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## The SWI/SNF complex in cancer — biology, biomarkers and therapy

Priya Mittal, Charles W. M. Roberts<sup>†</sup>

Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA.

### Abstract

Cancer genome-sequencing studies have revealed a remarkably high prevalence of mutations in genes encoding subunits of the SWI/SNF chromatin-remodelling complexes, with nearly 25% of all cancers harbouring aberrations in one or more of these genes. A role for such aberrations in tumorigenesis is evidenced by cancer predisposition in both carriers of germline loss-of-function mutations and genetically engineered mouse models with inactivation of any of several SWI/SNF subunits. Whereas many of the most frequently mutated oncogenes and tumour-suppressor genes have been studied for several decades, the cancer-promoting roles of mutations in SWI/SNF genes has been recognized only more recently, and thus comparatively less is known about these alterations. Consequently, increasing research interest is being focused on understanding the prognostic and, in particular, the potential therapeutic implications of mutations in genes encoding SWI/SNF subunits. Herein, we review the burgeoning data on the mechanisms by which mutations affecting SWI/SNF complexes promote cancer and describe promising emerging opportunities for targeted therapy, including immunotherapy with immune-checkpoint inhibitors, presented by these mutations. We also highlight ongoing clinical trials open specifically to patients with cancers harbouring mutations in certain SWI/SNF genes.

### Introduction

The high prevalence of mutations in genes encoding chromatin regulatory proteins is one of the most notable insights into cancer biology that has been revealed by systematic sequencing of cancer genomes. Of these aberrations, mutations in genes encoding subunits of SWI/SNF chromatin-remodelling complexes are among the most frequent, collectively occurring in nearly 25% of all cancers<sup>1,2</sup>. Whereas most genes that are mutated at such

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<sup>†</sup> charles.roberts@stjude.org .

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high frequencies in cancer have been studied for many decades, recognition of a prominent role for SWI/SNF mutations is much more recent. Bi-allelic inactivating mutations in *SMARCB1* were identified in 1998 in a rare but highly aggressive type of paediatric soft-tissue sarcoma termed rhabdoid tumour<sup>3</sup>. Subsequently, genetically engineered mice with inactivation of *SMARCB1* were shown to rapidly develop cancer, with 100% penetrance<sup>4</sup>. However, it was not until the advent of results from cancer genome-sequencing studies that it became clear that *SMARCB1* was not alone<sup>5-7</sup>. It is now clear that at least nine genes encoding subunits of the SWI/SNF complexes are recurrently mutated in cancer, across a wide variety of tumour types<sup>1,2</sup>. Therefore, key questions emerge: what are the mechanisms by which these mutations contribute to cancer development? Do mutations affecting SWI/SNF subunits confer vulnerabilities upon these cancers? If so, are the vulnerabilities specific to the subunit mutated, or do any apply more broadly to cancers with diverse SWI/SNF aberrations? Most importantly, are any such vulnerabilities currently therapeutically actionable? In this Review, we provide insights into the mechanisms by which SWI/SNF mutations drive cancer and discuss some of the latest discoveries relating to therapeutic vulnerabilities, to both small-molecule drugs and immunotherapies, that are garnering substantial research and, in some cases, have led to the initiation of clinical trials.

## SWI/SNF — a chromatin remodeller

Within cells, DNA does not exist as a naked chain of nucleotides; rather, the ~3 billion base pairs of the human genome are tightly associated with histones and other proteins in a structure termed chromatin. Within chromatin, organization and compaction of the human genome are achieved by wrapping 146 base pairs of DNA around histone protein octamers, forming structures termed nucleosomes, thus enabling ~3 meters of DNA to be encased within a nucleus with an average diameter of only 5  $\mu\text{m}$ . Additionally, nucleosomes have a central role in controlling gene expression, as their presence generally prevents the binding of transcription factors, the proteins responsible for activating or inactivating the expression of specific genes. Consequently, an elaborate cellular machinery works in concert with transcription factors to mobilize nucleosomes in order to control gene expression, a process termed chromatin remodelling<sup>8,9</sup>. The SWI/SNF family of chromatin-remodelling complexes, also known as BRG1/BRM-associated factor (BAF) complexes (BOX 1), are key regulators of nucleosome positioning<sup>10</sup>. SWI/SNF complexes use the energy generated through hydrolysis of ATP to slide or eject nucleosomes<sup>11</sup>. Belying this seemingly straightforward role, SWI/SNF complexes are complicated macromolecular assemblies consisting of many diverse and variable subunits. Mammalian SWI/SNF complexes belong to three broad subfamilies: canonical BAF (cBAF)<sup>8,12</sup>; polybromo-associated BAF (PBAF)<sup>13,14</sup>; and the GLTSCR1 or GLTSCR1L-containing and BRD9-containing (GBAF) complex, which was only discovered in 2018 and is also known as non-canonical BAF (ncBAF)<sup>15-18</sup>. All three complexes contain the core subunits including SMARCC1, SMARCC2, and either of the ATPases SMARCA4 or SMARCA2, but also contain numerous variable subunits that provide each of the complexes with a distinct identity<sup>19</sup> (BOX 1). Additional heterogeneity occurs within each subfamily owing to the differential use of related subunits, which are often encoded by multi-gene families, such

that hundreds or even thousands of subtly different SWI/SNF complexes might exist within each broad subfamily.

The SWI/SNF complexes are evolutionarily conserved and were first discovered through pioneering studies in yeast, in which mutations affecting various component subunits were found to result in defective transcriptional control of mating-type switching (the SWI phenotype) or, in independent studies, of sucrose fermentation (the sucrose non-fermenting, or SNF, phenotype)<sup>20–23</sup>. Mammalian SWI/SNF complexes serve broad roles in transcriptional regulation and have been implicated in the facilitation of specific transcriptional programs such as in differentiation and lineage specification. Regions of the genome where the complexes have a clear role include enhancers, which are short non-protein-coding DNA elements that form binding sites for transcription factors and thereby regulate the transcriptional activity of adjacent genes. Enhancers constitute only a tiny percentage of the genome, but SWI/SNF complexes are highly enriched at these sites and have essential roles in modulating enhancer accessibility that is required for transcription factors to activate gene expression<sup>24–28</sup>. The functional implications of the hyper-diversity of SWI/SNF subunit composition is not entirely clear, but the different subfamilies have distinct location profiles across enhancers, promoters and gene bodies (FIG. 1), and their distinctive compositions are thought to provide specificity in interactions with transcription factors and other chromatin regulators<sup>17,19,25,29</sup>.

Transcription is not the only cellular process that requires access to specific stretches of DNA, and SWI/SNF complexes have been implicated in several mechanisms of DNA-damage repair (DDR)<sup>30</sup>. Different SWI/SNF family members have been shown to have distinct roles in DDR, ranging from modifying chromatin structure around sites of DNA damage to directly recruiting proteins required for DDR<sup>31–33</sup>. cBAF and PBAF complexes have been implicated in both non-homologous end joining (NHEJ) and homologous recombination (HR) repair processes<sup>31,34,35</sup>. Indeed, both SMARCA4 and the cBAF-specific subunit ARID1A have been shown to be recruited to sites of DNA damage and assist in HR-mediated DNA repair and NHEJ at double-strand breaks<sup>32,36</sup>. SMARCA4 has been reported to interact with poly(ADP-ribose) polymerase 1 (PARP1) at sites of DNA damage and to remodel chromatin in order to reduce nucleosome density at such sites, as well as to induce phosphorylation of histone H2AX (to produce the  $\gamma$ H2AX mark) that promotes DNA double-strand break (DSB) repair<sup>33,37</sup>. Similarly, the authors of another report identified a role for ARID1A in promoting DSB repair<sup>38</sup>. Furthermore, the loss of either SMARCA4 or ARID1A expression has been associated with delayed mitosis and abnormal chromosomal segregation, linked to roles in DNA decatenation or telomere cohesion<sup>39,40</sup>. The PBRM1 subunit of PBAF has also been implicated in DDR, with evidence suggesting a function for this protein in transcriptional silencing at DSBs, which facilitates the repair of these DNA lesions, as well as in the maintenance of centromeric cohesion that is important for the maintenance of genomic stability<sup>41,42</sup>. As discussed further below, the degree to which the tumour-suppressor activity of SWI/SNF complexes is derived from their roles in transcriptional regulation versus DDR is the subject of ongoing debate and continued investigation.

## SWI/SNF subunit mutations in cancer

SWI/SNF complexes were first implicated in oncogenesis upon the discovery that *SMARCB1* (also known as *INI1*, *SNF5* and *BAF47*; BOX 1) is inactivated by biallelic mutations in nearly all cases of rhabdoid tumour (FIG. 2)<sup>3,43,44</sup>. Rhabdoid tumours typically develop in children <3 years of age, often before the age of 1 year, and have a notably poor prognosis, with patients often surviving for <1 year after diagnosis<sup>45</sup>. Studies in genetically engineered mouse models (GEMM) demonstrated that *Smarchb1* is a bona-fide tumour-suppressor gene, with 10–30% of heterozygous mice developing cancers, mostly nervous-system and soft-tissue sarcomas (consistent with rhabdoid tumours), at a median age of 11 months<sup>46–48</sup>. Although germline homozygous inactivation of *Smarchb1* results in early embryonic lethality<sup>46–48</sup>, induced somatic homozygous inactivation results in the rapid onset of lymphomas and sarcomas in 100% of mice at a median of only 11 weeks, which is less than half the time required for cancer to form following *Tp53* inactivation<sup>4</sup>. Similarly, inactivation of *Smarchb1* in the brain of developing mice results in nearly all mice rapidly developing intracranial rhabdoid tumours<sup>49</sup>. In children, two-thirds of rhabdoid tumour arise in CNS sites (termed atypical teratoid rhabdoid tumor (ATRT), with the remainder being in kidney (termed malignant rhabdoid tumor (MRT)), or in soft tissues at other anatomical locations (sometimes termed extra-renal extra-cranial rhabdoid tumours (EERT)).<sup>45</sup> These findings clearly linked *SMARCB1* to cancer; however, as mentioned previously, not until the dawn of systematic cancer genome-sequencing studies was the breadth of SWI/SNF subunit mutations recognized.

In 2010, *ARID1A* was discovered to be mutated in nearly 50% of all ovarian clear cell carcinomas (OCCCs) and ovarian endometrioid carcinomas (OECs)<sup>5,6</sup>. Similarly, *PBRM1* mutations were identified in 41% of patients with clear-cell renal cell carcinoma (ccRCC)<sup>7</sup>. Subsequently, myriad cancers were found to harbour mutations in genes that encode SWI/SNF subunits. In total, at least nine different SWI/SNF subunits have been identified as being recurrently mutated in various cancers (FIG. 2), and such mutations are collectively found in nearly 25% of all cancers<sup>1,2</sup>. Interestingly, SWI/SNF subunit mutations are not randomly distributed across cancer types but rather exhibit patterns of association. For example, >95% of rhabdoid tumours have *SMARCB1* mutations, with the other 5% harbouring *SMARCA4* mutations<sup>50,51</sup>. Conversely, >90% of cases of small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), a rare form of ovarian cancer that predominantly occurs in young women with a median onset around 25 years of age<sup>52,53</sup>. SCCOHTs have been referred to as malignant rhabdoid tumour of the ovary and are the most common type of ovarian cancer in women aged <40 years. SCCOHTs are often characterized by biallelic *SMARCA4* inactivating mutations but rarely *SMARCB1* mutations<sup>53</sup>. Of note, *SMARCA2* is either epigenetically silenced and/or transcriptionally inactive in both rhabdoid tumour and SCCOHT, and transcriptional reactivation of this gene inhibits the proliferation of cell lines derived from these two tumour types<sup>52,54</sup>. Whether the absence of *SMARCA2* expression is pathogenic or simply a reflection of a non-*SMARCA2*-expressing cell of origin is unclear. Overall, *ARID1A* is the most frequently mutated SWI/SNF subunit across cancer types; however, *PBRM1* mutations are much more common than *ARID1A* mutations in ccRCC (FIG. 2). Mutations affecting components of the ncBAF

complex have been less frequently identified in cancer, although focal amplifications of *BRD9* have been identified in several cancer types<sup>55–57</sup>. Owing to the fact that mutations in *SMARCB1* were identified in cancer more than a decade before mutations in genes encoding other SWI/SNF subunits, and because *Smarca1* inactivation leads to the rapid onset of genomically simple cancers in mice, preclinical models with *SMARCB1* mutation have been central to the study of SWI/SNF function in cancer.

Mutations in genes encoding SWI/SNF subunits, which include nonsense, frameshift and deletion mutations, are often suggestive of loss-of-function phenotypes. Missense mutations might be the most common type of mutation and are preferentially located in conserved domains of SWI/SNF subunits, for example, within the enzymatic ATPase domain of SMARCA4<sup>58</sup>. A substantial body of data from in vitro and in vivo studies supports the notion that SWI/SNF subunit mutations are indeed tumour-promoting. For example, studies in GEMMs have shown that inactivation of *Smarca1*, *Arid1a*, *Smarca4* or *Pbrm1* results in cancer phenotypes<sup>24,59,60</sup>. Thus, these genes clearly qualify as tumour suppressors, but the cancer-driving mechanism involved might be somewhat complicated. For example, although genetic mutations result in the absence of SMARCB1 protein in rhabdoid tumours, residual SWI/SNF complexes are present and are essential for the survival of rhabdoid tumour cell lines<sup>15,17,18</sup>. This finding raises the possibility that *SMARCB1*-mutant cancers, rather than being driven by the absence of SMARCB1 protein per se, are driven by aberrant functioning of residual SWI/SNF complexes, thereby blurring the line between loss-of-function and gain-of-function phenotypes. Further adding to this complexity, SWI/SNF aberrations that result in gain-of-function chromatin phenotypes have also been identified; one such aberration is the *SS18–SSX* fusion found in synovial sarcoma, which confers SWI/SNF complexes with increased nucleosome mobilization activity<sup>61,62</sup>.

Within the spectrum of human disease, the pathogenic role of SWI/SNF subunit mutations is not confined to cancer. Germline heterozygous mutations of genes encoding specific SWI/SNF subunits form the aetiological basis of the rare neurodevelopmental disorders known as Coffin-Siris-syndrome (CSS; OMIM #135900) and Nicolaides-Baraitser syndrome (OMIM #601358). Patients with CSS harbour mutations in an array of genes belonging to the cBAF subfamily of SWI/SNF complexes: the most commonly mutated subunit is *ARID1B*, followed by *ARID1A*, *SMARCB1*, *SMARCA4*, *SMARCA2* and *SMARCE1*<sup>63</sup>. By contrast, Nicolaides-Baraitser syndrome is exclusively associated with missense mutations in *SMARCA2*<sup>64</sup>. Notably, specific missense mutations in *SMARCA4* (R885H and L921F) and *SMARCB1* (K364del and R377H) are found in both patients with CSS and those with cancer, suggesting that the CSS phenotype can provide insights into the functional consequences of the cancer-driving mutations<sup>55,65</sup>.

## Tumorigenic mechanism of aberrant SWI/SNF

Whether the tumour-suppressive effect of SWI/SNF complexes is a consequence of aberrant transcriptional regulation or impaired DDR, or both, has been the subject of longstanding debate. Understanding the central mechanism of tumour suppression is important because this knowledge can inform therapeutic approaches. The contributions of defective DDR to oncogenesis have been widely recognized, from Boveri's original reports of rearranged

chromosomes in cancer, to discoveries that defective telomere maintenance leads to both genome instability and cancer, followed by demonstration of the integral roles of genes encoding components of various DDR machineries in tumour suppression<sup>66–68</sup>. Given the identified roles of SWI/SNF complexes in DDR, a simple model can be postulated: SWI/SNF complexes are essential for the maintenance of genome integrity and, thus, dysfunction of these complexes leads to high rates of genetic mutations, which in turn drive cancer development. Numerous findings, however, are not easy to reconcile with such a model. Notably, rhabdoid tumors that result from germline *SMARCB1* mutation, despite being highly aggressive and lethal, have remarkably simple diploid genomes<sup>69,70</sup>. The same is true for SCCOHTs, which are often associated with germline *SMARCA4* mutations, and for ccRCCs with *PBRM1* mutations<sup>71,72</sup>. Some cancers with SWI/SNF subunit mutations do indeed have high mutational burdens, but in these cases, the SWI/SNF gene mutations are rarely, if ever, germline. Consequently, it is difficult to determine in these cases whether the SWI/SNF gene mutation predisposed cells to genomic instability or whether a pre-existing genomically unstable neoplastic cell subsequently acquired a SWI/SNF gene mutation that facilitated clonal expansion and cancer progression. Clear evidence of the latter scenario has been reported, with mutation of *ARID1A* being identified as one of the few genes that is more commonly mutated in metastatic than in primary endometrial or breast cancers<sup>73,74</sup>.

An additional finding that is challenging to reconcile with DDR as the central tumour-suppressive mechanism of SWI/SNF complexes relates to reports that restoration of SWI/SNF subunits in mutant cell lines typically results in cell-cycle arrest or death of the cells<sup>52,75</sup>. Expanding on this paradox, if aberrations of SWI/SNF subunits simply enable the generation of cancer-promoting mutations in DNA owing to genetic instability, such mutations would not be reversed upon restoration of SWI/SNF expression, and the cancer cells should continue to grow. Indeed, ongoing genetic instability can confer toxicity and negative selection on cancer cells, as illustrated in cancers driven by telomerase mutations wherein, after cancer development, the cancer cells often evolve mechanisms that restore telomerase function and maintain genome integrity<sup>67</sup>. Additionally, whereas agents that cause non-specific genomic toxicity, such as radiation, can result in many types of cancer, mutations in SWI/SNF subunits are often associated with remarkably specific cancer phenotypes. For example, inactivation of *SMARCB1* is largely confined to the aforementioned rare paediatric rhabdoid tumours and a few other rare types of cancer (FIG. 2). Consistent with such specificity, *Smarchb1* inactivation in mice results in the rapid development of lymphomas that are derived from a highly specific subset of memory CD8<sup>+</sup> T cells<sup>76</sup>. Notably, loss of SMARCB1 expression does not give rise to cancers derived from CD4<sup>+</sup> T cells, immature T cells, B cells or myeloid cells — only from CD8<sup>+</sup> memory cells<sup>76</sup>. Thus, although cancers that occur after *SMARCB1* inactivation arise rapidly, they are derived from exquisitely specific cell types, which argues against a non-specific promotion of cancer through genomic instability. Also inconsistent with DDR being the central tumour-suppressive function of SWI/SNF complexes, rhabdoid tumours caused by *SMARCB1* mutation are largely restricted to children aged < 3 years<sup>50</sup>. In older children, the risk of rhabdoid tumours decreases precipitously,<sup>50</sup>

Although DDR defects are often assumed to be a central cause of cancer, the links between defective transcriptional control and malignant transformation are remarkably



strong. Studies reported in the 1980s and 1990s revealed that recurrent chromosomal translocations in acute leukaemias do not perturb DDR or alter genome integrity, but rather cause aberrant expression of lineage-specifying master transcription factors<sup>77</sup>. Such cancers typically have simple genomes, suggesting that, in the setting of perturbation of the transcriptional control of lineage specification, chromosomal instability is not required — and might even be selected against — for cancer formation<sup>70,78,79</sup>. Moreover, mouse models of several cancers have been used to demonstrate that the disruption of transcriptional regulation can lead to remarkably rapid cancer onset, faster than that of cancers driven by mutations in genes encoding mediators of DDR<sup>80–83</sup>. Collectively, these findings allude to the power of dysfunctional transcriptional regulation in promoting cancer. Although SWI/SNF complexes have been linked to DDR pathways, their links to transcriptional regulation are more extensive<sup>25,84</sup>. Ultimately, the activities of SWI/SNF in DDR and transcriptional regulation both have the potential to suppress cancer, and disruption of each function might contribute to SWI/SNF subunit-mutant cancers; however, supported by the rationale described above, in our view, the evidence seems most consistent with disruption of the function of lineage-specifying transcription factors as the central mechanism.

### Prognosis of SWI/SNF-defective cancers

With mutations in SWI/SNF gene being found in nearly 25% of cancers, the question naturally arises whether such mutations have prognostic significance. These mutations have indeed been linked to a worse prognosis across several cancer types<sup>85</sup>. Of note, not only mutations but also overall changes in the expression of specific SWI/SNF subunits are implicated as prognostic markers for survival. In patients with hepatocellular carcinoma or cervical cancer, for example, loss of SMARCA2 and ARID1A expression, respectively, is associated with unfavourable overall survival<sup>86,87</sup>. However, the association between reduced expression and a poor prognosis is not universal: low expression of SMARCA4 and ARID1A proteins is associated with favourable outcomes in both patient with breast cancer and those with bladder cancer<sup>88–90</sup>. Conversely, high expression of SMARCA4 is associated with an unfavourable prognosis in patients with hepatocellular carcinoma<sup>86,90,91</sup>. These findings suggest that the effects of SWI/SNF aberrations on prognosis are subunit-specific and/or context-specific.

One of the starkest examples of the context-specific effects of SWI/SNF aberrations is provided by the distinct phenotypes of tumours associated with *SMARCB1* mutations<sup>92</sup>. *SMARCB1*-deficient rhabdoid tumours are among the most aggressive and lethal paediatric cancers; however, mutations in *SMARCB1* — although probably hypomorphic — also form the aetiological basis of familial schwannomatosis, which is characterized by a predisposition to benign tumours<sup>3,93,94–96</sup>. Thus, distinct mutations in the same gene can lead to markedly different tumour types and prognoses<sup>65,85,97,98</sup>.

Collectively, these findings indicate that the consequences of mutations and alterations of SWI/SNF subunit expression are highly context-specific and do not universally confer a poor prognosis. Such complexities are not unique to cancers with SWI/SNF aberrations. For example, mutation of the gene encoding enhancer of Zeste homologue 2 (*EZH2*), which is the catalytic histone-lysine *N*-methyltransferase subunit of the Polycomb repressive

complex 2 (PRC2) and thus another chromatin-remodelling factor, is also associated with cancer in discrepant contexts. Loss-of-function mutations of *EZH2* are found in T cell acute lymphoblastic leukaemia (T-ALL), whereas gain-of-function *EZH2* mutations are found in diffuse large B cell lymphoma (DLBCL)<sup>99,100</sup>. Mutations in *EZH2* also constitute the aetiological basis of Weaver syndrome (OMIM# 277590), a rare overgrowth syndrome that is reported to be associated with cancer predisposition<sup>101</sup>. Together, these data suggest that mutations affecting chromatin-remodelling factors, such as SWI/SNF complexes, do not directly dictate the level of aggressiveness or prognosis of cancers. Rather, we propose a model in which SWI/SNF gene mutations simply impair transcriptional control, and the variable consequences of that impairment are largely dictated by the underlying biology of cell in which the mutation arises and, in particular, the transcription factors expressed therein.

## Emerging therapeutic vulnerabilities

The fact that genes encoding SWI/SNF components are widely mutated in cancer raises several key questions, including whether such mutations, despite promoting cancer growth, result in synthetic lethal dependencies and, if so, are these dependencies therapeutically tractable. If tractable, defining whether any such dependencies are specific to the particular subunit that is mutated and/or the tissue of origin, or whether the mutations confer shared synthetic lethal dependencies regardless of which subunit is mutated, will be important. Emerging data indicate that mutations in SWI/SNF gene do indeed result in vulnerabilities in cancers, some of which are subunit and/or cell-type specific, although others are potentially more broadly applicable. The pursuit of therapeutic translation is underway for several of these vulnerabilities (FIG. 3), with a number of treatment approaches being tested in ongoing clinical trials involving patients whose cancers harbour SWI/SNF aberrations (TABLE 1).

## Directly targeting SWI/SNF complexes

One type of vulnerability has been clearly recognized based on findings that mutations in certain genes encoding SWI/SNF subunits often create specific dependencies on genes encoding other SWI/SNF subunits. Such data suggests a model whereby subunit mutations do not fully inactivate SWI/SNF function but rather result in aberrant cell function owing to a reliance on the activity of alternative residual SWI/SNF complexes<sup>102,103</sup>. For example, screens revealing that *ARID1A*-mutant cell lines are specifically dependent on its paralogue, *ARID1B*<sup>102</sup> were among the first studies to illustrate a broader concept of paralogue dependencies. Similarly, *SMARCA4*-mutant cell lines have been shown to be enriched for dependence on its paralogue, *SMARCA2*<sup>102,104,105</sup>. These findings suggest a mechanism whereby loss of a SWI/SNF subunit is partially compensated for by a paralogue, making the paralogue a particular vulnerability. Such intra-complex dependencies are not restricted to paralogous subunits, as *SMARCB1*-mutant cell lines have been shown to have an increased dependence on the non-paralogous SWI/SNF subunit BRD9<sup>17,18</sup>. Indeed, the identification of this dependency contributed to the recent discovery of the third subfamily of SWI/SNF complexes, that is, the BRD9-containing ncBAF complexes that lack SMARCB1<sup>15</sup>. Thus, disruption of the two SMARCB1-containing subfamilies of



SWI/SNF complexes (cBAF and PBAF) might increase dependence on this third subfamily. Collectively, the discovery of these dependencies has led to testing of whether they can be exploited therapeutically.

Several molecules capable of inhibiting SWI/SNF ATPase activity have been identified. For example, an orally available allosteric inhibitor of both SMARCA2 and SMARCA4 has been discovered and has demonstrated antiproliferative activity in a mouse xenograft model of *SMARCA4*-mutant lung cancer<sup>106</sup>. Protein degraders are being pursued as another means of targeting SMARCA2 and SMARCA4<sup>107</sup> (FIG. 3). In particular, the development of proteolysis targeting chimeras (PROTACs) has enabled targeting of previously intractable targets<sup>108–110</sup>. PROTACs are bifunctional molecules that use either the Von Hippel-Lindau (VHL) or cereblon E3 ubiquitin ligases, covalently linked to a target-binding ligand, to directly target the protein of interest for proteosomal degradation<sup>108–110</sup>. The structure-based design of a PROTAC targeting bromodomains present in SWI/SNF components resulted in the development of ACBI1, which binds to and mediates the degradation of SMARCA4, SMARCA2, and PBRM1 and has demonstrated anti-proliferative effects in *SMARCA4*-mutant cancer cell lines in vitro at concentrations ranging from 30 nM to 400nM<sup>107</sup>. PROTACs as a class of drugs have entered clinical trials in 2019, and, therefore, much remains unknown about their potential for therapeutic translation.

Importantly, the development of therapeutic strategies to target aberrant residual SWI/SNF complex warrants consideration since some *SMARCA4*-mutant cancers, such as SCCOHTs and a subset of non-small-cell lung carcinomas, lack expression of SMARCA2 and can, therefore, grow in the absence of both ATPase subunits<sup>52,111</sup>. Given the high degree of context-specificity in the association of SWI/SNF aberrations with specific types of cancer, further study will be required to determine whether cancers deficient in one subunit paralogue are addicted to that state and thus vulnerable to agents targeting the other paralogue, or whether they can evolve paralogue independence and adapt to a dual-deficient state. Notably, however, a dual-deficient state might in turn result in specific dependencies, as demonstrated preclinically by the high sensitivity of lung and ovarian cancers lacking both SWI/SNF ATPases to bromodomain inhibitors<sup>112</sup>.

Similar to targeting of the residual SWI/SNF in other cancers, the potential to target BRD9 in *SMARCB1*-mutant cancers is also of interest, particularly as small-molecule inhibitors of BRD9 (such as BI-7273 and I-BRD9), with half maximal inhibitory concentrations of <50 nM, have been developed and have anticancer activity in models of AML<sup>113,114</sup>. Given the finding of preferential dependence upon BRD9 in *SMARCB1*-mutant cancers, these molecules have been tested in rhabdoid tumour and synovial sarcoma cell lines. Whereas knockdown or deletion of *BRD9* impaired proliferation, inhibitors that bind to the bromodomain had no effect<sup>17,18,113,114</sup>. By contrast, a ‘degron’ compound that causes the degradation of BRD9 (dBRD9) was effective in such models<sup>16,17</sup>. Together, these findings indicate that simply blocking the bromodomain of BRD9 might be sufficient for anticancer activity against AML, but degradation of BRD9 is likely to be required in *SMARCB1*-mutant cancers perhaps suggesting a need for structural disruption of ncBAF in the latter case (FIG. 3).

## Targeting PRC2 via EZH2

The relationship between SWI/SNF complexes and Polycomb repressive complexes and, in particular, whether cancers with mutations affecting select SWI/SNF subunits are sensitive to inhibition of EZH2, the enzymatic subunit of PRC2, have been the subjects of a substantial body of research. Upon the discovery of the tumour-suppressor activity of SWI/SNF, the Polycomb repressive complexes became of immediate interest because earlier genetic studies in fruit flies had revealed that SWI/SNF complexes and Polycomb repressor complexes have opposing gene-regulatory functions (FIG. 1)<sup>115,116</sup>. Subsequent investigations of this phenomenon in mammalian systems and models of cancer revealed that the functional antagonism between SWI/SNF and Polycomb repressive complexes was evolutionarily conserved<sup>117</sup>. For genes bound by SWI/SNF complexes, inactivation of *SMARCB1* was shown to result in increased levels of histone H3 lysine-27 trimethylation (H3K27me3), which is a repressive chromatin mark written by PRC2<sup>118</sup>. Elegant work in model systems subsequently elucidated the mechanism involved, with recruitment of SWI/SNF complexes resulting in rapid displacement of both PRC2 and PRC1 that was abolished by mutation of *SMARCB1* (REF.<sup>119</sup>). In some models, mutations in SWI/SNF genes also resulted in increased sensitivity to EZH2 inhibition<sup>120,121</sup> (FIG. 3). Additional complexity of this relationship was unveiled when a study of human *SMARCB1*-mutant primary rhabdoid tumour specimens revealed that levels of H3K27me3 were increased at SWI/SNF-target genes, but were extremely low elsewhere in the tumour genome<sup>118</sup>. This finding suggests that *SMARCB1* mutation results in the hyper-deposition of Polycomb repressive complexes locally but, potentially as a consequence, leads to the downregulation of the overall activity of these complexes as the cells attempt to restore a balanced gene-expression profile. Thus, tumour cells might have hyper-repression at some genes but hypo-repression at others, a finding that complicates prediction of the effects of EZH2 inhibition in these cancers.

The EZH2 inhibitor tazemetostat is currently being tested in several phase I–II trials involving adults with DLBCL or *SMARCB1*-negative or *SMARCA4*-negative solid tumours and in phase I–II trials involving paediatric patients with rhabdoid tumours, synovial sarcoma, epithelioid sarcomas or other cancers harbouring *SMARCB1*, *SMARCA4* or *EZH2* mutations (TABLE 1)<sup>120,122–126</sup>. One trial is in patients with epithelioid sarcomas, a cancer type in which nearly all tumors have homozygous deletion of *SMARCB1*<sup>127</sup>. Interim data from this trial demonstrated an overall response rate of 15% with 1.6% (2 of 43) of patients having a complete response and 13% (8 of 62) a partial response. Of the patients who responded, 67% had a response lasting six months or longer. In January of 2020, based in part on these data, FDA accelerated approval was granted for the use of tazemetostat in patients aged ≥ 16 years with metastatic or unresectable epithelioid sarcomas. Additional clinical studies evaluating alternative strategies to inhibit PRC2 with either a novel allosteric inhibitor of EED or with a compound capable of dually inhibiting both EZH2 and its paralogue, EZH1 are currently ongoing<sup>128,129</sup>.

Separately from the investigation of specific hypothesized dependencies of SWI/SNF-aberrant cancers, several broad screening endeavours have been pursued with the goal of identifying either genetic or pharmacological vulnerabilities of these cancer. Although still

in their early stages, these projects have yielded mechanistic insights into SWI/SNF function and have identified several novel avenues for therapeutic investigation.

### Targeting downstream vulnerabilities

Given the findings that SWI/SNF complexes contribute to the regulation of enhancer function and, as part of this role, facilitate the acetylation of H3K27 (FIG. 1), investigation of compounds that alter histone acetylation levels are obviously of interest in the context of SWI/SNF-aberrant cancers<sup>25–27</sup>. Several studies have demonstrated the activity of histone deacetylase (HDAC) inhibitors LAQ824, SAHA and trichostatin A in ATRT cell lines<sup>130,131</sup> (FIG. 3).

In 2016, Torchia et al.<sup>130</sup> and Johann et al.<sup>132</sup> independently demonstrated that ATRT can be classified into three major groups according to their distinct epigenetic and molecular profiles: ATRT-MYC, ATRT-Sonic hedgehog (SHH) and ATRT-tyrosinase (TYR)<sup>133</sup>. In the same year, Chun et al.<sup>134</sup> reported that extra-CNS RTs could similarly be stratified into two main subgroups. Mechanistically, several independent lines of investigation have linked the loss of SMARCB1 expression with aberrant activation of the MYC or non-canonical Hedgehog (GLI1) signalling pathways, consistent with the molecular characterization of ATRT subgroups<sup>135,136</sup>. These findings have generated interest in applying targeted therapies according to the dominant molecular networks of each particular subgroup, including the bromodomain and extra-terminal motif (BET) protein inhibitor JQ1 for the MYC subgroup and Smoothed (SMO) inhibitors for the ATRT-SHH subgroup<sup>137</sup>.

Drug screens coupled with functional genomic depletion screens in rhabdoid tumour, SCCOHT and non-small-cell lung carcinoma cell lines have identified specific dependencies on kinases involved in the cell cycle, such as cyclin dependent kinase 4 and/or 6 (CDK4/6) and Aurora A, owing to disrupted transcriptional control of these pathways upon mutation of SWI/SNF genes (FIG. 3)<sup>138–141</sup>. Data from a phase I trial of the CDK4/6 inhibitor ribociclib has shown some benefit, in the form of stable disease, in paediatric patients with rhabdoid tumours<sup>142,143</sup>, and the Aurora A kinase inhibitor alisertib is being testing in an ongoing phase II trial involving children and young adults with such tumours (TABLE 1)<sup>142,143</sup>.

Similar to the cell-cycle kinases, studies have revealed the dependency of rhabdoid tumours and *ARID1A*-mutant ovarian clear cell carcinomas on several receptor tyrosine kinases (RTKs), including platelet-derived growth factor receptors (PDGFRs), fibroblast growth factor receptor 1 (FGFR1) and MET<sup>130,144–147</sup>. Thus, co-targeting of multiple RTKs using either a single multi-kinase inhibitor, such as dasatinib or ponatinib, or a combination of inhibitors might also hold promise in patients with rhabdoid tumours, SCCOHT or OCCC (FIG. 3)<sup>144,146–148</sup>. A phase II trial of dasatinib in patients with ovarian cancer, including *ARID1A*-mutant disease, is ongoing (TABLE 1).

Loss-of-function mutations in *ARID1A* often co-occur with activating mutations in PI3K, AKT or mTOR or with loss of PTEN, which all result in upregulation of PI3K–AKT signalling<sup>149,150</sup>. Several independent lines of investigation, including initial genome-wide RNA interference dropout (negative-selection) screens conducted as part of Project Achilles and mutational analyses of OCCC and OEC specimens, have revealed *PIK3CA*, which

encodes the PI3K catalytic subunit  $\alpha$  isoform, to be one of the most predominant vulnerabilities of *ARID1A*-mutant cancers<sup>151–153</sup>. Consistent with these findings, data from drug screens demonstrate increased sensitivity to PI3K and AKT inhibitors in subsets of breast and endometrial cancers harbouring loss-of-function *ARID1A* mutations<sup>152,154</sup>. These findings raise the possibility of clinical benefit from PI3K and/or AKT inhibition in patients with *ARID1A*-mutant cancers. Importantly, this approach is likely to be clinically feasible considering that >30 different inhibitors of the PI3K pathway are currently being tested in clinical trials<sup>155</sup>. However, the finding that the small-molecule SMARCA4/2 inhibitor PFI-3 has promising therapeutic activity in preclinical models of PTEN-deficient prostate cancer suggests additional complexity in the relationship between the PI3K–AKT axis and SWI/SNF function<sup>156</sup>.

MDM2 has been identified as another, probably rhabdoid tumour-specific, vulnerability: although rhabdoid tumours are typically p53 wild type, a heightened dependence on MDM2 has been demonstrated in *SMARCB1*-mutant cancers<sup>157</sup>. The mechanism of dependence remains unclear, but might relate to the role of p53 in proteostasis in *SMARCB1*-deficient cancers, as evidenced by the sensitivity of rhabdoid tumours to the proteasome and autophagy inhibitors bortezomib and chloroquine, respectively<sup>158</sup> (FIG. 3).

### Inhibitors of DNA damage repair

Therapeutic vulnerabilities relating to the role of SWI/SNF complexes in facilitating DDR have also been identified. Preclinical data demonstrate the synergy between *ARID1A* loss and VX-970<sup>159</sup>, an inhibitor of the DNA damage-checkpoint kinase ATR, as well as the efficacy of PARP inhibitors in concert with radiation in *ARID1A*-mutant tumours<sup>38</sup> (FIG. 3). Indeed, long-term remissions of *ARID1A*-mutant patient-derived xenograft tumours in mice after combined treatment with radiation and PARP inhibition support the translation of this approach into clinical studies<sup>160</sup>. PARP or ATR inhibitors are currently being evaluated in several trials involving patients with *ARID1A*-mutant cancers (TABLE 1). Data from these trials will be key to understanding the feasibility and efficacy of this therapeutic strategy across different *ARID1A*-mutant cancers. Further study is required to determine whether vulnerabilities derived from impairment of DDR extend to other forms of SWI/SNF aberration.

### Immune-checkpoint inhibition

One of the most exciting vulnerabilities associated with mutations in SWI/SNF genes that has emerged to date relates to sensitivity to immune-checkpoint inhibition (ICI). In a clinical trial involving 35 patients with metastatic ccRCC who underwent ICI with anti-programmed cell death 1 (PD-1) or anti-programmed cell death 1 ligand 1 (PD-L1) antibodies, loss-of-function mutations in the PBAF-specific gene *PBRM1* were correlated with clinical benefit, defined as a complete or partial response, or a smaller reduction in tumour burden lasting >6 months (odds ratio (OR) 12.93, 95% confidence interval (CI) 1.54–190.8;  $P=0.012$ )<sup>161</sup>. This finding was validated in an independent expansion cohort of 63 patients treated with anti-PD-1 or anti-PD-L1 antibodies alone or in combination with anti-cytotoxic T lymphocyte protein 4 (CTLA-4) antibodies (OR 6.10, 95% CI 1.42–32.64;  $P=0.0071$ )<sup>161</sup>. Accompanying in vitro studies demonstrated that loss of *PBRM1* expression facilitates

broad transcriptional changes of genes involved in the JAK–STAT and other immune-related signalling pathways, as well as hypoxia-responsive genes, that might underlie the improved responsiveness to ICI<sup>161</sup>. Separately but contemporarily, a genome-scale CRISPR screen revealed that inactivation of *Pbrm1* or either of two other genes of the PBAF SWI/SNF subfamily, *Arid2* and *Brd7*, sensitized mouse melanoma cells to T cell-mediated cytotoxicity in vitro<sup>162</sup>. These mutations were also associated with enhanced chemokine secretion by the tumour cells in response to IFN $\gamma$ , as well as higher levels of cytotoxic T cell infiltration into tumours and sensitivity to ICI with anti-PD-1 plus anti-CTLA-4 antibodies in mouse models<sup>162</sup>. *PBRM1* is mutated in 40% of patients with ccRCC<sup>7</sup>, at lower frequencies in a range of other tumour types, and ARID2 mutations occur in cancers including urothelial carcinoma and melanoma (FIG. 2); thus, a substantial number of patients could potentially benefit from ICI.

In a preclinical study, mice bearing *Arid1a*-deficient ovarian cancers treated with an anti-PD-L1 antibody had substantially reduced tumour burdens and prolonged survival compared with mice treated with a control antibody<sup>163</sup>. Additionally, such effects were not observed in treatment of *Arid1a*-wild-type tumors with anti-PD-L1 antibody, although those tumors were inherently less aggressive. Similar to the *Pbrm1*-deficient tumours, the *Arid1a*-mutant tumours contained increased numbers of cytotoxic T cell, when compared with *Arid1a*-wild-type tumours, as well as higher levels of PD-L1 expression, with similar association observed in patient-derived ovarian cancer specimens<sup>163</sup>. However, the reported mechanisms underlying the sensitivity to ICI differ between *Pbrm1*-mutant and *Arid1a*-mutant tumours. Whereas *Pbrm1* mutation enhances the immunogenicity of tumour cells via increased expression of immune-related genes. ARID1A was found to interact with the mismatch repair protein MSH2 and inactivation of *Arid1a* compromising DNA mismatch repair, resulting in increases in tumour mutational load, cytotoxic T cell infiltration and PD-L1 expression<sup>163</sup>. Other studies have revealed that levels of PD-L1 are increased in patient-derived *ARID1A*-mutant gastric cancer specimen and in *ARID1A*-mutant cell lines, relative to their wild-type counterparts, and have linked this finding to observed benefits of ICI<sup>164–166</sup>. Of note, the link between *ARID1A* mutation and immune activation may be context dependent rather than universal as a 2020 analysis found that *ARID1A* mutations correlated with markedly higher immune infiltrates in endometrial, stomach and colon cancer but dramatically lower CD8<sup>+</sup> T cell infiltrations in renal clear cell carcinoma<sup>167</sup>.

The association between SWI/SNF aberrations and immunogenicity has been extended with the finding that human *SMARCB1*-mutant rhabdoid tumours are infiltrated by clonally expanded subpopulations of T cells, suggesting a tumour-specific immune response<sup>168–170</sup>. Moreover, ICI resulted in tumour regression in up to 70% mice harbouring *Smarcb1*-mutant rhabdoid tumours<sup>168</sup>. In this model, the implicated mechanism was somewhat distinct from those proposed for other SWI/SNF aberrations. Loss of SMARCB1 caused expression of endogenous retroviruses triggering double-stranded RNA-sensing pathway and subsequent induction of interferon signalling<sup>168</sup>. Another study in four patients with *SMARCA4*-mutant SCCOHT showed that these tumours also have an immune-active microenvironment and are responsive to ICI, despite having a low mutational burden<sup>171</sup>.

Thus, emerging and increasing evidence links mutations in several genes encoding SWI/SNF subunits with sensitivity to ICI. However, in the context of treatment of current patients, it should be kept in mind that almost all of the studies involved small cohorts of patients, that not all of the preclinical findings have been corroborated clinically and that the proposed mechanisms do not clearly align<sup>172,173</sup>. Further evidence from experimental models and clinical studies will be required to determine the extent to which mutations in SWI/SNF genes correlate with, and confer, susceptibility to ICI.

## Conclusions

The discovery that genes encoding subunits of SWI/SNF complexes are mutated at high frequency across a wide variety of cancers was largely unanticipated at the time when these complexes were identified. In contrast to mutations in classical oncogenes and tumour-suppressor genes, such as *MYC*, *RAS* and *TP53*, the roles of which have been studied in cancers for >40 years, the discovery of widespread SWI/SNF gene mutations in cancer is only a decade old. Consequently, our understanding of the mechanisms and any corresponding therapeutic implications remains in its infancy. Although it is now clear that inactivating mutations affecting individual SWI/SNF subunits can confer specific dependencies on other genes or pathways, whether any broad dependencies extend across all SWI/SNF cancers remains a key question and an active area of research.

With repeated discoveries that mutations in SWI/SNF subunits often increase dependencies on other components of residual SWI/SNF complexes, growing interest surrounds the possibility to therapeutically target the SWI/SNF complex itself. The potential for such an approach is enhanced by the existence of domains within these proteins, such as bromodomains and enzymatic ATPase domains, that can be targeted using small molecules. A point of caution relates to the fact that these complexes have bona fide tumour-suppressor activity and, specifically, whether inhibiting certain subunits could actually promote cancer development and/or growth, rather than suppressing these processes. Although tumour-promoting effects are likely to be reversible with cessation of therapy, this risk needs to be monitored in trials of such agents, particularly with long-term use.

The discovery of vulnerabilities, both genetic and pharmacological, has been accelerated by the advances in high-throughput screening assays. Such assays have proved powerful for the identification of synthetic lethality and other similar relationships; however, whether dependencies identified using cell lines will be sufficiently robust to translate into true therapeutic vulnerabilities in clinical trials remains to be determined.

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## References

1. Shain AH & Pollack JR The spectrum of SWI/SNF mutations, ubiquitous in human cancers. *PLoS One* 8, e55119, doi:10.1371/journal.pone.0055119 (2013). [PubMed: 23355908]
2. Kadoch C et al. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat Genet* 45, 592–601, doi:10.1038/ng.2628 (2013). [PubMed: 23644491]
3. Versteeg I et al. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature* 394, 203–206, doi:10.1038/28212 (1998). [PubMed: 9671307]
4. Roberts CW, Leroux MM, Fleming MD & Orkin SH Highly penetrant, rapid tumorigenesis through conditional inversion of the tumor suppressor gene *Snf5*. *Cancer Cell* 2, 415–425, doi:10.1016/s1535-6108(02)00185-x (2002). [PubMed: 12450796]
5. Wiegand KC et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med* 363, 1532–1543, doi:10.1056/NEJMoa1008433 (2010). [PubMed: 20942669]
6. Jones S et al. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. *Science* 330, 228–231, doi:10.1126/science.1196333 (2010). [PubMed: 20826764]
7. Varela I et al. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. *Nature* 469, 539–542, doi:10.1038/nature09639 (2011). [PubMed: 21248752]
8. Clapier CR & Cairns BR The biology of chromatin remodeling complexes. *Annu Rev Biochem* 78, 273–304, doi:10.1146/annurev.biochem.77.062706.153223 (2009). [PubMed: 19355820]
9. Wilson BG & Roberts CW SWI/SNF nucleosome remodellers and cancer. *Nat Rev Cancer* 11, 481–492, doi:10.1038/nrc3068 (2011). [PubMed: 21654818]
10. Euskirchen G, Auerbach RK & Snyder M SWI/SNF chromatin-remodeling factors: multiscale analyses and diverse functions. *J Biol Chem* 287, 30897–30905, doi:10.1074/jbc.R111.309302 (2012). [PubMed: 22952240]
11. Kwon H, Imbalzano AN, Khavari PA, Kingston RE & Green MR Nucleosome disruption and enhancement of activator binding by a human SWI/SNF complex. *Nature* 370, 477–481, doi:10.1038/370477a0 (1994). [PubMed: 8047169]
12. Wang W et al. Purification and biochemical heterogeneity of the mammalian SWI-SNF complex. *EMBO J* 15, 5370–5382 (1996). [PubMed: 8895581]
13. Lemon B, Inouye C, King DS & Tjian R Selectivity of chromatin-remodelling cofactors for ligand-activated transcription. *Nature* 414, 924–928, doi:10.1038/414924a (2001). [PubMed: 11780067]
14. Raab JR, Resnick S & Magnuson T Genome-Wide Transcriptional Regulation Mediated by Biochemically Distinct SWI/SNF Complexes. *PLoS Genet* 11, e1005748, doi:10.1371/journal.pgen.1005748 (2015). [PubMed: 26716708]
15. Alps A & Dykhuizen EC Glioma tumor suppressor candidate region gene 1 (GLTSCR1) and its paralog GLTSCR1-like form SWI/SNF chromatin remodeling subcomplexes. *J Biol Chem* 293, 3892–3903, doi:10.1074/jbc.RA117.001065 (2018). [PubMed: 29374058]
16. Brien GL et al. Targeted degradation of BRD9 reverses oncogenic gene expression in synovial sarcoma. *Elife* 7, doi:ARTN e41305 10.7554/eLife.41305 (2018).
17. Michel BC et al. A non-canonical SWI/SNF complex is a synthetic lethal target in cancers driven by BAF complex perturbation. *Nat Cell Biol* 20, 1410–1420, doi:10.1038/s41556-018-0221-1 (2018). [PubMed: 30397315]
18. Wang X et al. BRD9 defines a SWI/SNF sub-complex and constitutes a specific vulnerability in malignant rhabdoid tumors. *Nat Commun* 10, 1881, doi:10.1038/s41467-019-09891-7 (2019). [PubMed: 31015438]
19. Mashtalir N et al. Modular Organization and Assembly of SWI/SNF Family Chromatin Remodeling Complexes. *Cell* 175, 1272–1288 e1220, doi:10.1016/j.cell.2018.09.032 (2018). [PubMed: 30343899]
20. Cairns BR, Kim YJ, Sayre MH, Laurent BC & Kornberg RD A multisubunit complex containing the SWI1/ADR6, SWI2/SNF2, SWI3, SNF5, and SNF6 gene products isolated from yeast. *Proc Natl Acad Sci U S A* 91, 1950–1954, doi:10.1073/pnas.91.5.1950 (1994). [PubMed: 8127913]

21. Neigeborn L & Carlson M Genes affecting the regulation of SUC2 gene expression by glucose repression in *Saccharomyces cerevisiae*. *Genetics* 108, 845–858 (1984). [PubMed: 6392017]
22. Stern M, Jensen R & Herskowitz I Five SWI genes are required for expression of the HO gene in yeast. *J Mol Biol* 178, 853–868, doi:10.1016/0022-2836(84)90315-2 (1984). [PubMed: 6436497]
23. Martens JA, Wu PY & Winston F Regulation of an intergenic transcript controls adjacent gene transcription in *Saccharomyces cerevisiae*. *Genes Dev* 19, 2695–2704, doi:10.1101/gad.1367605 (2005). [PubMed: 16291644]
24. Mathur R et al. ARID1A loss impairs enhancer-mediated gene regulation and drives colon cancer in mice. *Nat Genet* 49, 296–302, doi:10.1038/ng.3744 (2017). [PubMed: 27941798]
25. Wang X et al. SMARCB1-mediated SWI/SNF complex function is essential for enhancer regulation. *Nat Genet* 49, 289–295, doi:10.1038/ng.3746 (2017). [PubMed: 27941797]
26. Nakayama RT et al. SMARCB1 is required for widespread BAF complex-mediated activation of enhancers and bivalent promoters. *Nat Genet* 49, 1613–1623, doi:10.1038/ng.3958 (2017). [PubMed: 28945250]
27. Alver BH et al. The SWI/SNF chromatin remodelling complex is required for maintenance of lineage specific enhancers. *Nat Commun* 8, 14648, doi:10.1038/ncomms14648 (2017). [PubMed: 28262751]
28. Lu C & Allis CD SWI/SNF complex in cancer. *Nat Genet* 49, 178–179, doi:10.1038/ng.3779 (2017). [PubMed: 28138149]
29. Gatchalian J et al. A non-canonical BRD9-containing BAF chromatin remodeling complex regulates naive pluripotency in mouse embryonic stem cells. *Nat Commun* 9, 5139, doi:10.1038/s41467-018-07528-9 (2018). [PubMed: 30510198]
30. Hodges C, Kirkland JG & Crabtree GR The Many Roles of BAF (mSWI/SNF) and PBAF Complexes in Cancer. *Csh Perspect Med* 6, doi:ARTN a026930 10.1101/cshperspect.a026930 (2016).
31. Ogiwara H et al. Histone acetylation by CBP and p300 at double-strand break sites facilitates SWI/SNF chromatin remodeling and the recruitment of non-homologous end joining factors. *Oncogene* 30, 2135–2146, doi:10.1038/onc.2010.592; 10.1038/onc.2010.592 (2011). [PubMed: 21217779]
32. Qi W et al. BRG1 promotes the repair of DNA double-strand breaks by facilitating the replacement of RPA with RAD51. *J Cell Sci* 128, 317–330, doi:10.1242/jcs.159103 (2015). [PubMed: 25395584]
33. Chen Y et al. A PARP1-BRG1-SIRT1 axis promotes HR repair by reducing nucleosome density at DNA damage sites. *Nucleic Acids Res* 47, 8563–8580, doi:10.1093/nar/gkz592 (2019). [PubMed: 31291457]
34. Brownlee PM, Meisenberg C & Downs JA The SWI/SNF chromatin remodelling complex: Its role in maintaining genome stability and preventing tumorigenesis. *DNA Repair (Amst)* 32, 127–133, doi:10.1016/j.dnarep.2015.04.023 (2015). [PubMed: 25981841]
35. Chabanon RM, Morel D & Postel-Vinay S Exploiting epigenetic vulnerabilities in solid tumors: Novel therapeutic opportunities in the treatment of SWI/SNF-defective cancers. *Semin Cancer Biol*, doi:10.1016/j.semcancer.2019.09.018 (2019).
36. Watanabe R et al. SWI/SNF factors required for cellular resistance to DNA damage include ARID1A and ARID1B and show interdependent protein stability. *Cancer Res* 74, 2465–2475, doi:10.1158/0008-5472.CAN-13-3608 (2014). [PubMed: 24788099]
37. Park JH et al. Mammalian SWI/SNF complexes facilitate DNA double-strand break repair by promoting gamma-H2AX induction. *EMBO J* 25, 3986–3997, doi:10.1038/sj.emboj.7601291 (2006). [PubMed: 16932743]
38. Shen J et al. ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors. *Cancer Discov* 5, 752–767, doi:10.1158/2159-8290.CD-14-0849 (2015). [PubMed: 26069190]
39. Dykhuizen EC et al. BAF complexes facilitate decatenation of DNA by topoisomerase IIalpha. *Nature* 497, 624–627, doi:10.1038/nature12146 (2013). [PubMed: 23698369]
40. Zhao B et al. ARID1A promotes genomic stability through protecting telomere cohesion. *Nat Commun* 10, 4067, doi:10.1038/s41467-019-12037-4 (2019). [PubMed: 31492885]

41. Kakaroungkas A et al. Requirement for PBAF in transcriptional repression and repair at DNA breaks in actively transcribed regions of chromatin. *Mol Cell* 55, 723–732, doi:10.1016/j.molcel.2014.06.028 (2014). [PubMed: 25066234]
42. Brownlee PM, Chambers AL, Cloney R, Bianchi A & Downs JA BAF180 promotes cohesion and prevents genome instability and aneuploidy. *Cell Rep* 6, 973–981, doi:10.1016/j.celrep.2014.02.012 (2014). [PubMed: 24613357]
43. Biegel JA et al. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. *Cancer Res* 59, 74–79 (1999). [PubMed: 9892189]
44. Sevenet N et al. Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancers. *Am J Hum Genet* 65, 1342–1348, doi:10.1086/302639 (1999). [PubMed: 10521299]
45. Finetti MA, Grabovska Y, Bailey S & Williamson D Translational genomics of malignant rhabdoid tumours: Current impact and future possibilities. *Semin Cancer Biol*, doi:10.1016/j.semcancer.2019.12.017 (2020).
46. Roberts CW, Galusha SA, McMenamin ME, Fletcher CD & Orkin SH Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. *Proc Natl Acad Sci U S A* 97, 13796–13800, doi:10.1073/pnas.250492697 (2000). [PubMed: 11095756]
47. Guidi CJ et al. Disruption of Ini1 leads to peri-implantation lethality and tumorigenesis in mice. *Mol Cell Biol* 21, 3598–3603, doi:10.1128/MCB.21.10.3598-3603.2001 (2001). [PubMed: 11313485]
48. Klochendler-Yeivin A et al. The murine SNF5/INI1 chromatin remodeling factor is essential for embryonic development and tumor suppression. *EMBO Rep* 1, 500–506, doi:10.1093/embo-reports/kvd129 (2000). [PubMed: 11263494]
49. Han ZY et al. The occurrence of intracranial rhabdoid tumours in mice depends on temporal control of Smarcb1 inactivation. *Nat Commun* 7, 10421, doi:10.1038/ncomms10421 (2016). [PubMed: 26818002]
50. Brennan B, Stiller C & Bourdeaut F Extracranial rhabdoid tumours: what we have learned so far and future directions. *Lancet Oncol* 14, e329–336, doi:10.1016/S1470-2045(13)70088-3 (2013). [PubMed: 23816299]
51. Hasselblatt M et al. SMARCA4-mutated atypical teratoid/rhabdoid tumors are associated with inherited germline alterations and poor prognosis. *Acta Neuropathol* 128, 453–456, doi:10.1007/s00401-014-1323-x (2014). [PubMed: 25060813]
52. Karnezis AN et al. Dual loss of the SWI/SNF complex ATPases SMARCA4/BRG1 and SMARCA2/BRM is highly sensitive and specific for small cell carcinoma of the ovary, hypercalcaemic type. *J Pathol* 238, 389–400, doi:10.1002/path.4633 (2016). [PubMed: 26356327]
53. Lu B & Shi H An In-Depth Look at Small Cell Carcinoma of the Ovary, Hypercalcaemic Type (SCCOHT): Clinical Implications from Recent Molecular Findings. *J Cancer* 10, 223–237, doi:10.7150/jca.26978 (2019). [PubMed: 30662543]
54. Kahali B et al. The silencing of the SWI/SNF subunit and anticancer gene BRM in Rhabdoid tumors. *Oncotarget* 5, 3316–3332, doi:10.18632/oncotarget.1945 (2014). [PubMed: 24913006]
55. Cerami E et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov* 2, 401–404, doi:10.1158/2159-8290.CD-12-0095 (2012). [PubMed: 22588877]
56. Sima X et al. The genetic alteration spectrum of the SWI/SNF complex: The oncogenic roles of BRD9 and ACTL6A. *PLoS One* 14, e0222305, doi:10.1371/journal.pone.0222305 (2019). [PubMed: 31504061]
57. Hu Z et al. Genomic characterization of genes encoding histone acetylation modulator proteins identifies therapeutic targets for cancer treatment. *Nat Commun* 10, 733, doi:10.1038/s41467-019-08554-x (2019). [PubMed: 30760718]
58. Hodges HC et al. Dominant-negative SMARCA4 mutants alter the accessibility landscape of tissue-unrestricted enhancers. *Nat Struct Mol Biol* 25, 61–72, doi:10.1038/s41594-017-0007-3 (2018). [PubMed: 29323272]
59. Gu YF et al. Modeling Renal Cell Carcinoma in Mice: Bap1 and Pbrm1 Inactivation Drive Tumor Grade. *Cancer Discov* 7, 900–917, doi:10.1158/2159-8290.CD-17-0292 (2017). [PubMed: 28473526]

60. Bultman SJ et al. Characterization of mammary tumors from Brg1 heterozygous mice. *Oncogene* 27, 460–468, doi:10.1038/sj.onc.1210664 (2008). [PubMed: 17637742]
61. Kadoch C & Crabtree GR Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. *Cell* 153, 71–85, doi:10.1016/j.cell.2013.02.036 (2013). [PubMed: 23540691]
62. McBride MJ et al. The SS18-SSX Fusion Oncoprotein Hijacks BAF Complex Targeting and Function to Drive Synovial Sarcoma. *Cancer Cell* 33, 1128–1141 e1127, doi:10.1016/j.ccell.2018.05.002 (2018). [PubMed: 29861296]
63. Tsurusaki Y et al. Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. *Nat Genet* 44, 376–378, doi:10.1038/ng.2219 (2012). [PubMed: 22426308]
64. Van Houdt JK et al. Heterozygous missense mutations in SMARCA2 cause Nicolaides-Baraitser syndrome. *Nat Genet* 44, 445–449, S441, doi:10.1038/ng.1105 (2012). [PubMed: 22366787]
65. Orlando KA, Nguyen V, Raab JR, Walhart T & Weissman BE Remodeling the cancer epigenome: mutations in the SWI/SNF complex offer new therapeutic opportunities. *Expert Rev Anticancer Ther* 19, 375–391, doi:10.1080/14737140.2019.1605905 (2019). [PubMed: 30986130]
66. Stern C Boveri and the early days of genetics. *Nature* 166, 446, doi:10.1038/166446a0 (1950).
67. Lazzarini-Denchi E & Sfeir A Stop pulling my strings - what telomeres taught us about the DNA damage response. *Nat Rev Mol Cell Biol* 17, 364–378, doi:10.1038/nrm.2016.43 (2016). [PubMed: 27165790]
68. Li SKH & Martin A Mismatch Repair and Colon Cancer: Mechanisms and Therapies Explored. *Trends Mol Med* 22, 274–289, doi:10.1016/j.molmed.2016.02.003 (2016). [PubMed: 26970951]
69. Lee RS et al. A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. *J Clin Invest* 122, 2983–2988, doi:10.1172/JCI64400 (2012). [PubMed: 22797305]
70. Lawrence MS et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* 499, 214–218, doi:10.1038/nature12213 (2013). [PubMed: 23770567]
71. Creighton CJ et al. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature* 499, 43–, doi:10.1038/nature12222 (2013). [PubMed: 23792563]
72. Ramos P et al. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. *Nat Genet* 46, 427–429, doi:10.1038/ng.2928 (2014). [PubMed: 24658001]
73. Yates LR et al. Genomic Evolution of Breast Cancer Metastasis and Relapse. *Cancer Cell* 32, 169–184 e167, doi:10.1016/j.ccell.2017.07.005 (2017). [PubMed: 28810143]
74. Gibson WJ et al. The genomic landscape and evolution of endometrial carcinoma progression and abdominopelvic metastasis. *Nat Genet* 48, 848–855, doi:10.1038/ng.3602 (2016). [PubMed: 27348297]
75. Betz BL, Strobeck MW, Reisman DN, Knudsen ES & Weissman BE Re-expression of hSNF5/INI1/BAF47 in pediatric tumor cells leads to G1 arrest associated with induction of p16ink4a and activation of RB. *Oncogene* 21, 5193–5203, doi:10.1038/sj.onc.1205706 (2002). [PubMed: 12149641]
76. Wang X et al. TCR-dependent transformation of mature memory phenotype T cells in mice. *J Clin Invest* 121, 3834–3845, doi:10.1172/JCI37210 (2011). [PubMed: 21926465]
77. Look AT Oncogenic transcription factors in the human acute leukemias. *Science* 278, 1059–1064, doi:10.1126/science.278.5340.1059 (1997). [PubMed: 9353180]
78. Andersson AK et al. The landscape of somatic mutations in infant MLL-rearranged acute lymphoblastic leukemias. *Nat Genet* 47, 330–337, doi:10.1038/ng.3230 (2015). [PubMed: 25730765]
79. Huether R et al. The landscape of somatic mutations in epigenetic regulators across 1,000 paediatric cancer genomes. *Nat Commun* 5, 3630, doi:10.1038/ncomms4630 (2014). [PubMed: 24710217]
80. van der Weyden L et al. Somatic drivers of B-ALL in a model of ETV6-RUNX1; Pax5(+/-) leukemia. *BMC Cancer* 15, 585, doi:10.1186/s12885-015-1586-1 (2015). [PubMed: 26269126]
81. Aster JC et al. Essential roles for ankyrin repeat and transactivation domains in induction of T-cell leukemia by notch1. *Mol Cell Biol* 20, 7505–7515, doi:10.1128/mcb.20.20.7505-7515.2000 (2000). [PubMed: 11003647]

82. Adams JM et al. The c-myc oncogene driven by immunoglobulin enhancers induces lymphoid malignancy in transgenic mice. *Nature* 318, 533–538, doi:10.1038/318533a0 (1985). [PubMed: 3906410]
83. Condorelli GL et al. T-cell-directed TAL-1 expression induces T-cell malignancies in transgenic mice. *Cancer Res* 56, 5113–5119 (1996). [PubMed: 8912842]
84. Peterson CL & Herskowitz I Characterization of the yeast SWI1, SWI2, and SWI3 genes, which encode a global activator of transcription. *Cell* 68, 573–583, doi:10.1016/0092-8674(92)90192-f (1992). [PubMed: 1339306]
85. Savas S & Skardasi G The SWI/SNF complex subunit genes: Their functions, variations, and links to risk and survival outcomes in human cancers. *Crit Rev Oncol Hematol* 123, 114–131, doi:10.1016/j.critrevonc.2018.01.009 (2018). [PubMed: 29482773]
86. Endo M et al. Alterations of the SWI/SNF chromatin remodelling subunit-BRG1 and BRM in hepatocellular carcinoma. *Liver Int* 33, 105–117, doi:10.1111/liv.12005 (2013).
87. Cho H et al. Loss of ARID1A/BAF250a expression is linked to tumor progression and adverse prognosis in cervical cancer. *Hum Pathol* 44, 1365–1374, doi:10.1016/j.humphath.2012.11.007 (2013). [PubMed: 23427874]
88. Faraj SF et al. ARID1A immunohistochemistry improves outcome prediction in invasive urothelial carcinoma of urinary bladder. *Hum Pathol* 45, 2233–2239, doi:10.1016/j.humphath.2014.07.003 (2014). [PubMed: 25175170]
89. Bai J et al. BRG1 is a prognostic marker and potential therapeutic target in human breast cancer. *PLoS One* 8, e59772, doi:10.1371/journal.pone.0059772 (2013). [PubMed: 23533649]
90. Kaufmann B et al. BRG1 promotes hepatocarcinogenesis by regulating proliferation and invasiveness. *PLoS One* 12, e0180225, doi:10.1371/journal.pone.0180225 (2017). [PubMed: 28700662]
91. Zhu P et al. LncBRM initiates YAP1 signalling activation to drive self-renewal of liver cancer stem cells. *Nat Commun* 7, 13608, doi:10.1038/ncomms13608 (2016). [PubMed: 27905400]
92. Agaimy A SWI/SNF Complex-Deficient Soft Tissue Neoplasms: A Pattern-Based Approach to Diagnosis and Differential Diagnosis. *Surg Pathol Clin* 12, 149–163, doi:10.1016/j.jpath.2018.10.006 (2019). [PubMed: 30709441]
93. Hadfield KD et al. Molecular characterisation of SMARCB1 and NF2 in familial and sporadic schwannomatosis. *J Med Genet* 45, 332–339, doi:10.1136/jmg.2007.056499 (2008). [PubMed: 18285426]
94. Smith MJ et al. Expression of SMARCB1 (INI1) mutations in familial schwannomatosis. *Hum Mol Genet* 21, 5239–5245, doi:10.1093/hmg/dd3370 (2012). [PubMed: 22949514]
95. Smith MJ, Wallace AJ, Bowers NL, Eaton H & Evans DG SMARCB1 mutations in schwannomatosis and genotype correlations with rhabdoid tumors. *Cancer Genet* 207, 373–378, doi:10.1016/j.cancergen.2014.04.001 (2014). [PubMed: 24933152]
96. Bourdeaut F et al. Frequent hSNF5/INI1 germline mutations in patients with rhabdoid tumor. *Clin Cancer Res* 17, 31–38, doi:10.1158/1078-0432.CCR-10-1795 (2011). [PubMed: 21208904]
97. Anaya J, Reon B, Chen WM, Bekiranov S & Dutta A A pan-cancer analysis of prognostic genes. *PeerJ* 3, e1499, doi:10.7717/peerj.1499 (2015). [PubMed: 27047702]
98. Agaimy A & Foulkes WD Hereditary SWI/SNF complex deficiency syndromes. *Semin Diagn Pathol* 35, 193–198, doi:10.1053/j.semmp.2018.01.002 (2018). [PubMed: 29397238]
99. Morin RD et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat Genet* 42, 181–185, doi:10.1038/ng.518 (2010). [PubMed: 20081860]
100. Ntziachristos P et al. Genetic inactivation of the polycomb repressive complex 2 in T cell acute lymphoblastic leukemia. *Nat Med* 18, 298–301, doi:10.1038/nm.2651 (2012). [PubMed: 22237151]
101. Gibson WT et al. Mutations in EZH2 cause Weaver syndrome. *Am J Hum Genet* 90, 110–118, doi:10.1016/j.ajhg.2011.11.018 (2012). [PubMed: 22177091]
102. Helming KC et al. ARID1B is a specific vulnerability in ARID1A-mutant cancers. *Nat Med* 20, 251–254, doi:10.1038/nm.3480 (2014). [PubMed: 24562383]



103. Wang X et al. Oncogenesis caused by loss of the SNF5 tumor suppressor is dependent on activity of BRG1, the ATPase of the SWI/SNF chromatin remodeling complex. *Cancer Res* 69, 8094–8101, doi:10.1158/0008-5472.CAN-09-0733 (2009). [PubMed: 19789351]
104. Hoffman GR et al. Functional epigenetics approach identifies BRM/SMARCA2 as a critical synthetic lethal target in BRG1-deficient cancers. *Proc Natl Acad Sci U S A* 111, 3128–3133, doi:10.1073/pnas.1316793111 (2014). [PubMed: 24520176]
105. Oike T et al. A synthetic lethality-based strategy to treat cancers harboring a genetic deficiency in the chromatin remodeling factor BRG1. *Cancer Res* 73, 5508–5518, doi:10.1158/0008-5472.CAN-12-4593 (2013). [PubMed: 23872584]
106. Papillon JPN et al. Discovery of Orally Active Inhibitors of Brahma Homolog (BRM)/SMARCA2 ATPase Activity for the Treatment of Brahma Related Gene 1 (BRG1)/SMARCA4-Mutant Cancers. *J Med Chem* 61, 10155–10172, doi:10.1021/acs.jmedchem.8b01318 (2018). [PubMed: 30339381]
107. Farnaby W et al. BAF complex vulnerabilities in cancer demonstrated via structure-based PROTAC design. *Nat Chem Biol* 15, 672–680, doi:10.1038/s41589-019-0294-6 (2019). [PubMed: 31178587]
108. Winter GE et al. DRUG DEVELOPMENT. Phthalimide conjugation as a strategy for in vivo target protein degradation. *Science* 348, 1376–1381, doi:10.1126/science.aab1433 (2015). [PubMed: 25999370]
109. Zengerle M, Chan KH & Ciulli A Selective Small Molecule Induced Degradation of the BET Bromodomain Protein BRD4. *ACS Chem Biol* 10, 1770–1777, doi:10.1021/acscchembio.5b00216 (2015). [PubMed: 26035625]
110. Lu J et al. Hijacking the E3 Ubiquitin Ligase Cereblon to Efficiently Target BRD4. *Chem Biol* 22, 755–763, doi:10.1016/j.chembiol.2015.05.009 (2015). [PubMed: 26051217]
111. Reisman DN, Sciarrotta J, Wang W, Funkhouser WK & Weissman BE Loss of BRG1/BRM in human lung cancer cell lines and primary lung cancers: correlation with poor prognosis. *Cancer Res* 63, 560–566 (2003). [PubMed: 12566296]
112. Shorstova T et al. SWI/SNF-Compromised Cancers Are Susceptible to Bromodomain Inhibitors. *Cancer Res* 79, 2761–2774, doi:10.1158/0008-5472.CAN-18-1545 (2019). [PubMed: 30877105]
113. Hohmann AF et al. Sensitivity and engineered resistance of myeloid leukemia cells to BRD9 inhibition. *Nature Chemical Biology* 12, 672–+, doi:10.1038/nchembio.2115 (2016). [PubMed: 27376689]
114. Theodoulou NH et al. Discovery of I-BRD9, a Selective Cell Active Chemical Probe for Bromodomain Containing Protein 9 Inhibition. *J Med Chem* 59, 1425–1439, doi:10.1021/acs.jmedchem.5b00256 (2016). [PubMed: 25856009]
115. Kennison JA & Tamkun JW Dosage-dependent modifiers of polycomb and antennapedia mutations in *Drosophila*. *Proc Natl Acad Sci U S A* 85, 8136–8140, doi:10.1073/pnas.85.21.8136 (1988). [PubMed: 3141923]
116. Tamkun JW et al. brahma: a regulator of *Drosophila* homeotic genes structurally related to the yeast transcriptional activator SNF2/SWI2. *Cell* 68, 561–572, doi:10.1016/0092-8674(92)90191-e (1992). [PubMed: 1346755]
117. Wilson BG et al. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell* 18, 316–328, doi:10.1016/j.ccr.2010.09.006 (2010). [PubMed: 20951942]
118. Erkek S et al. Comprehensive Analysis of Chromatin States in Atypical Teratoid/Rhabdoid Tumor Identifies Diverging Roles for SWI/SNF and Polycomb in Gene Regulation. *Cancer Cell* 35, 95–+, doi:10.1016/j.ccell.2018.11.014 (2019). [PubMed: 30595504]
119. Kadoch C et al. Dynamics of BAF-Polycomb complex opposition on heterochromatin in normal and oncogenic states. *Nat Genet* 49, 213–222, doi:10.1038/ng.3734 (2017). [PubMed: 27941796]
120. Kim KH et al. SWI/SNF-mutant cancers depend on catalytic and non-catalytic activity of EZH2. *Nat Med* 21, 1491–1496, doi:10.1038/nm.3968 (2015). [PubMed: 26552009]
121. Kim KH & Roberts CW Targeting EZH2 in cancer. *Nat Med* 22, 128–134, doi:10.1038/nm.4036 (2016). [PubMed: 26845405]



122. Knutson SK et al. A selective inhibitor of EZH2 blocks H3K27 methylation and kills mutant lymphoma cells. *Nat Chem Biol* 8, 890–896, doi:10.1038/nchembio.1084 (2012). [PubMed: 23023262]
123. Italiano A et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *Lancet Oncol* 19, 649–659, doi:10.1016/S1470-2045(18)30145-1 (2018). [PubMed: 29650362]
124. Kawano S et al. Preclinical Evidence of Anti-Tumor Activity Induced by EZH2 Inhibition in Human Models of Synovial Sarcoma. *PLoS One* 11, e0158888, doi:10.1371/journal.pone.0158888 (2016). [PubMed: 27391784]
125. Kurmasheva RT et al. Initial testing (stage 1) of tazemetostat (EPZ-6438), a novel EZH2 inhibitor, by the Pediatric Preclinical Testing Program. *Pediatr Blood Cancer* 64, doi:10.1002/pbc.26218 (2017).
126. Knutson SK et al. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. *Proc Natl Acad Sci U S A* 110, 7922–7927, doi:10.1073/pnas.1303800110 (2013). [PubMed: 23620515]
127. Le Loarer F et al. Consistent SMARCB1 homozygous deletions in epithelioid sarcoma and in a subset of myoepithelial carcinomas can be reliably detected by FISH in archival material. *Genes Chromosomes Cancer* 53, 475–486, doi:10.1002/gcc.22159 (2014). [PubMed: 24585572]
128. Maruyama D et al. First-in-Human Study of the EZH1/2 Dual Inhibitor DS-3201b in Patients with Relapsed or Refractory Non-Hodgkin Lymphomas — Preliminary Results. *Blood* 130, 4070–4070, doi:10.1182/blood.V130.Suppl\_1.4070.4070 (2017).
129. Mohammad HP, Barbash O & Creasy CL Targeting epigenetic modifications in cancer therapy: erasing the roadmap to cancer. *Nat Med* 25, 403–418, doi:10.1038/s41591-019-0376-8 (2019). [PubMed: 30842676]
130. Torchia J et al. Integrated (epi)-Genomic Analyses Identify Subgroup-Specific Therapeutic Targets in CNS Rhabdoid Tumors. *Cancer Cell* 30, 891–908, doi:10.1016/j.ccell.2016.11.003 (2016). [PubMed: 27960086]
131. Knipstein JA et al. Histone deacetylase inhibition decreases proliferation and potentiates the effect of ionizing radiation in atypical teratoid/rhabdoid tumor cells. *Neuro Oncol* 14, 175–183, doi:10.1093/neuonc/nor208 (2012). [PubMed: 22156471]
132. Johann PD et al. Atypical Teratoid/Rhabdoid Tumors Are Comprised of Three Epigenetic Subgroups with Distinct Enhancer Landscapes. *Cancer Cell* 29, 379–393, doi:10.1016/j.ccell.2016.02.001 (2016). [PubMed: 26923874]
133. Ho B et al. Molecular subgrouping of Atypical Teratoid / Rhabdoid Tumors (ATRT) - a reinvestigation and current consensus. *Neuro Oncol*, doi:10.1093/neuonc/noz235 (2019).
134. Chun HE et al. Genome-Wide Profiles of Extra-cranial Malignant Rhabdoid Tumors Reveal Heterogeneity and Dysregulated Developmental Pathways. *Cancer Cell* 29, 394–406, doi:10.1016/j.ccell.2016.02.009 (2016). [PubMed: 26977886]
135. Weissmiller AM et al. Inhibition of MYC by the SMARCB1 tumor suppressor. *Nat Commun* 10, 2014, doi:10.1038/s41467-019-10022-5 (2019). [PubMed: 31043611]
136. Jagani Z et al. Loss of the tumor suppressor Snf5 leads to aberrant activation of the Hedgehog-Gli pathway. *Nat Med* 16, 1429–1433, doi:10.1038/nm.2251 (2010). [PubMed: 21076395]
137. Alimova I et al. Inhibition of MYC attenuates tumor cell self-renewal and promotes senescence in SMARCB1-deficient Group 2 atypical teratoid rhabdoid tumors to suppress tumor growth in vivo. *Int J Cancer* 144, 1983–1995, doi:10.1002/ijc.31873 (2019). [PubMed: 30230537]
138. Venkataraman S et al. Targeting Aurora Kinase A enhances radiation sensitivity of atypical teratoid rhabdoid tumor cells. *J Neurooncol* 107, 517–526, doi:10.1007/s11060-011-0795-y (2012). [PubMed: 22246202]
139. Xue Y et al. SMARCA4 loss is synthetic lethal with CDK4/6 inhibition in non-small cell lung cancer. *Nat Commun* 10, 557, doi:10.1038/s41467-019-08380-1 (2019). [PubMed: 30718506]
140. Xue Y et al. CDK4/6 inhibitors target SMARCA4-determined cyclin D1 deficiency in hypercalcemic small cell carcinoma of the ovary. *Nat Commun* 10, 558, doi:10.1038/s41467-018-06958-9 (2019). [PubMed: 30718512]

141. Tagal V et al. SMARCA4-inactivating mutations increase sensitivity to Aurora kinase A inhibitor VX-680 in non-small cell lung cancers. *Nat Commun* 8, 14098, doi:10.1038/ncomms14098 (2017). [PubMed: 28102363]
142. Georger B et al. A Phase I Study of the CDK4/6 Inhibitor Ribociclib (LEE011) in Pediatric Patients with Malignant Rhabdoid Tumors, Neuroblastoma, and Other Solid Tumors. *Clin Cancer Res* 23, 2433–2441, doi:10.1158/1078-0432.CCR-16-2898 (2017). [PubMed: 28432176]
143. Mosse YP et al. A Phase II Study of Alisertib in Children with Recurrent/Refractory Solid Tumors or Leukemia: Children’s Oncology Group Phase I and Pilot Consortium (ADVL0921). *Clin Cancer Res* 25, 3229–3238, doi:10.1158/1078-0432.CCR-18-2675 (2019). [PubMed: 30777875]
144. Oberlick EM et al. Small-Molecule and CRISPR Screening Converge to Reveal Receptor Tyrosine Kinase Dependencies in Pediatric Rhabdoid Tumors. *Cell Rep* 28, 2331–2344 e2338, doi:10.1016/j.celrep.2019.07.021 (2019). [PubMed: 31461650]
145. Chauvin C et al. High-Throughput Drug Screening Identifies Pazopanib and Clofilium Tosylate as Promising Treatments for Malignant Rhabdoid Tumors. *Cell Rep* 21, 1737–1745, doi:10.1016/j.celrep.2017.10.076 (2017). [PubMed: 29141209]
146. Wong JP et al. Dual Targeting of PDGFRalpha and FGFR1 Displays Synergistic Efficacy in Malignant Rhabdoid Tumors. *Cell Rep* 17, 1265–1275, doi:10.1016/j.celrep.2016.10.005 (2016). [PubMed: 27783942]
147. Miller RE et al. Synthetic Lethal Targeting of ARID1A-Mutant Ovarian Clear Cell Tumors with Dasatinib. *Mol Cancer Ther* 15, 1472–1484, doi:10.1158/1535-7163.MCT-15-0554 (2016). [PubMed: 27364904]
148. Lang JD et al. Ponatinib Shows Potent Antitumor Activity in Small Cell Carcinoma of the Ovary Hypercalcemic Type (SCCOHT) through Multikinase Inhibition. *Clin Cancer Res* 24, 1932–1943, doi:10.1158/1078-0432.CCR-17-1928 (2018). [PubMed: 29440177]
149. Yamamoto S, Tsuda H, Takano M, Tamai S & Matsubara O PIK3CA mutations and loss of ARID1A protein expression are early events in the development of cystic ovarian clear cell adenocarcinoma. *Virchows Arch* 460, 77–87, doi:10.1007/s00428-011-1169-8 (2012). [PubMed: 22120431]
150. Bosse T et al. Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations, TP53 and microsatellite instability in endometrial cancer. *Mod Pathol* 26, 1525–1535, doi:10.1038/modpathol.2013.96 (2013). [PubMed: 23702729]
151. St Pierre R & Kadoch C Mammalian SWI/SNF complexes in cancer: emerging therapeutic opportunities. *Curr Opin Genet Dev* 42, 56–67, doi:10.1016/j.gde.2017.02.004 (2017). [PubMed: 28391084]
152. Samartzis EP et al. Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition. *Oncotarget* 5, 5295–5303, doi:10.18632/oncotarget.2092 (2014). [PubMed: 24979463]
153. Dal Molin M et al. Loss of expression of the SWI/SNF chromatin remodeling subunit BRG1/SMARCA4 is frequently observed in intraductal papillary mucinous neoplasms of the pancreas. *Hum Pathol* 43, 585–591, doi:10.1016/j.humpath.2011.06.009 (2012). [PubMed: 21940037]
154. Zhang Q et al. Chromatin remodeling gene AT-rich interactive domain-containing protein 1A suppresses gastric cancer cell proliferation by targeting PIK3CA and PDK1. *Oncotarget* 7, 46127–46141, doi:10.18632/oncotarget.10060 (2016). [PubMed: 27323812]
155. Yap TA, Bjerke L, Clarke PA & Workman P Drugging PI3K in cancer: refining targets and therapeutic strategies. *Curr Opin Pharmacol* 23, 98–107, doi:10.1016/j.coph.2015.05.016 (2015). [PubMed: 26117819]
156. Ding Y et al. Chromatin remodeling ATPase BRG1 and PTEN are synthetic lethal in prostate cancer. *J Clin Invest* 129, 759–773, doi:10.1172/JCI123557 (2019). [PubMed: 30496141]
157. Howard TP et al. MDM2 and MDM4 Are Therapeutic Vulnerabilities in Malignant Rhabdoid Tumors. *Cancer Res* 79, 2404–2414, doi:10.1158/0008-5472.CAN-18-3066 (2019). [PubMed: 30755442]
158. Carugo A et al. p53 Is a Master Regulator of Proteostasis in SMARCB1-Deficient Malignant Rhabdoid Tumors. *Cancer Cell* 35, 204–220 e209, doi:10.1016/j.ccell.2019.01.006 (2019). [PubMed: 30753823]

159. Williamson CT et al. ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A. *Nat Commun* 7, 13837, doi:10.1038/ncomms13837 (2016). [PubMed: 27958275]
160. Park Y et al. Loss of ARID1A in Tumor Cells Renders Selective Vulnerability to Combined Ionizing Radiation and PARP Inhibitor Therapy. *Clin Cancer Res* 25, 5584–5594, doi:10.1158/1078-0432.CCR-18-4222 (2019). [PubMed: 31196855]
161. Miao D et al. Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma. *Science* 359, 801–806, doi:10.1126/science.aan5951 (2018). [PubMed: 29301960]
162. Pan D et al. A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing. *Science* 359, 770–775, doi:10.1126/science.aao1710 (2018). [PubMed: 29301958]
163. Shen J et al. ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade. *Nat Med* 24, 556–562, doi:10.1038/s41591-018-0012-z (2018). [PubMed: 29736026]
164. Ashizawa M et al. Prognostic role of ARID1A negative expression in gastric cancer. *Sci Rep* 9, 6769, doi:10.1038/s41598-019-43293-5 (2019). [PubMed: 31043675]
165. Buglioni S et al. The clinical significance of PD-L1 in advanced gastric cancer is dependent on ARID1A mutations and ATM expression. *Oncoimmunology* 7, e1457602, doi:10.1080/2162402X.2018.1457602 (2018). [PubMed: 30221053]
166. Kim YB, Ahn JM, Bae WJ, Sung CO & Lee D Functional loss of ARID1A is tightly associated with high PD-L1 expression in gastric cancer. *Int J Cancer* 145, 916–926, doi:10.1002/ijc.32140 (2019). [PubMed: 30664822]
167. Jiang T, Chen X, Su C, Ren S & Zhou C Pan-cancer analysis of ARID1A Alterations as Biomarkers for Immunotherapy Outcomes. *J Cancer* 11, 776–780, doi:10.7150/jca.41296 (2020). [PubMed: 31949479]
168. Leruste A et al. Clonally Expanded T Cells Reveal Immunogenicity of Rhabdoid Tumors. *Cancer Cell*, doi:10.1016/j.ccell.2019.10.008 (2019).
169. Chun HE et al. Identification and Analyses of Extra-Cranial and Cranial Rhabdoid Tumor Molecular Subgroups Reveal Tumors with Cytotoxic T Cell Infiltration. *Cell Rep* 29, 2338–2354 e2337, doi:10.1016/j.celrep.2019.10.013 (2019). [PubMed: 31708418]
170. Forrest SJ et al. Genomic and immunologic characterization of INI1-deficient pediatric cancers. *Clin Cancer Res*, doi:10.1158/1078-0432.CCR-19-3089 (2020).
171. Jelinic P et al. Immune-Active Microenvironment in Small Cell Carcinoma of the Ovary, Hypercalcemic Type: Rationale for Immune Checkpoint Blockade. *J Natl Cancer Inst* 110, 787–790, doi:10.1093/jnci/djx277 (2018). [PubMed: 29365144]
172. McDermott DF et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med* 24, 749–757, doi:10.1038/s41591-018-0053-3 (2018). [PubMed: 29867230]
173. Keenan TE, Burke KP & Van Allen EM Genomic correlates of response to immune checkpoint blockade. *Nat Med* 25, 389–402, doi:10.1038/s41591-019-0382-x (2019). [PubMed: 30842677]
174. Schick S et al. Systematic characterization of BAF mutations provides insights into intracomplex synthetic lethality in human cancers. *Nat Genet* 51, 1399–1410, doi:10.1038/s41588-019-0477-9 (2019). [PubMed: 31427792]

### Key points

- At least nine different genes encoding subunits of the SWI/SNF family of chromatin-remodelling complexes are recurrently mutated in cancer and these mutations are collectively present in nearly 25% of cancers.
- Mutations in specific SWI/SNF genes are enriched in particular cancer types, suggesting differential roles for individual SWI/SNF components; consistent with this hypothesis, different SWI/SNF gene mutations confer distinct cancer vulnerabilities in mouse models.
- The tumour-suppressor activity of the SWI/SNF chromatin-regulatory complexes is most likely attributable to their roles in facilitating transcription factor function, which is central to cell-fate specification; however, roles of the complexes in facilitating DNA repair might also contribute.
- The identification of potential therapeutic vulnerabilities that arise from SWI/SNF gene mutations is leading to new areas of clinical investigation, including studies of immunotherapy in addition to kinase inhibitors and agents targeting mediators of DNA damage repair.

**Box 1 |****Nomenclature of SWI/SNF complexes**

The numerous nomenclature systems currently in use for the switch/sucrose non-fermentable (SWI/SNF) complexes and their subunits can create substantial challenges for neophytes. The SWI/SNF name itself is derived from original discoveries that orthologous complexes in yeast are required for mating-type switching and sucrose fermentation (with mutations affecting the complex leading to a sucrose non-fermenting phenotype). As the composition of SWI/SNF complexes becomes more diverse with evolution to higher-order organisms, the BRG1/BRM-associated factor (BAF) nomenclature was developed (BRG1 and BRM are core ATPases of SWI/SNF complexes). Subsequently, the SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin (SMARC) naming system was developed and became part of official Human Genome Organisation (HUGO) nomenclature, although evidence supporting matrix association of the complexes is limited. Consequently, owing to the varied evolutionary biology, compositional diversity and myriad different proposed functions of SWI/SNF complexes, the nomenclature remains problematic and is often variably used throughout literature. Commonly used HUGO gene names and interchangeable synonyms of SWI/SNF components are indicated below, with the subunits listed according to the SWI/SNF complexes subfamilies- canonical BAF (cBAF), polybromo-associated BAF (PBAF) and non-canonical BAF (ncBAF) -with which they are most frequently associated, although additional variability exists.

**Shared subunits**

- *SMARCC1 (BAF155)*
- *SMARCC2 (BAF170)*
- *SMARCA4 (BRG1 or BAF190A)*
- *SMARCA2 (BRM, BAF190B or SNF2L2)*
- *SMARCB1 (BAF47, INI1 or SNF5)*
- *SMARCE1 (BAF57)*
- *SMARCD1, SMARCD2 and SMARCD3 (BAF60A, BAF60B and BAF60C, respectively)*
- *ACTB*
- *ACTL6A and ACTL6B (BAF53A and BAF53B, respectively)*
- *BCL7A, BCL7B and BCL7C*
- *SS18 (SYT or SSXT)*

**cBAF subunits**

- *ARID1A (BAF250A or SMARCF1)*
- *ARID1B (BAF250B)*

- *DPF2* and *DPF3* (*BAF45D* and *BAF45C*, respectively)
- *BCL11A* and *BCL11B*

**PBAF subunits**

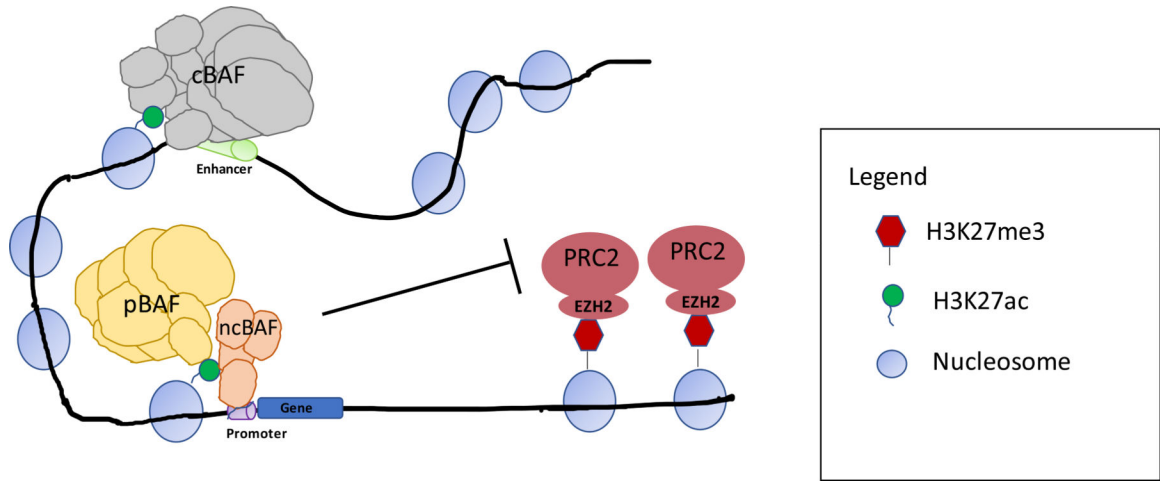
- *ARID2* (*BAF200*)
- *PBRM1* (*BAF180*)
- *BRD7*
- *PHF10* (*BAF45A*)

**ncBAF subunits**

- *BRD9*
- *BICRA* and *BICRAL* (*GLTSCR1* and *GLTSCR1L*)

cBAF, canonical BAF; ncBAF, non-canonical BAF; PBAF, polybromo-associated BAF.





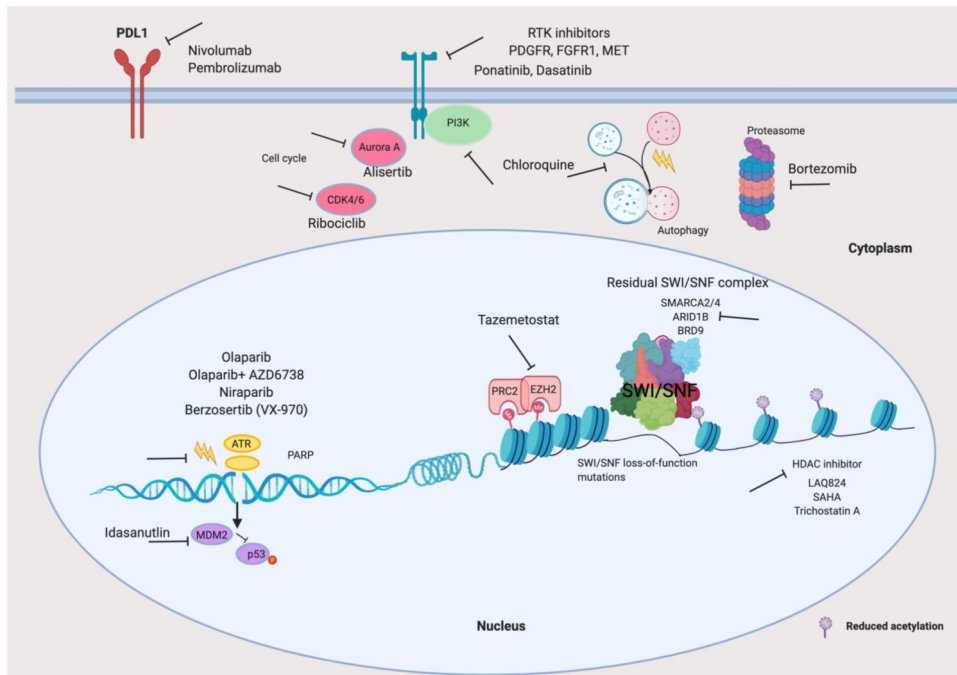
**Fig. 1|. Function of SWI/SNF chromatin-remodelling complexes.**

Illustration of SWI/SNF complex subfamilies and their genomic localization with respect to gene promoters and enhancers in nonmalignant cells. SWI/SNF complexes frequently localize at sites marked by histone H3 lysine 27 acetylation (H3K27ac), which is associated with active transcription, and cooperate with transcription factors to establish an open chromatin state<sup>25,26</sup>. This activity can be opposed by that of the Polycomb repressor complexes (PRCs), particularly PRC2 that places the repressive H3K27 trimethylation (H3K27me3) mark via its enzymatic subunit, enhancer of Zeste homologue 2 (EZH2)<sup>115,117</sup>. Canonical BAF (cBAF), polybromo-associated BAF (PBAF) and the most recently discovered non-canonical BAF (ncBAF, also known as GLTSCR1-containing BAF (GBAF)) are the three major SWI/SNF complex subfamilies<sup>17,18,29</sup>. cBAF activity might occur most strongly at enhancers, whereas PBAF and ncBAF are reported to be enriched at promoters, although also bind to some enhancers<sup>18,26,29,174</sup>. Understanding of the distinct functions of these three SWI/SNF subfamilies is limited and requires further study.



**Fig. 2. Frequency and pattern of SWI/SNF subunit mutations across human cancers.**

The heatmap depicts the frequency of non-synonymous mutations and deletions in select genes encoding components of SWI/SNF complexes across cancer types. Overall, the figure depicts the high prevalence of mutations affecting nine SWI/SNF subunits and the context-specificity of these mutations, with most being highly enriched in certain paediatric and adult malignancies. *ARID1A* is the most frequently mutated SWI/SNF complex gene, followed by *SMARCA4* and *PBRM1*. The heatmap was compiled using data generated by the The Cancer Genome Atlas (TCGA) Research Network, accessible through cBioPortal<sup>55</sup>, as well as datasets sourced from various publications<sup>1-3,5,6,35,56</sup>. The white background color indicates tumors in which less than 2.5% of tumors had mutations in the subunit.



**Fig. 3. Translational science of cancers with SWI/SNF complex aberrations.**

Illustration of reported vulnerabilities of cancers with loss-of-function mutations in SWI/SNF-complex genes, depicting both therapeutic opportunities supported only by preclinical evidence and treatments currently being evaluated in ongoing clinical trials (TABLE 1). The therapeutic targets include: residual SWI/SNF complexes<sup>17,18,102,104</sup>; Polycomb repressive complex 2 (PRC2), mainly its enzymatic subunit, enhancer of Zeste homologue 2 (EZH2), and predominantly in *SMARCB1*-mutant or *SMARCA4*-mutant<sup>120,122</sup>; components of the DNA damage repair pathway, in particular, poly(ADP-ribose) polymerase (PARP) and ATR in *ARID1A*-mutant cancers<sup>159,160</sup>; and receptor tyrosine kinases (RTKs) in several cancers enriched for mutations in SWI/SNF-complex genes, in a context-specific manner<sup>144,145,147,148</sup>. Targeting of Aurora A or CDK4/6 (cell-cycle kinases), MDM2 (a negative regulator of the tumour suppressor p53), autophagy or the proteasome could also be of potential therapeutic benefit in patients with cancers harbouring particular SWI/SNF-complex aberrations<sup>138,142,157,158</sup>. Additionally, mutations in several genes encoding SWI/SNF-complex subunits have been associated with sensitivity to immune-checkpoint inhibitors targeting programmed cell death 1 (PD-1) or programmed cell death 1 ligand 1 (PD-L1)<sup>161,163–166,168,172</sup>. ARID1A, AT-rich interactive domain-containing protein 1A; bromodomain-containing protein 9, BRD9; FGFR1, fibroblast growth factor receptor 1; HDACs, histone deacetylases; PDGFR, platelet-derived growth factor receptor; SMARCA2/4, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 2 or 4.

Table 1 |

Ongoing interventional clinical trials involving cancers harbouring mutated SWI/SNF components

Interventional agents (targets)	ClinicalTrial.gov ID	Disease setting	Study phase	Enrolment target	End points or objectives
<i>SMARCB1-mutant, SMARCA4-mutant or SS18-SSX rearranged cancers</i>					
Tazemetostat (EZH2)	NCT01897571	Adults with advanced-stage solid tumours or B cell lymphomas, including DLBCL	I/II	420	MTD, bioavailability, DDI, efficacy and safety of monotherapy or combination with prednisolone.
	NCT02601937	Children with R/R MRT, ATRT, RTK and other selected tumours with rhabdoid features and loss of <i>SMARCB1</i> or <i>SMARCA4</i> , other <i>SMARCB1</i> -negative tumours, or synovial sarcoma with <i>SS18-SSX</i> rearrangement,	I	82	Dose escalation to MTD and dose expansion at MTD
	NCT03213665	Children with R/R advanced-stage solid tumours, non-Hodgkin lymphoma or histiocytic disorders with <i>EZH2</i> , <i>SMARCB1</i> or <i>SMARCA4</i> mutations	II	49	ORR, PFS, tolerability of tazemetostat in children with R/R cancer
	NCT02601950	Adults with MRT, ATRT, RTK and other selected tumours with rhabdoid features and loss of <i>SMARCB1</i> or <i>SMARCA4</i> (including SCCHT), <i>SMARCB1</i> -negative tumours or tumours with with an <i>EZH2</i> gain-of-function mutation, refractory synovial sarcoma with <i>SS18-SSX</i> rearrangement, renal medullary carcinoma, epithelioid sarcoma, or poorly differentiated chordoma	II	250	ORR, DoR, PFS, and effect of tazemetostat on immune priming
	NCT02875548	Adults with various cancers (including MRT, ATRT, RTK, synovial or epithelioid sarcoma, mesothelioma and DLBCL) who have completed an antecedent tazemetostat study	II	300	Long-term safety profile, TTF and OS
Alisertib (Aurora A)	NCT02114229	Children and young adults (aged <22 years) with newly diagnosed or R/R ATRT and/or extra-CNS MRT (with loss of <i>SMARCB1</i> or <i>SMARCA4</i> )	II	180	Sustained ORR, PFS, and PK and PD of alisertib in paediatric patients <sup>142,143</sup>
<i>ARID1A-mutant cancers</i>					
Niraparib (PARP)	NCT03207347	Adults with <i>BAP1</i> -mutant and other DDR-deficient neoplasms, including tumours with <i>ARID1A</i> mutation	II	57	ORR, PFS and OS
Olaparib (PARP)	NCT04042831	Adults with biliary tract cancer with DDR gene aberrations, including <i>ARID1A</i> mutations	II	36	ORR, DoR and OS
Olaparib (PARP) + capivasertib (also known as AZD5363; AKT)	NCT02576444	Adults with cancer containing mutations in homologous DNA repair or other DDR genes, including <i>ARID1A</i>	II	64	ORR
Olaparib (PARP) + Ceralasertib (also known as AZD6738; ATR)	NCT04065269	Adults with relapsed gynaecological cancers with or without loss of <i>ARID1A</i>	II	40	ORR, PFS, TTP and OS

Interventional agents (targets)	ClinicalTrial.gov ID	Disease setting	Study phase	Enrolment target	End points or objectives
Berzosertib (also known as VX-970 and M6620; ATR)	<a href="https://clinicaltrials.gov/ct2/show/study/NCT03718091">NCT03718091</a>	Adults with advanced-stage solid tumours, including an <i>ARID1A</i> -mutant cohort	II	223	Validation of anticancer effect of VX-970 observed in preclinical studies: changes in Phospho-CHK1, $\gamma$ H2AX levels and DCR
Dasatinib (various tyrosine kinase)	<a href="https://clinicaltrials.gov/ct2/show/study/NCT02059265">NCT02059265</a>	Adults with recurrent or persistent ovarian, fallopian tube, endometrial or peritoneal cancer with and without loss of <i>ARID1A</i>	II	35	ORR, PFS, OS and toxicity profile
Dasatinib + PD-1	<a href="https://clinicaltrials.gov/ct2/show/study/NCT04284202">NCT04284202</a>	Adults with advanced NSCLC with <i>ARID1A</i> mutation as the third line of treatment.	I	30	PFS, ORR, OS and toxicity profile

Information on the clinical trials was obtained from <https://clinicaltrials.gov> on 15/03/2020.  $\gamma$ H2AX, phosphorylated histone H2AX; ATRT, atypical teratoid rhabdoid tumour; CNS, central nervous system; DCR, disease control rate; DDI, drug–drug interactions; DDR, DNA damage response and/or repair; DLBCL, diffuse large B cell lymphoma; DoR, duration of response; EZH2, enhancer of Zeste homologue 2; MRT, malignant rhabdoid tumour; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; R/R relapsed and/or refractory; RTK, rhabdoid tumour of kidney; SCCOHT, small cell carcinoma of the ovary, hypercalcemic type; TTP, time to progression; NSCLC, non-small cell lung cancer