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Remodeling the cancer epigenome: mutations in the SWI/SNF complex offer new therapeutic opportunities

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Abstract

Introduction: Cancer genome sequencing studies have discovered mutations in members of the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin-remodeling complex in nearly 25% of human cancers. The SWI/SNF complex, first discovered in *S. cerevisiae*, shows strong conservation from yeast to *Drosophila* to mammals, contains approximately 10–12 subunits and regulates nucleosome positioning through the energy generated by its ATPase subunits. The unexpected finding of frequent mutations in the complex has fueled studies to identify the mechanisms that drive tumor development and the accompanying therapeutic vulnerabilities.

Areas covered: In the review, we focus upon the potential roles different SWI/SNF subunit mutations play in human oncogenesis, their common and unique mechanisms of transformation and the potential for translating these mechanisms into targeted therapies for SWI/SNF-mutant tumors.

Expert opinion: We currently have limited insights into how mutations in different SWI/SNF subunits drive the development of human tumors. Because the SWI/SNF complex participates in a broad range of normal cellular functions, defining specific oncogenic pathways has proved difficult. In addition, therapeutic options for SWI/SNF-mutant cancers have mainly evolved from high-throughput screens of cell lines with mutations in different subunits. Future studies should follow a more coherent plan to pinpoint common vulnerabilities among these tumors.

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1. Background/introduction

1.1. The SWI/SNF chromatin remodeling complex- frequently mutated in human cancers.

Numerous studies over the past 40 years have given considerable insights into how mutations in classic oncogenes and tumor suppressor genes (TSGs), such as TP53, RAS, CDKN2A and PIK3CA, drive tumor development. Importantly, recent reports from large-scale cancer genome landscape studies such as the Cancer Genome Atlas (TCGA) and others firmly established the frequent occurrence of these pathogenic mutations across a broad range of human cancers (1). For example, TP53 bears somatic coding mutations in 27% of 148,281 tested tumors (COSMIC v87). However, one unexpected finding from these studies was pathogenic mutations in components of the SWI/SNF (Mating Type Switching/ Sucrose Non-Fermentable) chromatin remodeling complex in nearly 25% of all cancers, a rate that approaches the frequency of TP53 mutations.

1.2. The SWI/SNF complex- a key regulator of multiple cellular pathways.

The SWI/SNF complex, first discovered in *S. cerevisiae*, is an evolutionarily conserved multi-subunit complex that utilizes the energy of ATP hydrolysis to mobilize nucleosomes and remodel chromatin (2, 3) (4–6). Because the complex consists of 12–15 subunits, multiple complex configurations can appear, dependent upon the subunit composition (Figure 1). All complexes include a catalytic ATPase subunit (mutually exclusive SMARCA4/BRG1 or SMARCA2/BRM) and core subunits including BAF155 and SMARCB1(7). Separately, three broad sub-families of SWI/SNF complexes have been identified, BAF (BRG1 associated factors), PBAF (Polybromo-associated BAF) and the recently-described ncBAF, each defined by signature subunits including ARID1A or ARID1B (BAF), PBRM1 and ARID2 (PBAF) and GLTSCR1 (ncBAF) (8–10). SWI/SNF complex subfamilies also contain variant subunits, often encoded by multi-gene families. Multiple reports have shown roles for the complex in the regulation of a broad range of normal functions such as gene transcription, RNA processing, cell cycle, apoptosis, development, differentiation and DNA replication and repair (1). Thus, with its pivotal role in regulating these diverse pathways, one would predict an association of altered SWI/SNF function with disease.

1.3. Due to its relatively recent linkage to cancer, a paucity of mechanistic studies on SWI/SNF mutations exists.

Compared to the large number of reports detailing the mechanisms by which classic oncogenes/TSGs drive tumorigenesis, only a limited number of mechanistic studies have explored the actions of SWI/SNF mutations in human tumors. For example, in contrast to tumors with mutations in classic oncogenes/TSGs, many SWI/SNF-mutant tumors are genomically simple, possessing only the mutation in a single SWI/SNF subunit. The fact that mutations across members of the SWI/SNF complex appear at one of the highest rates across all human tumors emphasizes the need to accelerate the pace of research in this field to reach the same level of knowledge achieved for other cancer mutations. Whether the recurrently mutated genes that encode SWI/SNF subunits across a wide variety of cancers drive cellular transformation through shared mechanisms and/or share common therapeutic vulnerabilities remains an open question (1). This review will focus upon emerging

mechanisms that account for the development of SWI/SNF-mutant tumors and the potential for targeting them for treatment options. We will not cover the range of tumors that possess SWI/SNF subunit mutations or their genetics because of other recent reviews on these topics (1, 11, 12).

2. SWI/SNF complex mutations in human cancers

The first clue linking SWI/SNF complexes to cancer arose from studies identifying biallelic inactivation of *SMARCB1* in nearly all rhabdoid tumors, aggressive poorly differentiated pediatric solid tumors (13, 14). Since these seminal reports, the list of other human malignancies showing genetic loss of *SMARCB1* has greatly expanded, including epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumors, extraskeletal myxoid chondrosarcoma, myoepithelial carcinoma, renal medullary carcinoma, and poorly differentiated chordoma (15). Building upon these findings, recent next generation sequencing studies have revealed that mutations in genes encoding other SWI/SNF subunits occur broadly in cancer. For example, *SMARCA4* (*BRG1*), encoding a catalytic ATPase and a core subunit of SWI/SNF complexes, is recurrently mutated in lung cancer (16, 17), medulloblastoma (18), pancreatic cancer (19, 20), and small cell carcinoma of the ovary hypercalcemic type (SCCOHT) (21–23). Inactivating mutations of *ARID1A* occur in 45% of ovarian clear cell carcinomas, 30% of endometrioid carcinomas, 27% of gastric cancers, 18% of bladder cancers, and approximately 10% of colorectal, pancreatic and liver cancers (24–30). Finally, inactivating mutations of *PBRM1* are present in 40% of kidney cancers and 8% of pancreatic cancers (19, 31). Representative examples of tumors with significant frequencies of mutations in these SWI/SNF subunits are shown in Table 1.

2.1. Types of SWI/SNF subunit mutations-

The first studies characterizing *SMARCB1* loss in rhabdoid tumors showed a complete loss of protein, associated with either nonsense mutations or partial to complete gene deletions (32). Similarly, the preponderance of *SMARCA4* mutations in SCCOHTs results in loss of function (21–23). This paradigm has held true for other SWI/SNF subunits- the vast majority of mutations/deletions lead to a lack of protein in tumors (26, 31). Thus, most studies on SWI/SNF complex mutations have focused on genetic inactivation of SWI/SNF subunits.

However, TCGA data also demonstrate focal amplification, over-expression and/or somatic, potentially activating missense mutations in many SWI/SNF subunits including known tumor suppressors *SMARCA4* and *SMARCB1*. For example, approximately 5% of medulloblastomas, a pediatric brain tumor, possess missense mutations in *SMARCA4*, clustered within the SNF2 and Helicase domains (33–35). Of note, some of the same missense mutations found in human tumors, such as C-terminal K364del and R377H in *SMARCB1* and R885H and L921F in *SMARCA4*, occur in the rare neurodevelopmental disorder, Coffin-Siris syndrome (34–36). Whether these subunit genes with missense mutations produce altered proteins that can impact normal SWI/SNF complex functions and how they might contribute to tumor development remain unknown. A recent report did demonstrate that some *SMARCA4* missense mutations found in human tumors had aberrant

activities when assessed in mouse embryo fibroblasts (37). However, the authors did not address whether these mutant forms would drive tumor development.

2.2. Mutations in SWI/SNF can act as either tumor suppressors or oncogenes-

Multiple studies strongly support the notion that SWI/SNF loss of function mutations serve as drivers in multiple human tumors. For example, re-expression of SMARCB1 in rhabdoid tumor cell lines or SMARCA4 in SCCOHT cell lines leads to growth arrest followed by replicative senescence (38, 39). Reports using genetically engineered mouse models (GEMMs) have also established the bona fide tumor suppressor activity of SWI/SNF genes. Conditional inactivation of *Smarch1* results in 100% of mice developing cancer at a median of only 11 weeks (40). Inactivation of *Arid1a* in GEMMs contributes to the development of cancers of the colon, liver and ovary (41). In addition, deletion of *Smarca4* in GEMMs results in breast and uterine cancers (42, 43). Germline mutations in SWI/SNF subunits can also lead to familial cancers similar to other well-characterized TSGs such as *TP53* and *RB1* (11). Importantly, loss of SWI/SNF subunits often correlate with more aggressive tumors [reviewed in (1)]. Many of the pediatric/young adult cancers with a SWI/SNF subunit mutation represent some of the most aggressive tumors with little to no long-term survival (44). In adult malignancies, loss of a single SWI/SNF subunit can result in more aggressive tumor progression with decreased survival (1). Inactivation of SWI/SNF subunits in GEMMs also often leads to highly aggressive tumors. Therefore, the mutations in SWI/SNF subunits found in human cancers significantly impact the course of tumor development.

Several recent reports have implicated that overexpression of SWI/SNF complex subunits, such as ARID1A in liver cancer and SMARCA4 in breast cancer, may drive tumor development, i.e. they can also act as oncogenes (45, 46). The majority of these studies demonstrate overexpression of a SWI/SNF subunit in primary human tumors as well as inhibition of growth after knockdown of the subunit in cell line models. While these studies raise important questions about how cellular context determines the role of aberrant SWI/SNF complex activities in human tumor development, their relevance as therapeutic targets remain unclear. Briefly, the published reports do not address how overexpression of a single SWI/SNF subunit changes the functions of the entire complex. More importantly, loss of expression of individual SWI/SNF subunits often results in significant growth inhibition of normal cells and tissues raising concerns about potential side-effects if used as therapeutic targets (42, 47–50). Therefore, this review will focus upon loss of function/missense mutations in SWI/SNF subunits where therapeutic approaches have recently emerged.

2.3. Overview of individual subunit mutations-

Below, we provide brief overviews of studies of the most commonly mutated SWI/SNF subunits including some potential therapeutic vulnerabilities.

2.3.1. SMARCA2/A4—SMARCA4 (BRG1) is one of two mutually exclusive ATPases of the SWI/SNF complex. Mutations in *SMARCA4* occur more frequently than its sibling ATPase (*SMARCA2/BRM*) and generally do not appear in a particular tumor type. Mutations in *SMARCA4* can be categorized as: (1) a driver event with a simple genetic background (2) a defining characteristic in all tumors, but with a more complex genetic

background or (3) not a driver mutation, but adding to the genetic burden and acting as a tumor progression event in the tumor.

Cancers with putative *SMARCA4* driver mutations show nearly 100% of tumors with SMARCA4 protein loss, few chromosomal copy number aberrations, and rare mutations in other cancer driver genes. Only 2 tumors, small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) and SMARCA4-deficient/SMARCB1-intact rhabdoid tumors (Rhabdoid tumor predisposition syndrome 2) currently fit these criteria. SCCOHT, a rare and aggressive form of ovarian cancer found in young women, have mutational loss (germline or somatic) of *SMARCA4*, epigenetic silencing of *SMARCA2*, and rarely any other genetic abnormalities (21–23, 38, 51). Rhabdoid tumor predisposition syndrome 2 (RTPS2) defines patients with rhabdoid tumors possessing *SMARCA4* mutations rather than the hallmark SMARCB1 loss (52–54). However, SMARCA4-loss is relatively rare in childhood rhabdoid tumors in comparison to typical cases of SMARCB1-deficient tumors. The *SMARCA4* mutations in RTPS2 were mostly germline, occurred in children less than 12 months old and often associated with a poorer prognosis (52–55).

Recently, there have been tumors described with SMARCA4 loss as a defining characteristic in the context of a complex genetic background, such as SMARCA4-deficient thoracic sarcomas (SMARCA4-DTS) and potentially two newly described tumors. SMARCA4-DTS, a group of aggressive intrathoracic sarcomas, predominantly occur in men with a previous history of smoking (56–58). In addition to SMARCA4 loss in all cases, SMARCA4-DTS tumors have a more complex genetic background with mutations most commonly in *TP53* and occasionally alterations in other driver genes such as *CDKN2A*, *KRAS* and *MYC* (56–58). Other tumors with nearly 100% SMARCA4 loss include undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus) and sinonasal carcinoma (SNUC). In SMARCA4-deficient undifferentiated uterine sarcoma, a limited oncogene sequencing panel showed *TERT* promoter mutations, while SMARCA4-deficient SNUC has 3 reported cases with concurrent *APC* and *CDKN2A* mutations (59–62).

SMARCA4 mutations are also found in genetically-complex tumors presumably adding to their genetic burden. These mutations, while not found in all cases, can act as progression events in adult cancers and usually correlate with poorer prognosis, as observed with non-small cell lung cancer (17). Interestingly, *SMARCA4* mutations and protein loss have also been observed in poorly differentiated tumors, potentially associated with dedifferentiation, another progression event. This phenomenon has been noted in undifferentiated and dedifferentiated endometrial carcinomas (63–66), poorly differentiated endometrioid adenocarcinoma of the uterus (67), undifferentiated rhabdoid carcinomas of the gastrointestinal tract (68), and undifferentiated renal cell carcinoma (69).

2.3.2. SMARCA2—In stark contrast to SMARCA4, mutations in *SMARCA2* seldom occur across any tumor type. Only a few cancers to date have been described with *SMARCA2* mutations or deletions in addition to other mutational burdens, including adenoid cystic carcinoma (70–72), non-melanoma skin cancer (73, 74), hepatocellular carcinoma (75) and head and neck squamous cell carcinoma (76). Although not frequently mutated, loss of SMARCA2 expression occurs across numerous tumor types and cancer cell

lines through epigenetic silencing (77). The exact mechanism of the epigenetic silencing varies, but can arise through promoter methylation (78), promoter polymorphisms (79–81) or HDAC/EZH2-driven mechanisms (38, 82–84).

The frequency of SMARCA2 loss varies among cancers. In a few cases, nearly 100% of all tumors lose its expression, such as SCCOHT (38, 82–85) and SMARCA4-DTS (56). More commonly, SMARCA2 loss is seen in a subset of cases, e.g. undifferentiated carcinomas of the gastrointestinal tract (68). In SMARCA4-deficient cancers that retain SMARCA2 expression, several reports have shown that SMARCA2 acts a synthetic lethal target, making it a potential therapeutic vulnerability (86, 87). In contrast, tumors with dual SMARCA2/A4 loss do not show this vulnerability including SCCOHT (38, 85), SMARCA-DTS (56) and some cases of dedifferentiated (64) and undifferentiated (66) endometrium carcinomas, undifferentiated renal cell carcinoma (69) and non-small cell lung cancer (88).

2.3.3. SMARCB1—*SMARCB1* (also called *BAF47*, *INI1* and *SNF5*) regulates the epigenome as a core member of the SWI/SNF ATPase chromatin remodeling complex (89). Mutations in *SMARCB1* have previously been identified in 95% of pediatric rhabdoid tumors (RT), poorly differentiated and clinically aggressive tumors that arise primarily in the kidney and central nervous system (89). For many years, diagnosis rested upon the identification of prototypical rhabdoid cells by histopathology, often a difficult analysis for pathologists. They are now defined by biallelic alterations in the *SMARCB1* tumor suppressor gene located at chromosome 22q11.2, making loss of expression of SMARCB1 protein a diagnostic hallmark of this cancer (14, 15, 90). Beyond the common *SMARCB1* mutation, these tumors appear genetically simple and uniform, bearing no other recurrent driver mutations with primarily diploid genomes (91–93).

SMARCB1 mutations also drive development of other aggressive tumors in children and young adults- epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumors, extraskeletal myxoid chondrosarcoma, myoepithelial carcinoma, renal medullary carcinoma, and poorly differentiated chordoma (15, 94–96). Chordomas are rare tumors of the skull base and spine thought to arise from remnants of the embryonic notochord that can arise in adults and children (97). Their clinical behavior is marked by slow growth and a predilection to recur despite surgical resection. Most patients with recurrent or metastatic chordomas will eventually die from the disease (97). A subset of pediatric chordomas are described as “poorly differentiated” due to cytological atypia, increased mitotic activity, increased cellularity, and an unstructured growth pattern (95, 97). These tumors show an aggressive clinical course, high mortality, and loss of SMARCB1 expression, contrasting with the retention of SMARCB1 in conventional, less aggressive chordomas (95, 98). However, a discourse continues among the scientific community if poorly differentiated chordomas represent a distinct entity or part of an RT spectrum (95, 98).

Epithelioid sarcoma (ES) are rare and aggressive mesenchymal soft tissue neoplasms occurring in young individuals characterized by consistent loss of SMARCB1 nuclear expression, a feature also shared with RT and chordomas (99–101). A comprehensive investigation into how loss of SMARCB1 function drives ES tumorigenesis remains elusive. However, the results reported by Le Loarer et al. (2014), do corroborate two previous studies

suggesting the leading mechanism for *SMARCB1* loss of function is biallelic deletion in 22q11 encompassing the *SMARCB1* tumor suppressor gene locus (96, 102, 103).

Schwannomatosis, one form of a genetic disorder called neurofibromatosis, consists of multiple cutaneous schwannomas, central nervous system tumors, and other neurological complications (104). A mutation of the *SMARCB1* gene has been implicated in the development of schwannomatosis in both sporadic and familial cases (105, 106). *SMARCB1* mutations have been found in 45% of familial probands and 9% of sporadic patients (107). The comparison with germline *SMARCB1* mutations in patients with RT indicates that nontruncating mutations occur more significantly in schwannomatosis than in RTs ($p < 0.0001$) (107). Whereas *SMARCB1* mutations alone seemingly account for RT development, a substantial heterogeneity of mutations schwannomatosis exists even for familial disease. Schwannomas often possess mutations in the *NF2* tumor suppressor, located near the *SMARCB1* locus on chromosome 22 (108, 109) and in the *LZTR1* gene (110). As reported by Smith et al. (2014), the most common *SMARCB1* mutation in schwannomas is found within the 3'UTR- c.*82C>T (107). How this alteration contributes to the development of schwannomatosis remains unknown, but could act by regulating gene expression through alternative splicing within the UTR. Allen et al. (2015) also reported that *SMARCB1* mutations in schwannomatosis target an unidentified N-terminal winged helix DNA binding domain also present in BAF45a/PHF10 subunit of the SWI/SNF complex (111).

Several reports have linked *SMARCB1* activity to several types of DNA repair mechanisms [reviewed by (112)]. Considering the rapid course of development of *SMARCB1*-deficient RTs in newborns and young children, *SMARCB1* loss could drive tumorigenesis via the rapid accumulation of DNA mutations or chromosome instability. However, multiple studies have failed to detect any major effects of *SMARCB1* loss on DNA repair (93, 113, 114). In fact, RTs generally remain diploid and lack gene amplification or deletions detectable at the level of SNP arrays (91, 98). Interestingly, exome sequencing found RTs to have remarkably low rates of mutation with loss of *SMARCB1* being essentially the sole recurrent detectable event (91, 112, 113). Given the absence of genomic instability, the mechanisms that drive the onset of *SMARCB1*-deficient cancers in both humans and mice warrant greater attention.

2.3.4. ARID1A—*ARID1A* is an evolutionarily conserved gene that codes for the BAF250 subunit of the SWI/SNF complex (115). The protein product contains a region of amino acids that binds to AT-rich regions of DNA, the ARID region, accounting for its name (116). The subunit, along with its ARID1B paralog, appears in the SWI/SNF complex designated BAF (8, 117, 118) (Figure 1). Functionally, ARID1A plays a role in hormone signaling and development, with increased ARID1A raising the expression of glucocorticoid receptors and other steroid hormone receptors (117, 119). Mutations in *ARID1A* can also affect regulation of normal development, whereas its absence resulted in poor differentiation of stem cells (120, 121). *ARID1A* mutations appear in many types of cancers, ranging from nearly 50% in ovarian clear cell carcinoma (OCCC) to 2.5% in breast cancer (26, 122). Other cancers with significant frequencies of *ARID1A* mutations include gastric, endometrial, lung, medulloblastoma, hepatocellular carcinoma and pancreas (24, 29, 123,

124). In general, most tumors possess truncating mutations of *ARID1A* although some tumors contain missense mutations (29).

The mechanisms by which *ARID1A* loss drives tumorigenesis remain under investigation. One mechanism comes from ovarian cancer studies using a GEMM with *ARID1A* knockdown and *PI3K* mutations by Kim et al (125). They found that these mutations resulted in the loss of recruitment of an HDAC complex and promotion of an inflammation response (125). The group demonstrated that the loss of *ARID1A* impairs recruitment of the Sin3A-HDAC complex while the *PI3K* mutations increased NF-κB signaling (125). *ARID1A* loss has also been linked individually to either HDAC repression and *PI3K* pathway mutations. Chandler et al. showed that *ARID1A* inactivation along with activation of *PI3K/AKT* pathway upregulated inflammatory pathways resulting in tissue damage and subsequent carcinogenesis (126). Using a novel GEMM, the investigators found that *ARID1A* inactivation alone was not sufficient for tumor development, but required concurrent activation of *PIK3CA* (126). They also showed that inactivation of *ARID1A* and activation of *PIK3CA* led to an overproduction of IL-6, an inflammatory factor, that drove tumor growth (126). Based upon these results, they proposed that IL-6 could serve as a prognostic marker and therapeutic target (126). Another mechanism proposed by Bitler et al. implicates a dependence upon histone deacetylase 6 (HDAC6) activity for mutant *ARID1A*-driven tumor development (127). In both cellular and animal models, they found that inactivation of HDAC6 resulted in a reduction in the size of only mutant *ARID1A*-driven tumors (127). They also showed that *ARID1A* directly represses transcription of HDAC6 in RMG and TOVG21 ovarian cancer cell lines and in GEMMs. They further showed that HDAC6 inhibition promoted TP53 mediated apoptosis through HDAC6-catalyzed deacetylation of TP53 Lys120 resulting in its inactivation (127). Thus, loss of *ARID1A* increases HDAC6 expression and inhibits TP53-driven apoptosis implicating HDAC6 inactivation as a potential target for therapeutic intervention (127).

2.3.5. PBRM1—*PBRM1* is the second most commonly mutated gene in clear cell renal cell carcinoma, with mutations occurring in 29–41% of tumors and frequently co-occurring with *VHL* mutations (31, 128, 129). GEMMs demonstrated that *PBRM1* loss in ccRCC is secondary to *VHL* loss, and the combined disruption of these genes resulted in multifocal tumors (130). *PBRM1* contains six bromodomains important for association with acetylated histones. Little is known about the effects of individual bromodomains or the role they play in targeting the PBAF complex to specific genomic loci. However, recent work showed that they are not functionally equivalent in the context of ccRCC cell lines (131).

2.3.6. ARID2—Mutations in *ARID2* are found in a wide spectrum of tumor types including hepatocellular carcinoma (28, 132) and melanoma (133–135). In addition, *ARID2* mutations are found at lower levels in some cancers, such as stomach adenocarcinoma (8%) and non-small cell lung cancer (4%), that did not reach significance in reported studies. Nevertheless, cancers with moderate mutation rates in *ARID2* may also rely on disruption of the PBAF complex. Whether *ARID2* mutations can drive these diseases requires further evaluation. Only a few examples of mechanistic studies into the role of *ARID2* in tumor suppression appear in the literature. Studies from cell lines suggest that *ARID2* contributes

to tumor suppression by modulating the DNA damage response (136) or through control of transcriptional programs associated with oncogenesis and liver development (137). Because no ARID2-dependent mouse models of cancer currently exist, critical experiments monitoring the initiation and progression of ARID2-dependent tumors are lacking.

2.3.7. Other subunits—Mutations in other SWI/SNF subunits occur less frequently in human tumors. Examples include *SMARCE1* mutations in spinal meningiomas, *BCL7B/C* in gastric cancer and *SMARCC2* mutations in gastric and colorectal cancers (11). However, one of the most intriguing mutations involving SWI/SNF subunits are the fusion oncogenes possessing the SS18 subunit found in synovial sarcomas (138). Development of synovial sarcomas, aggressive and rare cancers occurring in the extremities of children and young adults, are driven by an in-frame fusion of the SS18 to the C-terminal end of SSX1 or SSX2 (139, 140). A landmark study by Kadoch and Crabtree demonstrated that the SS18–SSX protein competes with the normal SS18 protein present in SWI/SNF complexes to prevent recruitment of the SMARCB1 subunit into the complexes, resulting in its degradation (138). Therefore, initial models suggested that the fusion protein provided another mechanism for SMARCB1 loss and subsequent tumor development. However, a recent report from McBride et al. demonstrated that SWI/SNF complexes containing the SS18–SSX fusion protein rerouted the activity of the complex to drive tumorigenesis i.e. a gain-of-function event (141). This mechanism contrasts with the majority of studies where SWI/SNF subunits act as tumor suppressors (see above). A different oncogenic fusion protein, EWS-FLI1, also interacts with the SWI/SNF complex and alters its function to drive development of Ewing's Sarcoma, another pediatric cancer (142). As next-generation sequencing studies identify additional oncogenic fusion genes in human tumors, additional examples of tumorigenesis driven by their interactions with the SWI/SNF complex will likely appear.

3. Shared mechanisms of mutant SWI/SNF subunits that drive tumor development

3.1. Chromatin organization-

A consistent theme emerging from recent studies is mutations in key members of the SWI/SNF complex affect nucleosome positioning. In the absence of a normal complex, cells display genome-wide disruptions of normal patterns of nucleosome placement (5, 6, 143). While the chromatin remodeling activity of SWI/SNF predicted these findings, the non-random nature of the nucleosome positioning changes was unexpected. Recent studies from several laboratories have established that aberrant SWI/SNF complexes preferentially affect enhancers and/or super-enhancers (37, 144–146). Some of these studies have further implicated these changes as drivers of altered differentiation in SWI/SNF mutant cancers (6, 37, 144, 147). The mechanisms that determine SWI/SNF interactions with enhancers/super-enhancers and whether mutations in different subunits affect the same and/or different sites remains unknown. However, the recent development of CRISPR technologies, allowing the targeting of specific regions of the genome for deletion, silencing or activation, opens the possibilities of targeting therapeutic vulnerabilities caused by changes in enhancer/super-enhancer accessibilities.

3.2. Histone interactions-

Studies have shown that SWI/SNF complex interactions with histone modifying enzymes provides another mechanism of tumor development. The first described interaction demonstrated an antagonistic relationship between polycomb repressive complex 2 (PRC2) and SWI/SNF (148). Loss of the SMARCB1 subunit led to upregulation of the PRC2 catalytic methyltransferase subunit, EZH2, resulting in an increase in H3K27me3 marks (148). This antagonistic relationship led to uncovering the therapeutic vulnerability in SWI/SNF-mutant cancers to EZH2 inhibitors in (82, 149–151). Consistent with the antagonism with PRC2, restoration of SWI/SNF activity in deficient tumors will directly evict polycomb repressive complex 1 (PRC1) and PRC2 from chromatin, dependent upon the ATPase activity of the complex (152, 153). The chromatin independent interactions of SWI/SNF and PRC1 also depend on the ATPase activity of SMARCA4 because point mutations inactivating the its activity disrupt these interactions (152).

In addition to PRC1 and PRC2, the SWI/SNF complex also interacts with histone demethylases (HDMs), histone deacetylases (HDACs), and histone acetyltransferases (HATs). SMARCA4 interacts with KDM3A to determine the specificity of AP-1 target genes in hepatocellular carcinoma (154). In synovial sarcoma, the SS18-SSX fusion oncogene interacts with KDM2B histone demethylase, a component of the non-conical PRC1.1, to promote transformation (155). SWI/SNF also interacts with the histone acetyltransferases p300/CBP at enhancer sites, which are reduced in SMARCB1-deficient rhabdoid tumor cell lines (144). However, in SMARCB1-deficient AML, a residual SWI/SNF complex is recruited to oncogenic target genes with p300/CBP to promote H3K27Ac and gene expression (156).

3.3. Changes in SWI/SNF complex composition-

Recent studies have suggested that inactivation or loss of one subunit of the SWI/SNF complex may impact its composition, resulting in significant functional changes (145, 146, 157, 158). Co-inactivation of SMARCB1 and SMARCA2 expression occurs in cell lines and primary tumors, including RTs (84, 159, 160). The concomitant loss of SMARCB1, SMARCA2, and PBRM1 expression was detected in two epithelioid sarcomas with pure rhabdoid features (159, 161). These results suggest loss of SMARCB1 works in tandem with other SWI/SNF core subunits to drive tumorigenesis. Several recent reports underscore the impact of changes in the subunit composition of the SWI/SNF complex upon its normal activities. Mashtalir et al. have described the assembly of subcomplexes that ultimately unite to form the full SWI/SNF complex (162). Importantly, they also show that many of the subunit mutations found in human cancers alter the normal assembly of SWI/SNF complexes resulting in aberrant forms (162). Another recent report demonstrated that inhibition of BRD9, a SWI/SNF subunit that can appear in abnormal complexes induced by mutations in other subunits, can reactive epigenetically-silenced genes in tumors (163). They also demonstrated that BRD9 could regulate the activity of SWI/SNF through phosphorylation of the SMARCA4 ATPase subunit (163). Overall, these findings emphasize the critical need for further studies on the composition and activities of the SWI/SNF complex in cancers drive by mutations in different subunits, especially for identifying novel avenues for therapeutic interventions.

3.4. Interactions with established oncogenic pathways-

One of the first studies on proteins that interact with SWI/SNF complex members showed a direct and functional interaction between SMARCB1 and the CMYC transcription factor (164). This report provided a logical mechanism for how loss of SMARCB1 in tumors could fuel tumor development through increased expression of CMYC, a known oncogene. Since 1999, a growing number of reports have appeared showing direct interactions between SWI/SNF subunits and a broad array of oncogenes and TSGs such as LKB1/STK11, TP53, CDKN2A, BRCA1, CCNDE and NRF2 (165–171). However, many of these reports appear once, without validation from other laboratories. In addition, the functional consequences of these putative interactions remained unclear due to the lack of appropriate biological models. However, the role of several key oncogenic pathways to the SWI/SNF-mutant driven tumorigenesis appear clear. We discuss their interactions with the SWI/SNF complex below.

3.4.1. TP53—*TP53*, the most commonly mutated tumor suppressor in human cancers, regulates a diverse series of cellular functions including apoptosis, genomic stability, and cell cycle control (172). Nearly half of human cancers possess a *TP53* mutation and anti-cancer drugs often initiate TP53 activation to force cancer cell death (173). Several reports suggest that an interaction between the SWI/SNF complex and TP53 facilitates the latter's ability to mediate gene expression and perform its tumor suppressor functions. Lee et al. showed that SWI/SNF subunits bind to TP53 and were recruited to promoters of TP53 mediated genes (174). Inactivating mutations of *SMARCB1* and *SMARCA4* inhibited the cell growth suppression and apoptosis controlled by TP53 (174). Oh et al. later showed that the SMARCD1 (BAF60a) subunit directly interacted with TP53 through immunoprecipitation (171). They also found that TP53 could not exert its anti-cancer functions without direct interaction with the SWI/SNF complex and suggested that CDKN1A (p21) was the protein most dependent upon this interaction (171). Pfsiter et al. showed that expression of VEGFR2, a tyrosine kinase commonly mutated in breast cancer that regulates endothelial vascularization, depended upon a TP53-SWI/SNF (175). They found that mutant TP53 interacts with the SWI/SNF complex to regulate the VEGFR2 promoter through chromatin remodeling (175). He et al. further demonstrated that SMARCE1 (BAF57), SMARCD1 (BAF60A), and SMARCB1 regulated replicative senescence by directly binding to TP53 (176). Mouse models have also established functional relationships between TP53 function and SWI/SNF complex activity (48, 177). Whether the recent efforts to therapeutically target TP53 in human cancers will extend to the treatment of SWI/SNF-mutant tumors remains an exciting possibility.

3.4.2. CDKN2A (p16^{INK4A})/RB1—Reports have also established the interaction of the SWI/SNF complex with the RB tumor suppressor pathway that regulates the progression of the cell from G1 to S phase of the cell cycle (178). Reports have shown that SMARCA4-deficient cell lines do not respond to RB-mediated cell cycle arrest (179, 180). Upon re-expression of SMARCA4, the RB growth arrest pathway was restored (179, 180). Of interest, re-expression of either SMARCA2 or SMARCA4 could restore RB mediated cell cycle arrest, suggesting that each ATPase subunit could compensate for one other in mediating RB pathways (160, 179, 180). Other groups later showed that the tumor

suppressor role of SMARCB1 also depended on the CDKN2A/RB pathway (48, 181). However, while cell culture models have established the interplay between SWI/SNF complex activities and the RB signaling pathway, mouse model studies remain ambiguous. Mice heterozygous for both the *Rb1* and *Smarchb1* null alleles develop mutually-exclusive RB1-deficient or SMARCB1-deficient pituitary tumors (182). Similarly, Bultman et al did not observe an effect of Rb1 loss on mammary gland tumor incidence in a mouse heterozygous for *Smarca4* null alleles (183). Furthermore, inactivation of CDKN2A or RB1 did not accelerate tumor formation in a SMARCB1-conditional mouse model, despite aberrant upregulation of genes regulated by the target of RB pathway regulation- the E2F transcription factor (48). While these finding suggest that therapies targeting the RB pathway will prove ineffective for SWI/SNF-mutant tumors, a recent report demonstrates efficacy of CDK4/6 inhibitors for SCCOHTs and SMARCA4-deficient lung tumors (184, 185).

3.4.3. Long non-coding RNAs (lncRNAs)—One other family of regulatory molecules solidly linked to the SWI/SNF complex in cancer are long non-coding RNAs (lncRNA). Prensner et al. reported that the lncRNA, SchLAP1, antagonizes the SWI/SNF complex by binding and impairing the tumor suppressor functions of the complex in prostate cancer (186). In bladder cancers, UCA1 was reported to bind to SMARCA4 and reduce the expression of the RB/CDKN2A pathway to inhibit cell cycle arrest (187). Some lncRNA, rather than binding to the complex, recruit it, such as lncTCF7 recruiting the SWI/SNF complex to the promoter of the TCF7 gene to activate the Wnt signaling pathway (188). Other reports implicate the SWI/SNF complex in the regulation of macrophage functions and assembly of nuclear bodies through direct interactions with lncRNAs (189, 190). Because effective treatment options based on targeting lncRNAs remain in their infancy, their application as therapeutic options for SWI/SNF-mutant cancers await further developments.

4. Therapeutic vulnerabilities

Evidence for clinical activity of approved or investigational agents in SWI/SNF-mutant tumors is limited with no drugs approved specifically for treatment of SWI/SNF-mutant cancers. In pediatric SWI/SNF-mutant tumors, such as RTs and SCCOHT, the standard of care remains non-specific – surgery, high dose chemotherapy with stem cell rescue, and radiation (191, 192). SWI/SNF therapeutic targets and developing opportunities have been extensively reviewed and readers are directed to recent ones (193, 194). Therefore, this review of SWI/SNF therapeutic vulnerabilities will focus on current studies connecting SWI/SNF subunits with neoplasms to associated vulnerability and clinical trials.

Targeted drug development in SWI/SNF-mutant cancers has focused on synthetic lethal relationships with loss of SWI/SNF subunits because no gene replacement strategies have yet proven clinically effective in cancer (Table 2). For example, elucidation of antagonism between the SWI/SNF complex and PRC2 that regulates transcriptional silencing through H3K27 methylation has identified the PRC2 catalytic subunit, EZH2, as synthetic lethal with SMARCB1 loss. Thus, EZH2, a promising therapeutic target in rhabdoid tumors and other SWI/SNF-mutant cancers, is currently in numerous clinical trials (195). For example,

Tazemetostat (EPZ-6438), a selective small molecule inhibitor of the histone-lysine methyltransferase EZH2 gene, is in clinical trial, NCT02601937, a phase I open-label, dose escalation and dose expansion study for patients with rhabdoid tumors, SMARCB1-negative tumors, synovial sarcoma, and SCCOHT (196). Tazemetostat is also in phase II clinical trial (NCT02601950), a multicenter study for adults with SMARCB1-negative tumors or relapsed/refractory synovial sarcoma (197). Although both clinical trials are on-going, Italiano et al. (2018) reported the first-in-human results of Tazemetostat showing a favorable safety profile and activity in patients with refractory B-cell non-Hodgkin lymphoma and advanced solid tumors, including epithelioid sarcoma (198). However, additional clinical investigation of tazemetostat monotherapy is ongoing in phase 2 studies in adults and a phase 1 study for children, who have B-cell non-Hodgkin lymphoma and SMARCB1-negative or SMARCA4-negative tumors. Although loss of SMARCA2 and SMARCA4 appears in numerous cancers, only one clinical trial is investigating the effectiveness of EZH2 inhibitors in other SWI/SNF-mutant tumors. The phase II Pediatric MATCH trial (NCT0321366) is investigating how well tazemetostat works in patients with metastatic, recurrent or non-responsive solid tumors, non-hodgkin lymphoma, or histiocytic disorders that have *EZH2*, *SMARCB1*, or *SMARCA4* gene mutations (199).

Similar to PRC2 and SWI/SNF antagonism promoting EZH2 inhibitor therapies, SWI/SNF interactions with HDACs may also provide therapeutic vulnerabilities for SWI/SNF-mutant cancers. Specifically pan-HDAC inhibitors have therapeutic potential in SCCOHT (83). Additionally, *ARID1A*-mutant ovarian clear cell carcinomas that depend on HDAC6 expression appear sensitive to HDAC6 inhibitors (127). Several recent reports have also discovered synergy between EZH2 and HDAC inhibition, laying the rationale for combination therapy (83, 151).

Given the relative abundance of approved receptor tyrosine kinase (RTK) inhibitors in oncology, several groups have explored the efficacy of such agents in RT and SCCOHT for rapid repurposing. These studies have led to identification of SWI/SNF-mutation-dependent sensitivities to RTK inhibitors such as ponatinib and NVP-BGJ398 that likely result from altered activity of mutant SWI/SNF complexes at RTK promoters (200, 201). Currently, the clinical activity of a protein kinase inhibitor, dasatinib, is being evaluated in phase II clinical trial (NCT02059265) (202). This ongoing trial focuses on patients with recurrent or persistent ovarian, fallopian tube, primary peritoneal and endometrial clear cell carcinoma, with or without the loss of ARID1A expression, using objective tumor response (complete and partial) (203). The clinical trial is ongoing and results are not yet available.

Because many SWI/SNF-mutant cancers, such as pediatric RT and SCCOHT, have low mutation-burden, they were considered unlikely to respond to immunologic checkpoint blockade. Excitingly, recent preclinical evidence suggests that SWI/SNF mutations may underlie inflammatory phenotypes that can drive response to checkpoint blockade (204, 205). These reports identified a relationship between expression of PBAF subunits and response to checkpoint inhibitors and T-cell mediated killing (204, 205). Using CRISPR screens and cohorts of responsive patients, the investigators uncovered a relationship between loss of PBAF expression and response to therapies. This work conflicts with the simple model that loss of PBAF and SWI/SNF subunits merely drives transformation. These

exciting studies illuminate a novel therapeutic window for immunotherapies specific to the expression of the PBAF complex and highlight their importance, considering the full repertoire of SWI/SNF activity in a tumor. Indeed, recent case reports and correlative analyses of the immune microenvironment in SCCOHT suggest that immunologic checkpoint blockade may be effective in relapsed/refractory SCCOHT (206).

Despite these emerging lines of preclinical and clinical inquiry into SWI/SNF-mutation dependent therapeutic vulnerabilities, whether SWI/SNF-mutant cancers may share these vulnerabilities and how they depend on mutant SWI/SNF subunit and/or tissue type remain underexplored questions. Key differences also exist between adult and pediatric SWI/SNF-mutant tumors. For example, SMARCA2 may comprise a therapeutic target in *SMARCA4*-mutant adult lung cancers, but most pediatric rhabdoid tumors and SCCOHTs lack SMARCA2 expression through epigenetic silencing.

5. Conclusions

The finding of frequent mutations of subunits of the SWI/SNF chromatin remodeling complex by the TCGA and other tumor sequencing projects across a broad range of cancers has sparked renewed interest in targeting the epigenome with new treatment options. Because many of these mutations result in loss of function, efforts at identifying therapeutic vulnerabilities have suffered the same hurdles encountered for tumor suppressor genes such as BRCA1, RB1 or TP53. While recent studies have implicated the underlying mechanisms by which mutant SWI/SNF subunits can drive tumorigenesis, this knowledge has translated into limited novel treatment options. The only options that have led to drugs in clinical trials for these cancers have come from characterizing downstream signaling pathways altered by these mutations or through synthetic lethality screens of tumor cell lines. Therefore, accelerating the pace of research for understanding how mutations in SWI/SNF subunits drive development of nearly 25% of human cancers should become a high priority.

6. Expert opinion

To identify therapeutic vulnerabilities in SWI/SNF-mutant cancers, most studies have focused on finding downstream dependencies i.e. a synthetic lethality, created by the specific subunit mutation. This approach has primarily relied upon high-throughput methods including RNAi, CRISPR and drug screens. As discussed above, several successful drug targets have come from these studies including EZH2 and tyrosine receptor kinase inhibitors. However, a major caveat to these studies comes from the use of tumor cell lines, generally grown on plastic dishes, that may not accurately represent the original tumor from the patient.

Another concern from the screening studies relates to the focus of each screen on one type of SWI/SNF-mutant tumor. For example, the discovery of the dependence of cells with SMARCB1-deficiency upon EZH2-catalyzed H3K27 methylation came from studies with rhabdoid tumors. Once EZH2 inhibitors became available, multiple groups subsequently assessed its effects on tumors with mutations in different SWI/SNF subunits. Similar stories have emerged for HDAC, DNMT and EGFR inhibitors. These efficacy studies continue to

expand as cell lines become available from tumors with newly-discovered mutations in SWI/SNF subunits. While this scheme works, it does not appear like the most efficient manner to find new treatment avenues for SWI/SNF-mutant tumors.

We advocate for a more unified approach to the study of SWI/SNF-mutant cancers that looks for the common mechanisms that drive tumorigenesis. We believe this approach will lead to novel insights into the roles of mutations in epigenetic regulators in human tumor development and to the identification of new targets for therapeutic intervention for aggressive cancers that often possess mutations in SWI/SNF subunits. As discussed in this review, shared mechanisms have already been identified, such as altered activities in enhancers and super-enhancers, disruption of the normal functions of the RB1 and TP53 tumor suppressors, changes in SWI/SNF complex interactions with histones, sensitivity to immune checkpoint inhibitors and aberrant activities of residual SWI/SNF complexes after subunit loss. High-throughput screening efforts using cell lines with mutations in different SWI/SNF subunits should lead to faster identification of potential therapeutic vulnerabilities and allow for their prioritization for drug discovery efforts.

Another emerging issue lies in the potential for development of drug resistance. As is the case for many single therapeutic agents, cases of resistance to some of these agents have begun to appear in clinical trials. This problem may be particularly relevant to SWI/SNF-mutant tumors where increased epigenetic fluidity appears more frequently than genomic instability. The plasticity in the epigenome of these tumors may allow for rapid acquisition of drug resistance. However, this feature could also prove beneficial when considering two agent therapies. For example, resistance to tyrosine kinase inhibitors can arise through the reactivation or increased expression of a related tyrosine kinase, generally through an epigenetic change. Therefore, treatment with an epigenetic inhibitor, such as tazemetostat, in combination with a tyrosine kinase inhibitor, such as dasatinib, could be synergistic and effective for SWI/SNF-mutant tumors. Again, rather than 2 agent screens on one type of SWI/SNF-mutant tumor, a combined approach on representative tumors may prove more expedient.

One last area that remains understudied is the potential role of missense mutation in SWI/SNF subunits. As discussed in the review, missense mutations appear at “hotspots” in *SMARCA4* and *SMARCB1* in SESCOHTs and rhabdoid tumors, respectively. Missense mutations also occur at specific sites in some of the other subunits including *SMARCA2*, *ARID1B* and *SMARCC1*. Of import, many of the same missense mutations appear to drive the development of several human developmental disorders. The few studies that have assessed the effects of these missense mutations on SWI/SNF activities report significant functional consequences. Considering that the SS18-SSX and EWS-FLI1 fusion proteins imbue the SWI/SNF complex with de novo oncogenic features, these missense mutations could exert similar effects. Therapeutic vulnerabilities may also arise in tumors with missense mutations that do appear in those with loss of function, similar to differences seen between TP53 deletions versus missense mutations upon tumorigenesis. Further characterization of these SWI/SNF missense mutations may also prove efficacious for adult malignancies which often have missense mutations in SWI/SNF subunits rather than loss of protein expression.

Studies that identify common mechanisms of tumor development among different epigenetic regulators such as the SWI/SNF complex, histone modification and substitutions and DNA methyltransferases will yield new drugs for more effective treatments of a broad range of human cancers. With the further development of CRISPR technologies, treatments for SWI/SNF-mutant tumors will appear that disrupt the key enhancers and/or super enhancers required for tumor development. The completion of clinical trials for targeting of epigenetic vulnerabilities in SWI/SNF-mutant tumors such as EZH2, HDACs and BRD9 will establish the efficacy of these treatment approaches.

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Article highlights

- Mutations in subunits of the SWI/SNF complex appear in nearly 25% of all human cancers. Many of these tumors behave aggressively with little to no long-term survival. Importantly, some of these tumors possess only a mutation in one SWI/SNF subunit along with little evidence of genomic instability. Therefore, these tumors may represent true “epigenetically-driven” cancers.
- The SWI/SNF complex regulates nucleosome positioning throughout the human epigenome through an energy-driven mechanism. Because of this central role in controlling chromatin organization, mutations in the complex can disrupt the regulation of many cellular processes such as proliferation, programmed cell death and differentiation as well as normal development.
- Because of its broad regulatory roles, studies have identified multiple mechanisms underlying the development of SWI/SNF-mutant tumors including changes in enhancer and super-enhancer sites, altered interactions with key histone modifications, aberrant regulation of the RB and TP53 tumor suppressor pathways and changes in interactions with non-coding RNAs.
- Identification of targeted therapies for SWI/SNF-mutant cancers is in its infancy. However, a notable new class of drugs inhibits the EZH2 histone methyltransferase, a synthetic lethality in a subset of cancers with loss of expression of specific SWI/SNF subunits. Other studies have implicated existing tyrosine kinase inhibitors and immune checkpoint inhibitors as effective on SWI/SNF-mutant tumors. However, the efforts to identify new and effective treatments for these tumors would benefit from a unified approach of seeking common therapeutic vulnerabilities among the mutations in different subunits.

Figure 1.
Major SWI/SNF Complex Configurations.

Table 1.

Representative Spectrum of Mutations in SWI/SNF Complex Subunits Found in Human Cancers.

SWI/SNF Subunit	Tumor	Frequency	Reference(s)
SMARCA4	small cell carcinoma of the ovary- hypercalcemic type(SCCOHT) SMARCA4-deficient thoracic sarcomas(SMARCA4-DTS) undifferentiated uterine sarcoma sinonasal undifferentiated carcinoma (SNUC) lung adenocarcinoma (LUAD)	>95% ~100% ~100% ~100% 10%	(21–23) (56–58) (61) (59) (17, 207, 208)
SMARCA2	Adenoid cystic carcinoma(ACC)	<2%	(71)
SMARCB1	rhabdoid tumors epithelioid sarcoma renal medullary carcinomas	95% 55–80% 55–100%	(13, 14) (101, 209) (94, 210, 211)
ARID1A	ovarian clear cell carcinoma(OCCC) endometrial cancers gastric cancers	50% 40% 19%	(24) (24) (124)
PBRM1	clear cell renal cell carcinoma	29–41%	(31, 128, 129)
ARID2	hepatocellular carcinoma melanoma	6–18% 7%–14%	(28, 132) (133–135)

Table 2.

Synthetic Lethality Targets For The Most Commonly Mutated SWI/SNF Complex Subunits.

TUMOR	SUBUNIT	TARGET	DRUG	REFERENCE
LUAD SCCOHT		CDK4/6 BRD4 HDAC FGFR EZH2	Palbociclib OTX015 Quisinostat Ponatinib Tazemetostat	(184, 185) (212) (83) (201) (82, 151)
Gastric Endometrial Ovarian Clear Cell Colorectal		AKT Protein Kinases ATR BRD2 PI3K, PARP AURKA EZH2 HDAC6	MK-2206 Dasatinib VX-970 JQ1, iBET762 BKM120, Olaparib AURKai GSK126 Rocilinostat	(213) (214) (215) (216) (217) (218) (150, 219) (127)
Renal Clear Cell		EZH2 PD1 PDL1	GSK126 Nivolumab Atezolizumab	(150) (204, 205) (204, 205)
Epithelioid Sarcoma AT/RT RTK		MDM2/4 Proteosome FGFR EZH2	Idasanutlin, ATSP-7041 Ixazomib NVP-BGJ398 Tazemetostat	(220) (221) (200) (82, 151)
Synovial Sarcomas AT/RT RTK		BRD9	dBRD9	(10)