genome repair (GGR) [66]. SWI/SNF increases NER efficiency on nucleosomal DNA by making it accessible to DNA repair enzymes [67,68] and has been reported to recruit NER factors, including XPC, ATM, XPG, PCNA, ERCC1, and ERCC5 in cells [69–71]. SWI/SNF increases base excision repair (BER) of nucleosomal DNA *in vitro* [72]. ARID1A-deficient cells accumulate abasic (AP) sites, exhibit delayed recruitment of BER repair proteins, and are highly sensitive to the combination of temozolomide and PARP inhibitors [73]. ARID1A promotes mismatch repair (MMR) by recruiting MSH2 to chromatin during DNA replication. A deficiency in SWI/SNF subunits is associated with defective mismatch repair and enhanced mutation load, rendering ARID1A-deficient tumors responsive to immune check point inhibitors [74–76]. Conversely, mismatch repair enzymes also interact with SMARCA4 to rewire the chromatin landscape in a manner that is conducive to tumorigenesis [77]. The SMARCA4 subunit is required for replication fork progression [78], and both SMARCA4 and ARID1A contribute to the resolution of transcription–replication conflicts which can lead to replication stress [79,80]. SWI/SNF deficiency in lung cancer cells results in increased origin firing, increased replication stress, and heightened sensitivity to ATR inhibitors [81]. In combination, these findings point to an important role for SWI/SNF in maintaining genome integrity and survival in response to DNA damage.

2. SWI/SNF in Cancer

Approximately 20% of human cancers have mutations in SWI/SNF genes, many of which are loss-of-function mutations, suggesting that the disruption of SWI/SNF activity promotes cancer initiation or progression [82,83]. Indeed, some SWI/SNF subunits are verified tumor suppressors (see [84–87] for detailed recent reviews on SWI/SNF loss in cancer). The loss of ARID1A occurs in a variety of human cancers and de-regulates gene expression by disrupting SWI/SNF occupancy at enhancers, leading to the initiation of liver cancer [53,88]. The disruption of the SMARCB1 subunit frequently occurs in pediatric malignant rhabdoid tumors (MRT), epithelioid sarcomas, chordomas, and renal medullary carcinomas [89]. In the absence of SMARCB1, SWI/SNF binding to lineage-

specific enhancers is disrupted while binding to oncogenic super-enhancers is retained, thus favoring tumorigenic gene expression [90]. The rescue of SMARCB1 in SMARCB1-deficient cancer cells abrogates proliferation and promotes differentiation [91,92]. The disruption of one allele of SMARCB1 in mice results in tumorigenesis with a loss of heterozygosity, which is consistent with the classical definition of a tumor suppressor [93,94]. The loss of ARID2 occurs frequently in hepatocellular carcinoma and melanoma [95,96] and disrupts PBAF complex assembly, also altering BAF genomic distribution to favor the expression of genes that promote invasion [55]. PBRM1 loss in renal clear cell carcinoma results in histone modifications at promoters, leads to genomic re-distribution of PBAF complexes, and promotes tumorigenic gene expression [97,98]. Many other studies indicate that alterations in the SWI/SNF complex occurring in cancer perturb enhancer dynamics, histone modifications, and transcription factor binding [48,99,100]. Hence, particular SWI/SNF subunits are tumor suppressors and their loss in cancer leads to the de-regulation of gene expression.

The SWI/SNF complex stands out as a highly promising target for cancer therapeutics. Strategies directed at targeting SWI/SNF encompass the inhibition of its catalytic activity or the suppression of specific subunit functions. The decision to inhibit the SWI/SNF complex, despite its recognized tumor-suppressive function, is rooted in a multifaceted rationale. SMARCA4 has a context-dependent pro-tumorigenic function. In hematological malignancies, SMARCA4 promotes transcription factor binding to lineage-specific *MYC* enhancer elements, driving long-range chromatin looping interactions with the *MYC* promoter to favor oncogenic gene expression [101]. Similarly, SMARCA4 is required to maintain chromatin accessibility at lineage-specific enhancers to favor binding of transcription factors that drive prostate cancer cell proliferation [102]. In several cancer types, SWI/SNF is also hijacked by oncogenes to elicit gene expression profiles that promote tumorigenesis [98,103–107]. The pharmacological inhibition of SWI/SNF function is useful in these cancer contexts.

The inhibition of SWI/SNF function is also useful in cancers where there is a loss of a SWI/SNF subunit because residual SWI/SNF complexes can be rewired to take on oncogenic roles. Synthetic lethal relationships among SWI/SNF subunits render cancers with a loss-of-function mutation in one SWI/SNF subunit vulnerable to the inhibition of a second subunit. For example, SMARCA4-deficient cancer cells lose tumorigenicity and undergo cell cycle arrest and senescence upon the depletion of SMARCA2 [108–110]. ARID1A-deficient cancer cells are vulnerable to the loss of ARID1B, such that a concomitant loss of ARID1A and ARID1B disturbs enhancer dynamics at growth promoting loci [48]. Cancer cells lacking SMARCB1 or SMARCE1 demonstrate heightened ncBAF activity, leading to the induction of a growth-promoting gene expression signature. Consequently, these tumors exhibit a heightened susceptibility to BRD9 inhibition [9,57]. Therefore, there are multiple examples which show that SWI/SNF-deficient cancer cells can be targeted for elimination by further impairing SWI/SNF function.

SWI/SNF subunit loss can sensitize cancer cells to a wide range of therapeutics. There is a synthetic lethal relationship between SMARCA4 and the PTEN tumor suppressor in prostate cancer, rendering PTEN-deficient cells sensitive to SMARCA4 inhibition [111]. SMARCA4 loss sensitizes non-small cell lung cancer cells to CDK4/6 inhibition [112]. ARID1A loss in ovarian, breast, and pancreatic cancer cells sensitizes them to HDAC inhibitors [113–115]. SMARCA4-deficient lung and ovarian cancer cells are insensitive to HDAC inhibition but are highly sensitive to KDM6 histone demethylase inhibition [116]. The loss of other SWI/SNF subunits has been associated with an enhanced response to CDK4/6 inhibitors, immunotherapy, and other therapeutics [73,81,117]. In a recent Phase I clinical trial, durable responses to the ATR inhibitor, Ceralasertib, occurred in patients whose tumors were ARID1A-deficient and had high levels of DNA damage and inflammation [118]. In some contexts, SWI/SNF activity is required for proliferation and tumorigenesis [119], with high levels of SWI/SNF subunits associated with poorer patient survival [120,121]. Some missense mutations in SMARCA4 have been determined to be

gain-of-function mutations, increasing remodeling efficiency and promoting promiscuous chromatin accessibility [25]. These observations have been the impetus to develop pharmacological approaches that intentionally inhibit SWI/SNF function in order to induce synthetic lethality or to exploit vulnerabilities that render tumors responsive to cancer therapeutics.

3. Pharmacological Inhibition of SWI/SNF Function

Several types of drugs are available to pharmacologically suppress SWI/SNF function (Table 1).

Table 1. Drugs that inhibit SWI/SNF function and their effects on cancer cells.

Drug Name	Mechanism of Action	Cancer Models in Which Drug Is Effective
ADAADi	Inhibitor of DNA-dependent ATPase activity	Prostate, breast, hepatoblastoma, lung cancers, and HeLa cells
BRM014	Allosteric inhibitor of SMARCA4/2 catalytic activity	Glioma, leukemia
BRM011	Allosteric inhibitor of SMARCA4/2 catalytic activity	Leukemia
JQ-dS-4	PROTAC: CRBN-based allosteric inhibitor of SMARCA4/2 catalytic activity	Glioma
FHD-286	Allosteric inhibitor of SMARCA4/2 catalytic activity	Leukemia, uveal melanoma
PFI-3	Class VIII-selective SWI/SNF bromodomain inhibitor: SMARCA4/2, PBRM1	Multiple myeloma, glioblastoma when combined with temozolomide
PB16	PBRM1-selective bromodomain inhibitor	Prostate cancer
GNE-235	PBRM1-selective bromodomain inhibitor	Not yet tested
ACBI1	PROTAC: VHL-based Class VIII bromodomain-selective ligand that degrades SMARCA4/2 and PBRM1	Alveolar rhabdomyosarcoma, leukemia
AU15330	PROTAC: VHL-based Class VIII bromodomain-selective ligand that degrades SMARCA4/2 and PBRM1	Prostate, glioma, breast cancers, multiple myeloma, lymphoma, EWING sarcoma, SMARCA4-null melanoma, synergistic with enzalutamide in prostate cancer
A947	PROTAC: VHL-based Class VIII bromodomain-selective ligand that selectively degrades SMARCA2	Lung cancer
LP99	Class IV bromodomain inhibitor that inhibits BRD9 and BRD7	Germ tumor cells
BI-7271	Class IV bromodomain inhibitor that selectively inhibits BRD9	Leukemia
BI-7273	Class IV bromodomain inhibitor that selectively inhibits BRD9	Leukemia
BI-9564	Class IV bromodomain inhibitor that selectively inhibits BRD9	Leukemia

Table 1. Cont.

Drug Name	Mechanism of Action	Cancer Models in Which Drug Is Effective
I-BRD9	Class IV bromodomain inhibitor that selectively inhibits BRD9	Leukemia, clear cell renal carcinoma, colorectal cancer, ovarian cancer in combination with DNA damaging agents
T-472	Class IV bromodomain inhibitor that selectively inhibits BRD9	Melanoma and uterine leiomyosarcoma
dBRD9	PROTAC: CRBN-based Class VIII bromodomain-selective ligand (uses BI7273) that degrades BRD9	Leukemia, synovial sarcoma, multiple myeloma, clear cell meningioma
C6	PROTAC: CRBN-based Class VIII bromodomain-selective ligand (uses BI7271) that degrades BRD9	Leukemia
VZ-185	PROTAC: VHL-based Class VIII bromodomain-selective ligand that degrades BRD7 and BRD9	Leukemia, malignant rhabdoid tumor
CFT8634	PROTAC: CRBN-based Class VIII bromodomain-selective ligand that degrades BRD9	Synovial sarcoma and soft-tissue sarcomas null for SMARCB1
FHD-609	PROTAC: CRBN-based Class VIII bromodomain-selective ligand that degrades BRD9	Synovial sarcoma and soft-tissue sarcomas null for SMARCB1
I-78	Class IV bromodomain inhibitor that selectively inhibits BRD7	Prostate cancer
2-77	Class IV bromodomain inhibitor that selectively inhibits BRD7	Prostate cancer
BD98	cBAF inhibitor, binds to cBAF complexes, and de-represses BMI1	Colon and breast cancer cells when combined with ATR inhibitor

A unique approach that led to identification of cBAF-specific inhibitors involved screening molecules for the ability to de-repress the expression of the *BMI1* gene [122]. The binding of the macrolactam inhibitor, BD98, phenocopied some features of ARID1A/ARID1B loss and synergized with ATR inhibitors to kill a diverse array of cancer cells. The inhibition of ARID1A/ARID1B with BD98 in naïve CD8+T cells also improved the efficacy of adoptive T cell therapy by preventing differentiation [123]. Although BD98 is a promising drug, the most common approaches to pharmacologically suppress SWI/SNF function have been to use inhibitors of the SMARCA4/2 ATPases (Figure 2A) or with small molecules that bind Family VIII SWI/SNF bromodomains in SMARCA4, SMARCA2, PBRM1 (Figure 2A,B), as well as Family IV bromodomains in BRD7 and BRD9 (Figure 2C,D).

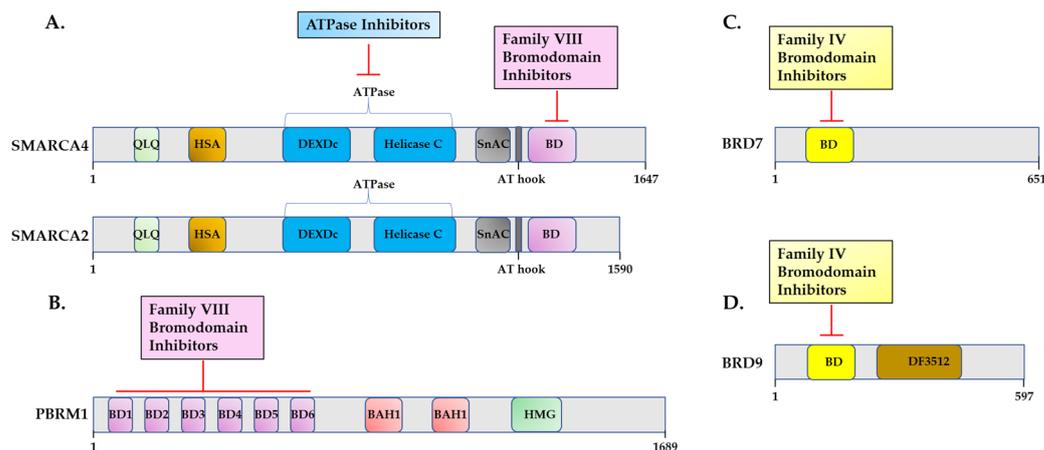


Figure 2. SWI/SNF subunits and the targeted domains. The most frequent approaches to inhibiting SWI/SNF function include the following: (A) Inhibition of the SMARCA4/SMARCA2 ATPase or inhibition of the SMARCA4 and SMARCA2 bromodomains with Family VIII inhibitors. (B) Family VIII inhibitors also bind to PBRM1 bromodomains. There are also several PBRM1-selective inhibitors. (C,D) Family IV bromodomain inhibitors bind to BRD7 and BRD9 bromodomains with varying selectivity for BRD9 or BRD7.

The effectiveness of these small molecules can be extended or enhanced by constructing proteolysis-targeting chimeras (PROTACs) [124], which covalently link the bromodomain or ATPase-binding ligand to an E3 ligase-binding ligand to achieve degradation of particular SWI/SNF subunits. An ample number of preclinical studies on these drugs have provided evidence of their therapeutic potential. Some of the drugs have recently progressed to clinical trials (Table 2).

Table 2. Clinical trials that target SWI/SNF components (<https://clinicaltrials.gov/>). Accessed on 28 December 2023.

Study Title	NCT Number	Phase/Status	Conditions	Drug/ Intervention:	Mechanism	References
FHD-286 as Monotherapy or Combination Therapy in Subjects With Advanced Hematologic Malignancies	NCT04891757	Phase 1/recruiting	Advanced hematologic malignancies like R/R AML, R/R MDS, and R/R CMML not in blast crisis	FHD-286, low-dose cytarabine, decitabine	Selective, oral inhibitor of SMARCA4/2	[125]
FHD-286 in Subjects With Metastatic Uveal Melanoma	NCT04879017	Phase 1/active, not recruiting	Metastatic uveal melanoma	FHD-286	Selective, oral inhibitor of SMARCA4/2	[126]
A Study of PRT3789 in Participants With Select Advanced or Metastatic Solid Tumors With a SMARCA4 Mutation	NCT05639751	Phase 1/recruiting	Advanced, recurrent, or metastatic solid tumor malignancies with loss of SMARCA4 due to truncating mutation and/or deletion without concomitant SMARCA2 mutation or loss of SMARCA2 protein expression	PRT3789	Smarca2-bromodomain-binding degrader	[127]

Table 2. Cont.

Study Title	NCT Number	Phase/Status	Conditions	Drug/ Intervention:	Mechanism	References
FHD-609 in Subjects With Advanced Synovial Sarcoma or Advanced SMARCB1-Loss Tumors	NCT04965753	Phase 1/active, not recruiting	Advanced synovial sarcoma or advanced SMARCB1-loss tumors	FHD-609	Intravenously administered agent that binds the BRD9 bromodomain and leads to degradation of the BRD9 protein	[128]
A Study to Assess the Safety and Tolerability of CFT8634 in Locally Advanced or Metastatic SMARCB1-Perturbed Cancers, Including Synovial Sarcoma and SMARCB1-Null Tumors	NCT05355753	Phase 1, Phase 2/active, not recruiting	Synovial or soft tissue sarcoma and SMARCB1-null tumors who have received prior systemic therapy, have relapsed/refractory tumors, have unresectable or metastatic disease, and are not candidates for available therapies known to confer clinical benefit	CFT8634	Orally taken agent that binds the BRD9 bromodomain and leads to BRD9 degradation	[129]

3.1. Inhibitors of SWI/SNF Catalytic Activity

Active DNA-dependent ATPase A Domain inhibitor (ADAADi), generated by the activity of aminoglycoside phosphotransferases, was the first inhibitor of SWI/SNF catalytic activity to be discovered [130]. ADAADi competes with DNA for binding to DNA-dependent ATPase domains and potently inhibits SWI/SNF ATPase activity and ATP-dependent chromatin remodeling [131,132]. ADAADi was found to suppress prostate cancer tumor growth and to sensitize breast cancer cells to chemotherapeutics [133,134]. ADAADi also potently suppressed the proliferation of a number of other cancer cells, including HeLa, lung cancer, and hepatoblastoma cells. Although it is unclear how specific ADAADi is for SWI/SNF ATPases over that of other DNA-dependent ATPases, as the first SWI/SNF inhibitor, it has laid the foundation for subsequent advancements in this field.

Allosteric inhibitors of the SMARCA4/SMARCA2 ATPase domains such as the compound, BRM014, are promising drugs for specific inhibition of SWI/SNF activity [135]. BRM014 and other ATPase inhibitors elicit very rapid changes in chromatin accessibility, occurring within minutes [59,60]. BRM014 potently inhibited the growth of an aggressive type of glioma harboring the histone H3 lysine 27 to a methionine mutation (H3K27M) *in vitro* and *in vivo* [136,137]. An ATPase degrader, JQ-dS-4, constructed by linking a BRG1 ATPase inhibitor to a phthalimide, which is a target for cereblon (CRBN) ubiquitin ligase, led to a reduction in chromatin accessibility at BRG1 binding sites and reduced the proliferation of H3K27M-driven gliomas. However, the degrader was less effective at curtailing tumor growth than the original ATPase inhibitor compound when used in an H3K27M glioma subcutaneous xenograft model, likely due to a reduced bioavailability of the drug. This study has demonstrated the potent anti-tumor effects of a SWI/SNF allosteric ATPase inhibitor on a highly aggressive brain cancer. It remains unclear whether generating a PROTAC from SWI/SNF ATPase inhibitors will be therapeutically advantageous over the unlinked molecule. Although promising, this study did not find that the drugs could cross

the blood–brain barrier. This is a major challenge for translating these SWI/SNF inhibitors to the clinic for treating gliomas and other brain cancers.

Acute myeloid leukemia (AML) cells were found to be highly sensitive to allosteric SMARCA4/SMARCA2 inhibitors, BRM011 and BRM014 [138]. Previous studies had determined that a subset of AML cells that are dependent on the MYC oncogene are sensitive to SMARCA4 depletion [101]. However, these allosteric ATPase compounds curtailed the proliferation of a wider range of leukemia cells. These cells were sensitive to the dual depletion of SMARCA4 and SMARCA2, but not to the depletion of SMARCA4 alone. BRM011 promoted both apoptosis and differentiation through the regulation of MYC and other oncogenic pathways, including mTORC1, IL2/STAT5, KRAS, and EMT pathways, curtailing tumor growth in AML xenograft models with no evidence of toxicity. The SMARCA4/SMARCA2 allosteric inhibitor, FHD-286, effectively suppressed the proliferation of a broad collection of patient-derived AML cells, promoted differentiation, and decreased tumor growth in vivo [125]. FHD-286 is currently in Phase I clinical trials as a monotherapy or combination therapy with the DNA-hypomethylating agent, decitabine, and low-dose antimetabolite, cytarabine, for patients with advanced hematological malignancies.

Uveal melanoma is another cancer type that is highly sensitive to treatment with allosteric SMARCA4/SMARCA2 inhibitors [139]. This rare melanoma of the eye is dependent on the cooperation between the SWI/SNF complex and the melanocyte-inducing transcription factor (MITF) to drive a transcriptional program essential for uveal melanoma cell survival. Some uveal melanoma cell lines were highly sensitive to the depletion of SMARCA4 alone and others were only sensitive to the dual depletion of both SMARCA4 and SMARCA2. The treatment of uveal melanoma cells with BRM011 decreased chromatin accessibility at MITF binding sites and suppressed MITF and MITF target gene expression. Furthermore, BRM011 suppressed tumor growth in a uveal melanoma xenograft model, with no evidence of toxicity. The potential use of allosteric inhibitors of SMARCA4/SMARCA2 is a significant breakthrough for a cancer type that has few treatment options. Uveal melanoma is a highly aggressive cancer that metastasizes in half of all patients and, unlike cutaneous melanoma, does not respond to targeted and immunotherapy approaches [140]. The inhibition of SMARCA4/SMARCA2 with FHD-286 has advanced to Phase I clinical trials for patients with metastatic uveal melanoma [126].

3.2. Targeting SWI/SNF Bromodomains

An alternative approach toward inhibiting SWI/SNF function is with the use of bromodomain inhibitors that selectively bind any of the five SWI/SNF subunits bearing bromodomains [141]. Bromodomains are protein modules that bind acetylated lysines on histones and other proteins. They are important readers of the epigenetic code and can help recruit chromatin-remodeling complexes to regions containing acetylated chromatin [142]. In mammalian cells, the sixty-one different bromodomains are contained within forty-six proteins, all sharing a conserved structural motif consisting of a left-handed bundle of four α helices, linked by loop regions of variable length to form a hydrophobic pocket. Although the bromodomain is a conserved module, there are considerable sequence variations that impart specificity in the recognition of acetylated lysine motifs. The different bromodomains are classified into eight different families based on sequence and structural similarities. The enormous therapeutic potential of drugs, which selectively bind the extraterminal (BET) family of bromodomains in Family II, has stimulated interest in developing selective drugs that target other cancer-relevant bromodomains [143–148]. Drugs that selectively target Family VIII bromodomains, including SMARCA4, SMARCA2, and PBRM1, [141,149] as well as those which target Family IV, including BRD7 and BRD9 [150], disrupt SWI/SNF interactions with chromatin, and thereby exert genomic effects.

3.2.1. Targeting SWI/SNF Family VIII Bromodomains

Several small molecules that bind Family VIII were developed and studied for their potential as cancer therapeutic agents. The first of these drugs to be characterized was PFI-3, which selectively binds to the bromodomains of SMARCA4, SMARCA2, and PBRM1 [151]. PFI-3-compromised embryonic stem cell maintenance and lineage specification, inhibited myogenesis and adipogenesis, and had mild effects on melanogenesis [152–155]. However, the inhibition with PFI-3 as a single drug had limited effects on breast cancer cell proliferation [156]. PFI-3 failed to completely displace SWI/SNF catalytic subunits from chromatin and did not re-capitulate synthetic lethality in SWI/SNF-deficient cancer cells as did the loss of the ATPase domain [157]. However, in multiple myeloma cells, PFI-3 displaced SMARCA2 and the oncogenic driver, NSD, from chromatin, suppressing oncogenic gene expression and tumor growth [158]. PFI-3 also enhanced the anti-cancer effects of temozolomide and sensitized highly resistant glioblastoma cells to the drug [159]. In combination with other DNA damaging drugs, PFI-3 induced death by displacing SMARCA4 from chromatin, compromising DSB repair [160]. These studies demonstrate that the anti-cancer effects of PFI-3 are contingent on whether the SWI/SNF VIII bromodomains are required for SWI/SNF recruitment to specific genomic sites that promote tumorigenesis or affect sensitivity to other chemotherapeutics. Furthermore, there is therapeutic potential in combining Family VIII bromodomain inhibitors with chemotherapeutics. Building upon PFI-3, next generation Family VIII bromodomain inhibitors were developed, which exert cellular effects [161,162]. Some of these newer drugs enhance cytotoxicity when combined with DNA-damaging agents in glioblastoma cells [161].

Family VIII inhibitors that are selective for PBRM1 bromodomains over those of SMARCA4 and SMARCA2 have also been developed and studied for anti-cancer effects [163–165]. Although a tumor suppressor in some cancers [166], PBRM1 promotes prostate cancer growth and progression [167,168]. As discussed previously, cancers with a loss of PBRM1 are more responsive to DNA damage and immune checkpoint inhibitors [50–52], suggesting that small molecule inhibitors selective for PBRM1 would be therapeutically useful. PBRM1-selective compounds were developed by targeting the second bromodomain of PBRM1 using an NMR-based fragment screen [164]. These drugs effectively inhibited the proliferation of an androgen receptor (AR)-positive prostate cancer cell line, with the most potent compound, PB16, exerting its effects in the sub-micromolar range. GNE-235 is a promising new PBRM1-selective inhibitor that has not yet been tested for its anti-tumor effects [165]. The promising results obtained with PB16 suggest that GNE-235 and other PBRM1-selective inhibitors should be further explored for anti-cancer effects as single drugs and in combination with DNA damaging agents and checkpoint inhibitors.

The anti-cancer effects of Class VIII SWI/SNF bromodomain inhibitors can be enhanced by linking the bromodomain-binding ligand to an E3 ligase-binding ligand [102, 165,169]. These PROTACs expand the anti-cancer effects of bromodomain inhibitors by degrading the bromodomain-containing subunits and taking them out of action. As a result, there is an inhibition of the whole subunit, not just the bromodomain. This strategy can displace SWI/SNF and suppress SWI/SNF activity at sites or in contexts that do not require SWI/SNF bromodomains for tumorigenesis.

The PROTAC, ACBI1, is a Class VIII bromodomain-binding ligand [169] linked to a ligand of the von Hippel–Lindau (VHL) E3 ubiquitin ligase that induces rapid degradation of SMARCA4, SMARCA2, and PBRM1, altering the composition of both BAF and PBAF complexes. In contrast to the non-degrader form of ACBI1, which had no anti-cancer effect, the ACBI1 PROTAC killed SMARCA4-dependent leukemia cells as well as SWI/SNF-deficient cancer cells that are dependent on residual SWI/SNF activity. ACBI1 also compromised the growth of alveolar rhabdomyosarcoma tumors harboring the PAX3:FOXO1 oncogene, demonstrating its anti-cancer effects in vivo [170].

AU-15330 is another SWI/SNF subunit degrader that similarly links a Class VIII bromodomain ligand to the VHL ligand to rapidly degrade SMARCA4, SMARCA2, and PBRM1 [102]. The treatment of AR-positive prostate cancer cells with AU-15330 reduced

DNA accessibility at oncogenic enhancer elements and disrupted enhancer–promoter loops and AR and FOXA1 occupancy, thereby suppressing oncogenic gene expression. Changes in chromatin accessibility were also elicited by the concurrent genetic depletion of SMARCA4 and SMARCA2, indicating that the degradation of the catalytic subunits underlies the effects of AU-1530. AU-1530 suppressed tumor growth in xenograft models of prostate cancer and synergized with the AR antagonist, enzalutamide. AU-1530 was effective in other cancer types. The proliferation of MYC-driven multiple myeloma cells and estrogen receptor (ER)- and/or AR-positive breast cancer cells was also inhibited by AU-15330, with no toxicity to normal cells or to animals. H3K27M gliomas were highly sensitive to AU-15330 [171]. AU-15330 reduced chromatin accessibility at non-promoter sites, including the FOXO1 enhancer. The loss of FOXO1 expression led to the loss of oncogenic gene expression and suppression of glioma cell proliferation. The anti-cancer effects of AU-15330 were attributed to the loss of SMARCA4. SMARCA4 was found to maintain gliomas in an undifferentiated stem cell state, regulate genes involved in cell growth and extracellular matrix, and promote tumor growth in vivo in an H3K27M-dependent manner [136,137]. These studies demonstrate that AU-15330 suppresses SWI/SNF activity to exert anti-cancer effects on multiple cancer types driven by oncogenic enhancer circuitry. Furthermore, the synergy observed with the AU-15330 and enzalutamide combination provides compelling evidence for combining these drugs to enhance the effects of other therapeutics.

A SMARCA2-selective degrader, A947, was generated by linking a Family IV bromodomain ligand to a moiety that is targeted to the von Hippel–Lindau (VHL) ubiquitin ligase complex [172]. Although the ligand could bind to SMARCA4, SMARCA2, and PBRM1 bromodomains, A947 rapidly degraded SMARCA2 with moderate selectivity over SMARCA4 and PBRM1. This change in ligand selectivity upon the generation of a PROTAC has been previously demonstrated and likely involves differential protein–protein interactions between the target proteins and the E3 ligase with some favoring degradation more than others [173]. Hence, the enhanced target selectivity that can be achieved with the proper design of the PROTAC demonstrates another advantage of using these molecules for inhibiting SWI/SNF bromodomains. A947 suppressed SMARCA4 mutant lung cancer growth in vivo and synergized with an inhibitor to the MCL1 anti-apoptotic protein to enhance apoptosis. PRT3789 is another potent and selective SMARCA2-targeted degrader that demonstrated synthetic lethality in SMARCA4-deficient cancers in vitro and in vivo and is currently in Phase I clinical trials for patients with SMARCA4 mutant solid tumors that express SMARCA2 [127].

3.2.2. Targeting SWI/SNF Family IV Bromodomains

BRD9 and BRD7 are paralogous subunits with highly similar Family IV bromodomains [141], but are assembled into different SWI/SNF complexes (Figure 1). Loss-of-function mutations in the gene encoding BRD9 are rare; the BRD9 gene is amplified in multiple cancers [82] and is considered an oncogene in some of them. BRD9 is therefore an attractive target in cancer. The paralog, BRD7, has context-dependent tumor suppressive or tumor-promoting functions [174–176]. The depletion of BRD7 improves the response to the immune checkpoint and CHK1 inhibitors [52,177], suggesting that BRD7 is also a potential therapeutic target in some cancers. LP99 was the first drug to bind the BRD9 and BRD7 bromodomains, displacing both proteins from acetylated histones and inhibiting the proliferation of germ tumor cell lines, with EC50s in the micromolar range [178,179]. Drugs with higher potency and varying selectivity for either BRD9 and/or BRD7 have since been developed and tested for their anti-cancer effects [180].

Many inhibitors of the SWI/SNF Family IV bromodomains have focused on BRD9. BI-7271, BI-7273, and BI-9564 are potent selective BRD9 inhibitors that suppress leukemia cell proliferation [181]. AML cells depend on BRD9 to sustain the expression of the MYC oncogene and MYC transcriptional programs to prevent differentiation and promote proliferation. BI-7273 suppressed the MYC transcriptional program and proliferation in a BRD9 bromodomain-dependent manner, but did not affect proliferation of epithelial cancer

cells [106]. I-BRD9, which has 700-fold selectivity over the BET family and 200-fold selectivity over BRD7 [182], also effectively suppressed leukemia cell proliferation [183]. I-BRD9 has been studied for its anti-cancer effects in a wide variety of cancers. I-BRD9 suppressed clear cell renal carcinoma tumor growth, a cancer in which BRD9 is up-regulated by FTO and recruited with SOX17 to enhancers that promote oncogenic gene expression [184]. I-BRD9 also blocked colorectal adenocarcinoma tumor growth through a mechanism that involves the regulation of glycolytic gene expression by BRD9 [185]. Natural phenols that inhibit BRD9 as well as I-BRD9 reduced colon cancer cell viability and colony formation by increasing DNA damage and apoptosis [186]. I-BRD9 sensitized ovarian cancer cells to DNA damaging agents, synergizing with PARP inhibitors to suppress ovarian cancer tumor growth [63]. TP-472, which has less selectivity for BRD9 over BRD7 compared to other BRD9 inhibitors, blocked melanoma tumorigenicity and tumor growth in vivo [121] as well as suppressed the proliferation of uterine leiomyosarcoma cells [187]. However, it is unclear whether BRD9 or BRD7, or both, were responsible for TP-472 anti-cancer effects. Another caveat is that TP-472 has been reported to have off-target effects on the efflux transporter ATP-binding cassette subfamily G member 2 (ABCG2) [188]. Therefore, although studies indicate that BRD9 inhibitors abrogate tumorigenicity in diverse cancer types, because the drugs differ in their selectivity, confirmation of the target via genetic depletion is crucial to understand drug mechanism in a particular cellular context.

Several BRD9 PROTACs have been constructed and shown to exert anti-cancer effects [189]. In an initial attempt to generate a BRD9 PROTAC, GSK39, a molecule with a structure similar to I-BRD9 was conjugated to a ligand that binds the cereblon (CRBN) ubiquitin ligase complex [182,190]. This compound was highly potent, but also degraded BRD7 and BET proteins, showing off-target effects. dBRD9 was then developed by utilizing BI-7273 to make the CRBN-targeting molecule. dBRD9 was highly selective for BRD9, did not degrade BRD7 or BET proteins in treated AML cells, and effectively blocked AML proliferation. dBRD9 suppressed oncogenic gene expression and induced synthetic lethality in synovial sarcoma cells more effectively than the parent compound, BI-7273, suggesting that a complete loss of the BRD9 protein is more deleterious than the sole inhibition of the bromodomain [5]. This is due, at least in part, to the bromodomain-independent binding of BRD9 to chromatin and the disruption of ncBAF when BRD9 expression is lost [191]. dBRD9 also suppressed multiple myeloma tumor growth by down-regulating ribosome biogenesis gene expression through a mechanism involving cooperation between BRD9 and BRD4, thereby increasing MYC transcriptional activity [192]. Clear cell meningioma cells with a loss of SMARCE1 were also highly sensitive to dBRD9 [57]. C6 is a recently developed orally active PROTAC that utilizes BI-7271 to make a CRBN-targeting molecule. This compound selectively degraded BRD9, did not demonstrate any observable degradation of BRD4 or BRD7, and potently suppressed AML growth in vitro and in vivo [193]. Other variations on BRD9 degraders include VZ-185, which degrades both BRD9 and BRD7 [194]. VZ-185 is VHL-based degrader that potently suppresses leukemia and malignant rhabdoid tumor cell proliferation. CFT8634 is a highly potent and orally bioavailable CRBN-based BRD9 degrader that is currently undergoing clinical trials for synovial or soft tissue sarcomas and SMARCB1-null tumors [129]. FHD-609 is a CRBN-based BRD9 degrader that is administered intravenously and is currently in Phase I clinical trials for patients with advanced synovial sarcoma or advanced SMARCB1-deficient tumors [128]. Hence, BRD9 inhibitors and degraders are promising drugs for the treatment of diverse cancers.

The first BRD7-selective inhibitors were recently developed and characterized [195]. The compounds 1-78 and 2-77 showed significantly increased affinity to the BRD7 bromodomain over that of BRD9 and were unable to displace BRD9 from chromatin, even at high concentrations. Both 1-78 and 2-77 inhibited AR target gene expression and cell growth in prostate cancer cells in a BRD7-dependent manner at sub-micromolar concentrations. In contrast, the BRD9 inhibitor, BI7273, had no effect on prostate cancer growth. These findings clearly demonstrate the selectivity of these compounds for BRD7. Interestingly, there was a high level of overlap in differentially regulated genes elicited via 2-77 and

the SMARCA4/SMARCA2 degrader (ACBI1) as well as the PBRM1 inhibitor (PB16), and less overlap with the BRD9 degrader (dBRD9) and cBAF inhibitor (BD98), suggesting sub-complex specific regulation of gene regulation in prostate cancer cells. These promising findings on these novel BRD7-selective inhibitors deserve further exploration in other cancer types and in mouse models.

4. Conclusions

The pharmacological inhibition of SWI/SNF complexes is a novel approach to treat cancer. The most frequently employed approaches for inhibiting SWI/SNF function are to utilize allosteric inhibitors of the SWI/SNF ATPases or compounds that selectively bind to the SWI/SNF bromodomains. All of these methods exert anti-cancer effects in a context-dependent manner and are surprisingly non-toxic even when combined with other drugs. It is difficult to predict which approach is better in a particular context because of the limited number of studies that have compared these different approaches. Allosteric inhibitors of ATPase function offer the advantage of rapid and effective suppression of all SWI/SNF chromatin-remodeling activities. According to one study, making a PROTAC from allosteric inhibitor molecules does not increase anti-cancer effects *in vitro* and may decrease efficiency *in vivo* due to lower bioavailability [136]. This suggests that generating PROTACs from SWI/SNF allosteric inhibitors may not be advantageous. However, given that SMARCA4 and SMARCA2 exhibit functions independent of catalytic activity [196], the development of a bioavailable PROTAC from allosteric inhibitors may hold therapeutic potential and deserves further exploration. Several studies indicate that combining bromodomain ligands to degraders frequently generates more potent molecules that can also be more selective. These studies demonstrate that, in many cases, the PROTACs are advantageous compared to the single-bromodomain ligands [169,172]. Despite the powerful effects of inhibiting bromodomain subunits, one study indicated that a disruption of SWI/SNF remodeling activity has a more profound effect on gene expression than the disruption of SWI/SNF sub-complexes through bromodomain inhibition and degradation [195]. However, the loss of ATPase subunits does not necessarily eliminate all SWI/SNF functions, as seen in cancers such as small cell carcinoma of the ovary—hypercalcemic type (SCCOHT)—where there is a dual loss of SMARCA4/2, but which retain residual complexes without the catalytic activity that may contribute to oncogenic gene expression [196].

While the chemical inhibition of SWI/SNF is a promising approach for treating many cancers, there are still unanswered questions and challenges to overcome. Although gliomas, as well as many cancers that metastasize to the brain, are sensitive to SWI/SNF inhibition, the inability to cross the blood–brain barrier will deter their efficacy in these contexts. Furthermore, although not toxic, the long-term effects of drugs that inhibit SWI/SNF function are not known. Given its tumor suppressor role, a long-term pharmacological inhibition of SWI/SNF could predispose cancer patients to secondary malignancies. Extended SWI/SNF inhibition may also compromise adult stem cell maintenance, the heart, and tissues that require SWI/SNF activity. Studies on long-term exposure, potential development of drug resistance, and the identification of biomarkers that predict efficacy are among the issues that need to be further explored.

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