Leukemia (2021) 35:2482–2495
https://doi.org/10.1038/s41375-021-01309-y

REVIEW ARTICLE

Therapeutic implications of menin inhibition in acute leukemias

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Received: 28 February 2021 / Revised: 19 May 2021 / Accepted: 24 May 2021 / Published online: 15 June 2021

Abstract

Menin inhibitors are novel targeted agents currently in clinical development for the treatment of genetically defined subsets of acute leukemia. Menin has a tumor suppressor function in endocrine glands. Germline mutations in the gene encoding menin cause the multiple endocrine neoplasia type 1 (MEN1) syndrome, a hereditary condition associated with tumors of the endocrine glands. However, menin is also critical for leukemogenesis in subsets driven by rearrangement of the *Lysine Methyltransferase 2A (KMT2A)* gene, previously known as *mixed-lineage leukemia (MLL)*, which encodes an epigenetic modifier. These seemingly opposing functions of menin can be explained by its various roles in gene regulation. Therefore, leukemias with rearrangement of *KMT2A* are predicted to respond to menin inhibition with early clinical data validating this proof-of-concept. These leukemias affect infants, children and adults, and lead to adverse outcomes with current standard therapies. Recent studies have identified novel targets in acute leukemia that are susceptible to menin inhibition, such as mutated *Nucleophosmin 1* (*NPM1*), the most common genetic alteration in adult acute myeloid leukemia (AML). In addition to these alterations, other leukemia subsets with similar transcriptional dependency could be targeted through menin inhibition. This led to rationally designed clinical studies, investigating small-molecule oral menin inhibitors in relapsed acute leukemias with promising early results. Herein, we discuss the physiologic and malignant biology of menin, the mechanisms of leukemia in these susceptible subsets, and future therapeutic strategies using these inhibitors in acute leukemia.

Introduction

Genomic characterization of cancer has led to development of numerous targeted therapies that have improved clinical outcomes [1–4]. For decades, the treatment of acute myeloid leukemia (AML) had not changed until the recent advent of small-molecule and targeted therapeutic strategies such as inhibitors of isocitrate dehydrogenase (IDH) or FMS-like tyrosine kinase 3 (FLT3) or B-cell lymphoma 2 (BCL2) [5–8]. These discoveries were largely driven by an improved understanding of the various mechanisms that cause leukemia. However, despite these advances, many subsets of acute leukemia remain challenging to treat.

Leukemias driven by rearrangement of the *Lysine Methyltransferase 2A* (*KMT2A*) gene, also known as *mixed-lineage leukemia* (*MLL*) are unique, with characteristic pathophysiology and phenotype. These leukemias could affect infants, children and adults, and in all these setting are associated with high rates of resistance and relapse following conventional treatments [9]. Since the first description of chromosomal translocations involving 11q23 where *KMT2A* is located, incremental and paradigm shifting research has led to the development of targeted therapies, with the notable recent example of menin inhibitors (Fig. 1) [10–29]. Of interest, emerging clinical data established proof-of-concept for use of investigational menin inhibitors in the treatment of acute leukemia with multiple genotypes in addition to *KMT2A* rearrangements (*KMT2Ar*). Here we provide an overview of the normal functions of menin, discuss its functions in cancer, focus on its role in driving leukemia, and discuss the path to clinical development of menin inhibitors.

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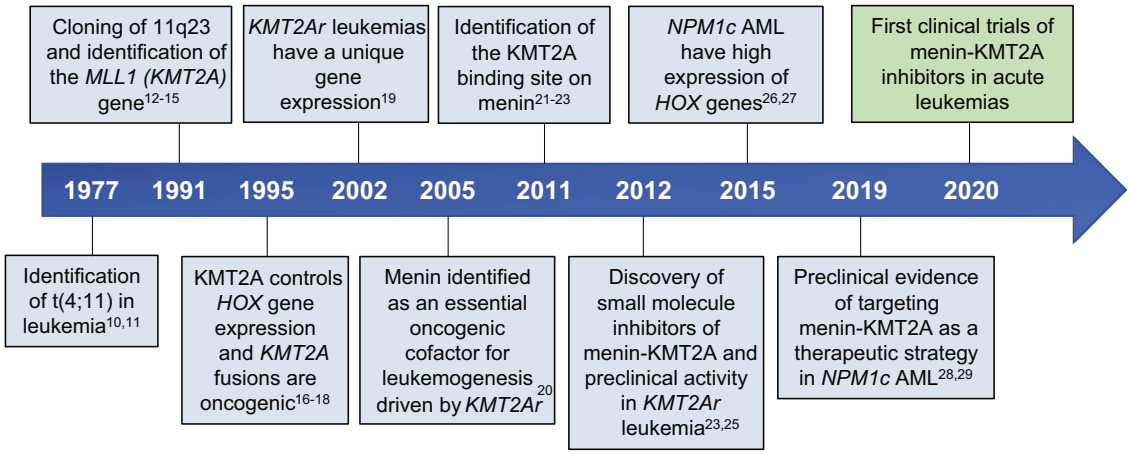

Fig. 1 Timeline of discoveries leading to investigation of menin inhibitors in acute leukemias. *MLL1*, mixed-lineage leukemia 1; *KMT2Ar*, rearranged Lysine Methyltransferase 2A; *HOX*, a subset of the homeobox genes; *NPM1c*, mutation of the *Nucleophosmin 1* resulting in a cytoplasmic localization of the protein.

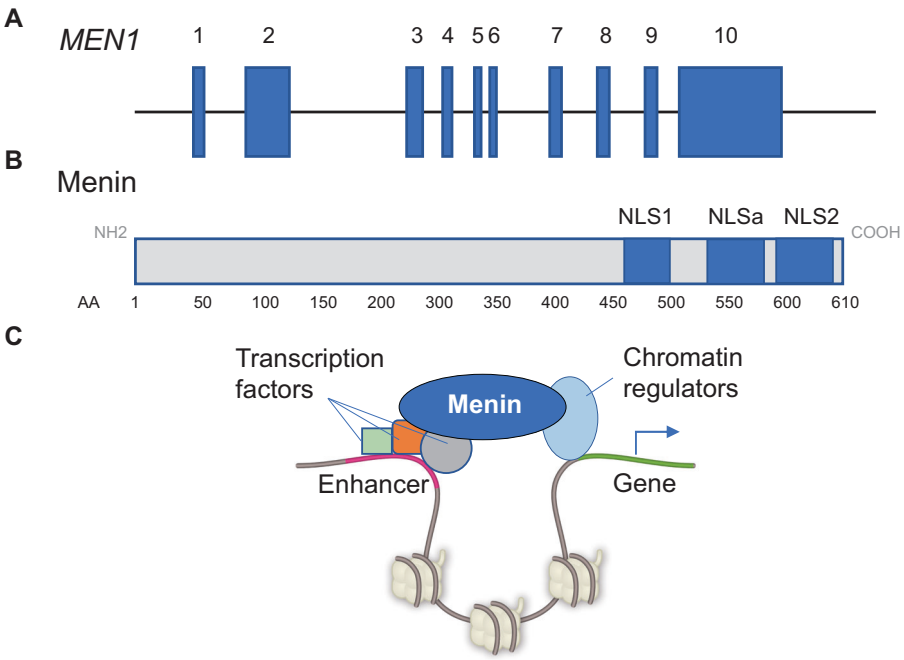

Fig. 2 Menin structure and function. Menin was first described after discovery of germline mutations in the gene responsible for the multiple endocrine neoplasia type 1 syndrome and was named *MEN1*. **A** The gene is located on chromosome 11q13 and contains 10 exons. Germline or somatic mutations are scattered through the coding exons with no hotspots indicating a tumor suppressor function in endocrine glands. **B** Menin is primarily a nuclear protein with nuclear localization sequences (NLSs) located in the C terminus. **C** Menin is a scaffold protein which regulates gene expression through interaction with various transcription factors and chromatin regulators.

Normal functions of menin and its binding partners

Menin has numerous functions, but most convincingly, regulates tissue-specific gene expression (Fig. 2) [30, 31]. The best examples to highlight the complex role of menin in homeostasis have resulted from studying cancer. Menin was first described after the discovery of germline mutations in the gene responsible for the multiple endocrine neoplasia type 1 (MEN1) syndrome and was therefore named *MEN1* [32]. *MEN1* germline or somatic mutations cause malignancies in endocrine glands and are scattered through the coding exons with no particular hotspots [32–35]. This indicates that menin is a tumor suppressor in this setting. And yet, menin can be critical for leukemogenesis [20, 36].

MEN1 is located on chromosome 11q13 and contains 10 exons (Fig. 2). Its product, menin, is a nuclear protein, expressed in multiple tissues at various levels [37, 38]. It is thought to be a scaffold protein that interacts with cell signaling and gene regulators (Fig. 2). It has no known similarities to any other protein and interacts with DNA through the nuclear localization sequences (NLSs) located in the C-terminal region (Fig. 2) [39, 40]. Results from chromatin immunoprecipitation followed by next-generation sequencing (ChIP-seq) showed that menin is present at sites of

active transcription and that occupancy correlates with high gene expression [41]. It is found at transcription start sites, bound to either gene promoters, transcription factors or enhancers thereby influencing transcription (Fig. 2) [31]. Resolving the structure of menin through crystallography revealed KMT2A (MLL1) and JunD as binding partners [23]. However, these interactions are not simultaneous and menin coordinates the functions of numerous other proteins (reviewed by Matkar, et al. and Dreijerink, et al.) [30, 31]. Homozygous deletion of menin is embryonically lethal with neural, craniofacial and heart malformations, though the mechanisms behind the physiologic roles of menin are not fully established [42, 43]. Determinants of what binds menin in various tissues and the resulting downstream functions have not been fully elucidated. Highlighting some of the identified binding partners could explain the cellular functions of menin.

KMT2A / KMT2D

KMT2A is a large protein expressed in hematopoietic cells and is required for normal development [9]. It consists of two subunits produced by cleavage of KMT2A forming the N and C terminus portions ($KMT2A^N$ and $KMT2A^C$, respectively) [9]. KMT2A along with partner proteins forming the KMT2A or MLL complex regulate gene expression through epigenetic modulation of transcription. It includes multiple functional domains such as the C-terminal SET domain with a histone H3 lysine 4 (H3K4) methyltransferase activity, and DNA binding domains (AT-hook motifs) at the N terminus among others (reviewed by Krivstov, et al. and Winters, et al.) [9, 44]. Binding of KMT2A to DNA is influenced by interactions of proteins in this complex such as menin. Both KMT2A and menin associate with the *HOXA9* promoter, a member of *Homeobox* (*HOX*) genes [20]. *Hox* genes encode transcription factors critical for early embryonic development, hematopoiesis, and development of the axial skeleton [45]. KMT2A associates with approximately 5000 genomic elements occupied by RNA polymerase II, suggesting a broad role in regulating transcription of not just the *HOX* genes [46, 47]. KMT2D (previously known as MLL2) is another SET domain-containing protein and a KMT2A paralog which also binds menin, but regulates distinct pathways including p53 [48, 49]. This supports the role of KMT2D as a tumor suppressor. Both KMT2A and KMT2D lead to H3K4 trimethylation, a marker of active gene promoters, and associate with RNA polymerase II [48, 50]. KMT2D plays an essential role in transcriptional activation of nuclear hormone receptors such as the estrogen receptor and PPARγ-dependent adipogenesis [51–54]. Additionally, KMT2D modulates retinoic acid-responsive gene transcription [49].

JunD

JunD is a member of the AP1 transcription factor complex that inhibits cell proliferation through binding and regulation of the cyclin D1 promoter, therefore functioning as a growth suppressor [41]. It was identified as one of the first menin-interacting proteins [23]. Menin inhibits Jun kinase-mediated phosphorylation, therefore repressing JunD-induced transcription [55]. Without menin, JunD switches from growth suppressor to growth promoter. Through this activity, menin may interfere with Ras-dependent cell transformation and oncogenesis [55].

MYC

MYC is a master regulator of cell proliferation [56]. It controls transcription of target genes in various contexts [56]. Menin interacts directly with the TAD domain of MYC by co-localizing to E-box and enhancing transcription of MYC target genes, which is independent of the role of menin within the KMT2A complex [57, 58]. In cancer models, through transcriptional promotion of MYC target genes, menin stimulated cell proliferation, cellular metabolism, and cancer progression [57]. This highlights menin's role as an oncogenic co-factor to MYC and its promotion of tumor growth.

The role of menin in cancer

Menin in MEN1 syndrome and other solid tumors

MEN1 is an autosomal dominant hereditary cancer syndrome with predisposition to tumors of the parathyroid glands, anterior pituitary, and neuroendocrine cells of the duodenum and pancreas. It is caused by pathogenic mutations in the *MEN1* gene which encodes for menin, a tumor suppressor in this setting [32]. These mutations are mostly nonsense and frameshift mutations causing premature stop codons, leading to a truncated menin protein which in turn is suppressed or degraded [59, 60]. Loss of menin causes disruption of anti-proliferative gene expression programs, therefore causing development of endocrine tumors [31]. Cyclin-dependent kinase inhibitor (CDKI) genes have been implicated in rare cases where germline mutations of these genes lead to MEN1-like phenotypes [61, 62]. CDKI genes such as CDKN2C and CDKN1B are regulated by menin and as targets of cyclin-dependent kinases, have an important role in cell cycle control [63]. This function is due, at least in part, to a cooperative interaction between menin and KMT2A, with loss-of-function of either KMT2A or menin resulting in downregulation of CDKI and deregulated cell growth [63].

Menin inhibition has been identified as a therapeutic strategy reversing aberrant gene expression in multiple

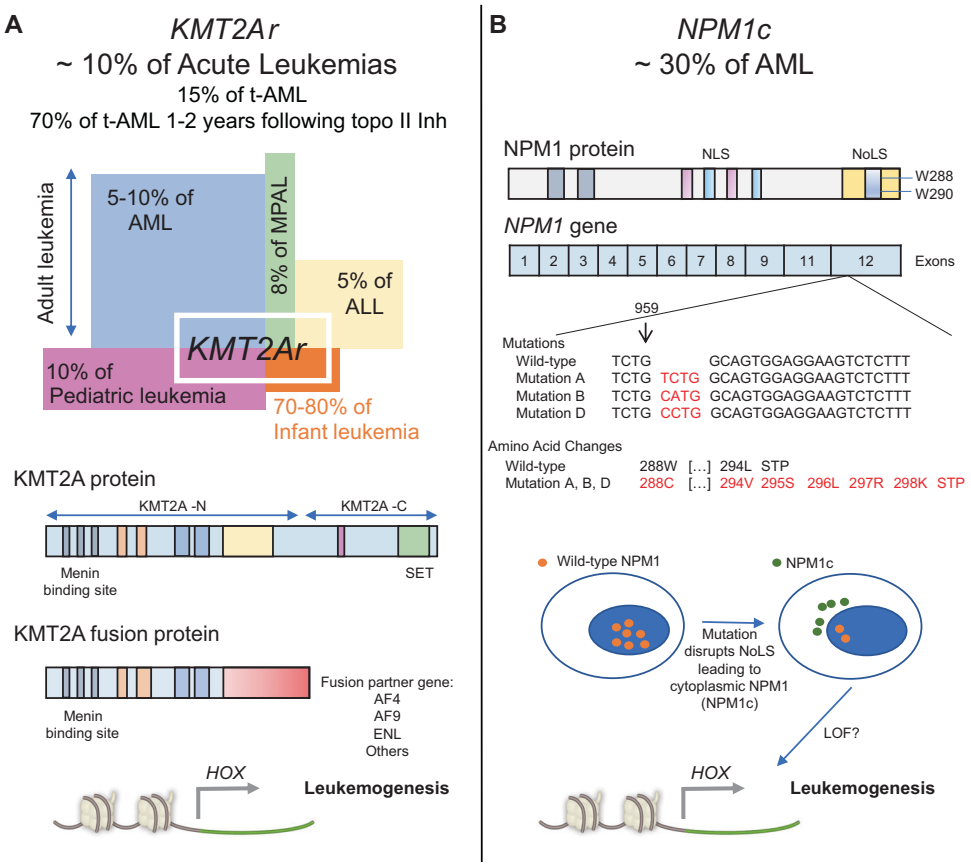

Fig. 3 Overview of menin inhibitor targets in leukemia. A Rearrangements of the *Lysine Methyltransferase 2A* (*KMT2A*) gene cause approximately 10% of acute leukemias with various phenotypes. By estimating from the Surveillance, Epidemiology, and End Results (SEER) database, approximately 5000 adults with AML, 300 adults with ALL, 40 adults with MPAL, 370 pediatric patients, and 160 infants are diagnosed each year in the United States with *KMT2A* rearranged leukemia. A representation reflecting incidence by phenotype is depicted in the colored squares and not made to scale. The menin binding site at the N terminus is preserved in all *KMT2A* fusions. KMT2A fusion proteins bind to menin, and this interaction causes leukemia by inducing an aberrant stem cell gene expression program mediated by the homeobox (*HOX*) genes. **B** Mutations in the *Nucleophosmin 1* (*NPM1*) are the most common alteration in AML. They consist of 4 base-pair frameshift insertions in exon 12, leading to truncation of the protein and disruption of the nucleolar localization signal (NoLS) responsible for shuttling of NPM1 to the nucleus turning *NPM1* exclusively cytoplasmic when mutated (thus termed NPM1c). Through unclear mechanisms, NPM1c causes upregulation of *HOX*, a central mechanism of leukemia. AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MPAL, mixed-phenotype acute leukemia; t-AML, therapy-related AML; topo II Inh, topoisomerase II inhibitors; LOF, loss-of-function.

laboratory investigations of solid tumors and diabetes [64–70]. This highlights the numerous functions played by menin which are likely tissue and context dependent.

Targeting menin in acute leukemia

KMT2Ar leukemias

Acute leukemia with rearrangements of the *KMT2A* gene have been recognized for decades as disease-defining abnormalities associated with an adverse prognosis [10, 11, 71]. They are driven by an oncogenic fusion of the *KMT2A* gene with more than 80 different partners identified [72]. These rearrangements occur in 5–10% of acute leukemias, and are the most common cause of infant leukemia (70–80%) (Fig. 3A). Fusion partners likely influence the leukemia phenotype where t(9;11) (p21;q23) or *KMT2A-MLLT3* (also known as *AF9*) is most common in AML, whereas t(4;11) (q21;q23) or *KMT2A-MLLT2* (also known as *AFF1* or *AF4*) is most common in acute lymphoblastic leukemia (ALL) [72]. These 2 translocations along with t(11;19)(q23;p13.3) or *KMT2A–MLLT1* (also known as *ENL*); t(11;19)(q23;p13.1) or *KMT2A–ELL;* t(10;11)(p12;q23) or *KMT2A–MLLT10* (also known as *AF10*); and t(6;11)(q27;q23) or *KMT2A–MLLT4* (also known as *AF6*) encompass 80% of all *KMT2Ar* leukemias [72, 73]. Phenotype is influenced by the cell-of-origin where a more primitive initiating cell in the hematopoietic hierarchy leads to a leukemia with an undifferentiated lineage [74]. All identified *KMT2Ar* contain the first 8–13 exons encoding

the N terminus and the menin-binding site (Fig. 3A). Failure of DNA double stranded breaks is the likely culprit of these translocations, as topoisomerase II cleavage sites between exons 8 and 13 are the most involved regions in these rearrangements [9, 75]. *KMT2Ar* are detected in up to 70% of therapy-related AML following treatment with a topoisomerase II inhibitor with a typical short latency to clinical presentation ranging from 6 months to 2 years [76, 77].

Prognosis of *KMT2Ar* *KMT2Ar* leukemias are associated with resistance to standard therapies and higher rates of relapse. Hyperleukocytosis, hepatosplenomegaly, and CNS involvement are common clinical presentation of this entity, especially in infants [78]. ALL with *KMT2Ar* often lack expression of CD10 and frequently co-express myeloid markers, with low expression of CD22 and negative CD20, corresponding to early stages of B cell differentiation [79, 80]. Given the specific mechanisms underlying *KMT2Ar* leukemias, it is not surprising that a myeloid or lymphoid lineage switch can occur over the course of treatments such as chimeric antigen receptor (CAR) T-cell therapy or Bispecific T cell Engager against CD19 [81, 82]. Infant leukemias with *KMT2Ar* are associated with in vitro resistance to prednisone and an exquisite sensitivity to cytarabine [83]. Despite major advances in the treatment of pediatric ALL with multiagent chemotherapy which led to a 5-year overall survival of 90%, outcomes of *KMT2A* rearranged infant leukemia has remained largely inferior with a 5-year overall survival of 20–44% [79, 84, 85]. Infants with relapsed or refractory *KMT2A* rearranged leukemia have less than 25% chance of survival at 5 years, therefore highlighting the unmet need for these patients [86]. AML with *KMT2Ar* is more likely to have a monocytic or monoblastic phenotype [87]. The 5-year overall survival rate for adults with *KMT2Ar* ALL is around 25%, with improved outcomes following an allogeneic stem cell transplant [88, 89]. AML with t(9;11)(p21.3;q23.3) have modestly improved outcomes compared to other *KMT2Ar* in adults with AML, though this may not apply to therapy-related disease [90, 91]. The 5-year overall survival rate associated with t(9;11) is between 27% and 35% compared to approximately 10% for all other translocations involving *KMT2A* in adults with AML [90, 91]. In this setting, an allogeneic stem cell transplant is associated with significant improvement in overall survival [91]. *KMT2A* partial tandem duplications (PTD) occur in 5% of AML, are more common in older patients and co-occur with a normal karyotype. They are associated with worse relapse-free survival compared to PTD-negative AML [92].

Diagnostic tests for *KMT2Ar* *KMT2Ar* can be detected by conventional cytogenetics where translocations involving 11q23 are seen or by fluorescence in situ hybridization (FISH) with some assays developed for detection of rearrangements regardless of the fusion partner gene (split-signal FISH concept) [93]. Another method recently developed relies on next-generation sequencing of RNA that allows detection of rearrangements without prior knowledge of the fusion partners or the breakpoints of the translocations [94]. In a recent analysis, whole-genome sequencing (WGS) was investigated as an alternative for cytogenetic analysis in myeloid malignancies [95]. This allowed for detection of cryptic chromosomal translocations leading to *KMT2A* rearrangements in 10 out 196 AML cases examined [95]. Therefore, WGS could be used in the future for an unbiased, initial screening of acute leukemias detecting all possible *KMT2Ar* (and all other genetic alterations), however, sensitive detection with WGS is currently cost prohibitive, and complimentary methods such as FISH or RNA-based methods would be necessary to track response to treatment.

Mechanisms of leukemia caused by *KMT2Ar* Genomic characterization of AML with *KMT2Ar* revealed significantly fewer mutations compared to other leukemia genotypes, highlighting the importance of these fusions as founding and essential events in leukemia development [96, 97]. This is particularly evident in infant *KMT2Ar* leukemia where the fusion is the sole driving event [98]. Co-occurring mutations in *RAS* signaling pathway genes or *FLT3* are more common in adult patients and are subclonal [97, 99]. Multiple mouse models of *KMT2Ar* leukemias have been developed using these fusions as potent oncogenes sufficient for leukemia development [100]. KMT2A has multiple functional domains exerting epigenetic roles including the methyltransferase SET domain at the C terminus [9]. It controls expression of *HOX* genes, which are stem cell genes essential for normal hematopoietic development [16]. *KMT2A* fusions bind promoters of *HOX* genes, which in turn activate an aberrant gene expression program in collaboration with their co-factor MEIS1, leading to leukemia with a differentiation block [101].

Menin inhibition in *KMT2Ar* leukemia *KMT2Ar* leukemias have a unique, highly distinct, gene expression profile characterized by overexpression of *HOX* along with their co-factor *MEIS1* [19]. These fusion proteins are all characterized by loss of the SET domain [9]. Menin binds KMT2A within the first 10 amino acids of the protein. The menin binding site is preserved throughout all KMT2A fusion proteins and is an essential co-factor for binding to *HOX* gene promoters. In mouse models of *KMT2Ar* leukemia, genetic ablation of menin reversed aberrant *Hox* gene expression, leading to abrogation of the differentiation arrest and the oncogenic properties of *KMT2Ar*. Therefore, menin is an essential oncogenic co-factor for

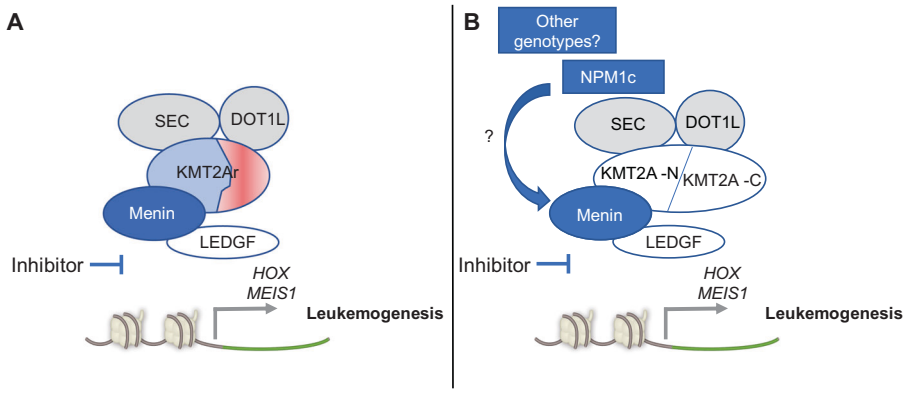

Fig. 4 Mechanisms of targeting leukemia through menin inhibition. A Menin inhibitor disrupt binding of menin to the KMT2A fusion protein therefore disrupting this chromatin complex leading to inhibition of the aberrant leukemogenic transcription program. **B** In *NPM1*-mutated acute myeloid leukemia, menin inhibitors reverse aberrant gene expression mediated by *HOX* genes and their co-factor *MEIS1* leading to leukemia regression. Other leukemia genotypes could be susceptible to menin inhibitors through disruption of aberrant gene expression. SEC, super elongation complex which consists of the RNA polymerase II (Pol II) elongation factors eleven-nineteen Lys-rich leukemia (ELL) proteins, positive transcription elongation factor b (P-TEFb) and several frequent KMT2A translocation partners; *DOT1L*, *DOT1 Like Histone Lysine Methyltransferase,* LEDGF, lens epithelium-derived growth factor; *HOX*, a subset of the homeobox genes.

leukemogenesis driven by *KMT2Ar*. This requirement for menin to maintain leukemogenesis is specific to leukemic cells but not normal hematopoietic stem cells which can tolerate its loss [102]. Identification of the KMT2A binding pocket on menin led to development of potent small-molecule inhibitors of the menin-KMT2A interaction [24]. Therefore, menin inhibitors disrupt binding of KMT2A to menin, an essential co-factor necessary for binding of the KMT2A complex to promoters of target genes. Pharmacologic inhibition of menin-KMT2A proved to be an effective antileukemic strategy in preclinical models of *KMT2Ar* leukemias without affecting normal hematopoiesis by downregulating the aberrant gene expression profile, specifically *Hox* and *Meis1* (Fig. 4) [24, 25, 103]. This led to release of the differentiation block caused by *KMT2Ar* in these leukemias, with a pronounced increase in markers of myeloid differentiation, and apoptosis following treatment [103]. This paved the way for the first clinical trials evaluating small-molecule menin inhibitors as targeted therapies in acute leukemia (Table 1).

AML with mutated *NPM1*

NPM1 mutations are the most common genetic alterations in adult AML, detected in 20–30% of cases at diagnosis [104]. These mutations are considered leukemia-initiating. They are often preceded by preleukemic mutations associated with clonal hematopoiesis (CH), but are not detected in CH [105, 106]. They consist of 4 base-pair frameshift insertions or duplications in exon 12, leading to truncation of the protein and disruption of the nuclear shuttling of NPM1. Therefore, mutated *NPM1* persists in the cytoplasm which explains why it is exclusively cytoplasmic when mutated (thus termed *NPM1c*) (Fig. 3B) [107, 108]. A dysfunction of the lymphoid enzyme terminal deoxynucleotidyl transferase (TdT), which increases diversity of the immunoglobulin and T-cell receptor loci in homeostasis, has been implicated in the etiology of both of *NPM1* and *FLT3* mutations [109]. This could explain why these mutations frequently co-occur [104]. Though the mechanism is unclear but presumed to be a loss of function, *NPM1c* is associated with upregulation of *HOX* genes, specifically *HOXA* and *MEIS1* [26, 110, 111]. The similarity in gene expression profiles between *NPM1c* and *KMT2Ar* led to the hypothesis that menin is implicated in this aberrant transcription, and that targeting menin could be also a therapeutic strategy in AML with mutated *NPM1*. Genetic editing studies confirmed dependency of *NPM1c* on menin and *MEIS1* to exert a leukemogenic function [112]. Using *Npm1c* mouse models and patient-derived xenografts, small-molecule menin inhibitors induced loss of MEIS1, a differentiation effect, and a potent antileukemia activity (Fig. 4) [28, 29].

AML with mutated *NPM1* without *FLT3* internal tandem duplication (ITD) is associated with a favorable prognosis using current standard treatments [113]. However, this prognosis is significantly altered by presence of co-occurring mutations. Concurrent *FLT3*-ITD mutations lead to a worse prognosis, especially when their allelic burden is high [113]. Co-occurrence of mutations in *DNMT3A*, *NPM1*, and *FLT3-ITD* is the single most common combination of mutations in AML and further influences prognosis with worse outcomes [114]. Therefore, *NPM1c*

Table 1 Phase 1/2 clinical trials investigating menin inhibitors in refractory acute leukemias.

Clinical trial/status	Drug	Dosing	Min. age	Phase 2 expansion cohorts
AUGMENT-101 NCT04065399 Syndax (recruiting)	SNDX-5613	PO BID	30 d	A. ALL or MPAL with *KMT2Ar* B. AML with *KMT2Ar* C. AML with *NPM1c*
KOMET-001 NCT04067336 Kura (recruiting)	KO-539	PO daily	18 yr	A. AML with *KMT2Ar* B. AML with *NPM1c*
NCT04752163 Daiichi Sankyo (recruiting)	DS-1594	PO BID	18 yr	A. *KMTAr* leukemia: single agent B. AML with *NPM1c*: single agent C. AML with *KMT2Ar* or *NPM1c*: in combination with azacytidine and venetoclax D. ALL with *KMT2Ar*: in combination with mini-HCVD
NCT04811560 Janssen (not yet recruiting)	JNJ-75276617	PO daily	18 yr	–
Biomea Fusion (IND enabling submission)	BMF-219	PO	–	–

Status of clinical trials as of May 2021. *ALL* acute lymphoblastic leukemia, *MPAL* mixed-phenotype acute leukemia, *KMT2Ar* rearranged *Lysine Methyltransferase 2A*, *AML* acute myeloid leukemia, *NPM1c* mutation of the *Nucleophosmin 1* resulting in a cytoplasmic localization of the protein, *Min. age* minimum age for enrollement, *d* days, *yr* years, *Mini-HCVD* dose reduced combination of cyclophosphamide and dexamethasone, methotrexate, and cytarabine.

mutations could be a shared vulnerability in these subsets, where menin inhibition would be a novel targeted therapy. *FLT3* mutations frequently arise in subclones of AML and are rarely founding events. Notably, *FLT3* is a putative transcriptional target of MEIS1 [112]. In preclinical models, combined menin and FLT3 inhibition were found to be synergistic supporting the use of these inhibitors in combination [115, 116]. In models expressing *Npm1* and *Flt3* mutations, menin knockdown downregulated and dephosphorylated Flt3, through downregulation of *MEIS1* [115]. The combination of a FLT3 and menin inhibitors induced enhanced inhibition of proliferation and apoptosis, compared with single-drug treatments therefore exerting synergistic antileukemic effects [115, 116]. Importantly, this combination seemed to overcome common mechanisms of drug resistance seen with FLT3 inhibition and led to complete and long-lasting remission of leukemia in mice [115, 116]. Menin inhibitors in this setting are expected to target the founding clone, and not just the subclones which is often the case in monotherapy with FLT3 inhibitors.

In addition to menin inhibitors, other promising investigational agents have been tested in *NPM1*-mutated AML indicating clinical activity [117, 118]. Namely, use of retinoic acid and arsenic trioxide induced proteasomal degradation of NPM1c in vitro, leading to growth arrest and apoptosis. Additionally, three patients treated with this combination had reduction in bone marrow blasts with restoration of the subnuclear localization of NPM1 [119]. Another example worth highlighting is the chemotherapeutic agent dactinomycin, which induced a complete response or a complete response with incomplete count recovery in 4 out of 10 patients in a phase 2 pilot study investigating this agent in patients with relapsed/refractory *NPM1*-mutated AML [120]. This clinical activity was associated with nucleolar stress response. Further investigations of these agents in larger clinical studies are warranted.

Menin-dependent transcription in AML

The current prevailing model of dependency on menin in acute leukemias is linked to overexpression of *HOXA* and/or *HOXB* genes and their co-factor *MEIS1*, therefore this gene expression profile (specifically *MEIS1* levels) can be used as a biomarker of response to menin inhibition (Fig. 4). However, given the current lack of validated assays to assess this biomarker, leukemia genotypes previously shown to have this gene expression signature could be used as a surrogate marker, and assessed for response to menin inhibition. This expression signature is identical to that of normal hematopoietic stem and progenitor cells but is also shared by other genotypes or recurrent cytogenetic abnormalities in AML in addition to *NPM1c* and *KMT2Ar* (Table 2) [121]. To

Table 2 Genetic alterations with overexpression of *HOXA* genes predicted to potentially respond to menin inhibitors.

Alteration/mutation	Cytogenetics	Phenotype				References
KMT2Ar	11q23 rearrangements	AML, ALL, MPAL	✓	✓	✓	[26, 132, 133]
KMT2A-PTD	Normal karyotype	AML	✓	✓		[26, 134]
NPM1c	Normal karyotype	AML	✓	✓	✓	[26, 135]
NPM1-MLF1	t(3;5)(q25;q34)	MDS, AML	✓			[136, 137]
NUP98r	11p15 rearrangements	AML, T-ALL, MDS	✓	✓	✓	[122–124]
SET-NUP214	t(9;9)(q34;q34)	AML, T-ALL, AUL	✓		✓	[138]
RUNX1-EVI1	t(3;21)(q26;q22)	AML	✓		✓	[139]
MYST3-CREBBP	t(8;16)(p11;p13)	AML	✓			[140]
CDX2-ETV6	t(12;13)(p13;q12)	AML		✓		[141]
CALM-AF10	t(10;11)(p13;q14-21)	T-ALL, AML, MPAL	✓	✓	✓	[142–144]
MN1-ETV6	t(12;22)(p13;q12)	AML, MDS		✓	✓	[145]
EZH2	–	MDS, AML	✓			[146]
IDH1/IDH2	–	MNs			✓	[147, 148]
ASXL1	–	MNs		✓		[149]
CEBPA	–	AML			✓	[150]
	Trisomy 8	MNs	✓			[151]

Denotes direct examination of patient samples with the corresponding genotype showing upregulation of *HOXA* genes.

Denotes mouse models of the corresponding genotype leading to upregulation of *Hox* genes.

Denotes examination of cells lines or other in vitro investigations demonstration a role of *HOX* genes or menin inhibition in the corresponding genotype.

AML acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *MPAL* mixed-phenotype acute leukemia, *MDS* myelodysplastic syndromes, *AUL* acute leukemia of undifferentiated lineage, *MNs* myeloid neoplasms.

highlight one example, leukemias with rearrangements involving the *Nuclear pore complexes 98 (NUP98)*, have overexpression of *HOXA9* in preclinical models and patient samples, and therefore could respond to menin inhibition [122–124]. These fusions are rare, however, they are associated with an adverse prognosis. A comprehensive analysis of *HOX* gene expression patterns in AML revealed clusters defined by presence or absence of *HOXA* and/or *HOXB* genes [26]. Leukemias with *PML-RARA* or *RUNX1-RUNX1T1* fusions had no expression of these genes unlike *KMT2Ar* with near-universal expression of *HOXA* and *NPM1c* with *HOXA* and *HOXB* expression. Interestingly, 75% of AML with normal karyotype expressed *HOXA* and *HOXB* which included all samples with *NPM1c* in that study, and also 11% of *NPM1* wild-type with normal karyotype AML. Therefore, it is conceivable to use this gene expression signature as a biomarker of response to menin inhibitors and identify leukemias with various genotypes or various settings (not just *NPM1c* or *KMT2Ar*) that could respond to these agents. This intriguing concept was bolstered recently by a complete response in a patient with relapsed AML and mutations in *RUNX1* and *SETD2* genes when treated with the menin inhibitor KO-539 on the phase 1 study [125]. The mechanisms of response in this case are not clear yet, in particular whether *RUNX1* or *SETD2* mutations confer sensitivity to menin inhibition or whether dysregulation of *HOX* genes constituted the critical vulnerability. Given the diverse role of menin in other tissues, and its interaction with multiple other gene regulators, it is also plausible that targeting menin disrupted the activity of another critical transcription factor in this setting. Future studies could allow identification of an ultimate biomarker of response to menin inhibition.

Investigation of mechanisms of resistance to venetoclax-based therapies in AML, the current standard of care for older patients or those unable to receive intensive chemotherapy, revealed activation of a *KMT2A*-like signature through upregulation of *HOXA9* and *MEIS1* at relapse [126]. Therefore, menin inhibition could be a promising therapy following resistance or relapse to venetoclax in AML where there exists a paucity of active agents, though this hypothesis has not been tested.

Early clinical results with menin inhibitors

Given the strong preclinical rationale justifying use of menin inhibitors as a novel class of targeted therapy in acute leukemias, multiple clinical trials with these agents have been started with early results demonstrating clinical activity (Table 1). In a press release in April 2021, Syndax announced early results from the ongoing phase 1 clinical trial (AUGMENT-101, NCT04065399). As of a March 2021 data cutoff, the overall response rate (ORR) in patients

with relapsed or refractory *KMT2Ar* leukemia was 54% (13 out of 24 evaluable patients) with an undetectable minimal residual disease (MRD) rate of 67%. These included patients with AML, ALL, or mixed-phenotype acute leukemia (MPAL) refractory to multiple prior lines of therapy (median of 3 lines), including stem cell transplant in approximately half of those enrolled. These results are highly encouraging given the low response rates with standard treatments for *KMTAr* leukemias in this setting. Given that SNDX-5613, the oral menin inhibitor in this trial, was found to be affected by CYP3A4, enrollment on this study proceeded with 2 arms, with and without concomitant strong CYP3A inhibitors, specifically azoles used for prevention of fungal infections, with responses seen in both arms. This treatment was overall well tolerated. Major related side effects (≥ grade 3), observed in at least 5% of patients, included QTc prolongation, and differentiation syndrome. Detection of differentiation syndrome in this setting justifies the preclinical evidence of a successful reversal of the differentiation block caused by *KMT2Ar* through menin inhibition. The ORR in *NPM1*-mutated AML was 29% (2 out of 7 evaluable patients). Data from the first patients enrolled on this study had been presented at the 2020 American Association for Cancer Research Annual Meeting [127]. A 69-year-old with relapsed mixed-phenotype acute leukemia and a t(10;11)(q22;q23) or *KMT2A-TET1* fusion along with a *FLT3*-ITD mutation, had progressed on two prior lines of therapy including the FLT3 inhibitor gilteritinib, achieved a complete response with SNDX-5613. *KMT2Ar* became undetectable by FISH along with morphologic remission and no minimal residual disease by flow cytometry indicating a profound and meaningful response. A 61-year-old with t(9;11)(p21.3; q23.3), had AML relapse after three prior lines of therapy, achieved a partial response with improvement in blood counts without complete count recovery. Both patients had achieved drug exposures consistent with levels predicted to be active based on preclinical models, unlike the third patient with *KMT2Ar* who did not respond, where effective levels were not reached.

Early data from the KOMET-001 trial (NCT04067336) presented at the 2020 American Society of Hematology (ASH) Annual meeting showed potential clinical activity of the oral menin inhibitor KO-539 [125]. At the time of that presentation data cutoff, 12 patients had been enrolled, 8 were evaluable for response. Pharmacokinetics of KO-539 were not altered by co-administration of CYP3A4 inhibitors, such as azoles. The drug was well tolerated with mostly grade 1 or 2 toxicities. One patient with KMT2Ar enrolled at the lowest dose level had tumor lysis syndrome, decrease in hydrea requirements, and stabilization of peripheral blood counts [125]. The preclinical concept of targeting NPM1c though menin inhibition was also validated in this trial [125]. There was clinical activity in two patients with *NPM1*-mutated AML treated with the oral menin inhibitor KO-539. One patient with *NPM1*-mutated AML had previously progressed on seven lines of therapy, achieved a complete remission with undetectable minimal residual disease after treatment with this agent. A second patient with mutated *NPM1* and *FLT3*-ITD had received four prior lines of therapy achieved a morphological leukemia-free state [97]. In addition, as mentioned above, there was a CR in a patient with relapsed AML and mutations in *RUNX1* and *SETD2* genes when treated with the menin inhibitor KO-539, therefore justifying investigation of menin inhibition in other susceptible leukemias.

Both structurally unrelated drugs (SNDX-5613 and KO-539) have been granted an orphan drug designation by the U. S. Food and Drug Administration (FDA). In addition, trials with other menin inhibitors have been recently launched (Table 1).

Future directions

Final results of the clinical trials investigating menin inhibitors are eagerly awaited. Though these are phase I studies aimed at evaluating safety, they could provide insights on activity in leukemia genotypes susceptible to menin inhibition, which would be further validated in the planned phase II expansion cohorts. Additionally, as we gather more information on safety of these agents predicted to be targeted with limited effects on normal hematopoiesis, certainly numerous questions remain unanswered. For example, whether biomarkers such as *HOX* or *MEIS1* expression would predict response or can be used to identify and target a larger population of patients who may benefit from menin inhibition. Or, whether menin inhibition would perturb physiologic functions in other organs, especially the endocrine system. However, the possibility of any "MEN1-like" syndrome secondary to menin inhibition is unlikely given that these tumors are often caused by a second hit prior to malignancy and certainly would not hinder development of these agents in deadly acute leukemias with limited treatment options.

Extraordinary efforts by numerous scientists over the years allowed these agents to reach investigation in clinic. Though this is only the beginning of clinical investigations of these molecules, early results are highly encouraging. In the future, a newer generation of menin inhibitors could perhaps leverage the novel protein degradation strategy, which could improve potency [128, 129]. The immediate next steps that follow investigation of safety and efficacy of these agents are optimal combination strategies. Many agents, either standard or investigational could be ideal partners. These include standard chemotherapeutic approaches, immunotherapy such as the CD3-CD19 bispecific

antibody blinatumumab for ALL, and venetoclax-based therapies for AML. FLT3 inhibitors should also be explored given the frequent co-mutation of *FLT3* with *NPM1c* mutations and KMT2Ar. However, which of these combinations and what agents to prioritize may require multiple parallel clinical investigations. Among investigational agents, the addition of DOT1L inhibitors would be a rational epigenetic combination strategy for *KMT2Ar*- or *NPM1*-mutated leukemia [112, 130, 131].

There are many reasons to be optimistic about the future of leukemia research. Dedicated scientists and clinicians, using innovative technologies, have delivered new effective therapies over the past few years, getting us closer to what ultimately matters, curing more patients with acute leukemia.

Author contributions G.C.I. designed and wrote the manuscript. F.R., C.D.D., E.J., H.M.K., and M.A. provided suggestions and revisions. All authors read and approved the final manuscript.

Funding G.C.I. received funding through the K12 Paul Calabresi Clinical Scholarship Award (NIH/NCI K12 CA088084).

Conflict of interest G.C.I. received research funding from Celgene, Kura Oncology, Syndax and Novartis, and received consultancy fees from Novartis and Kura Oncology. F.R. received research funding from Amgen, Bristol-Myers Squibb, Sunesis Pharmaceuticals, Pfizer, Xenecor, Macrogenetics, Taiho, Astex, Abbvie and honoraria for consulting or advisory role from Jazz, Amgen, Celgene, Astellas, Syros, Taiho, Novartis, AstraZeneca, Agios, Bristol Myers Squibb. C. D.D. received research funding from Abbvie, Agios, Calithera, Cleave, BMS/Celgene, Daiichi-Sankyo, Forma, ImmuneOnc, Loxo, and received consultancy or advisory board fees from AbbVie, Agios, Novartis, Agios, Aprea, Celgene/BMS, ImmuneOnc, Notable Laboratories, and Takeda. E.J. received research funding from Abbvie, Adaptive Biotechnologies, Amgen, Bristol-Myers Squibb, Pfizer and Takeda and received advisory board fees from Genetech. H.M.K. received research funding from Ariad, Astex, Bristol-Myers Squibb, Cyclacel, Daiichi-Sankyo, Pfizer, Immunogen, Jazz, Novartis and honoraria from Pfizer, Immunogen, Actinium and Takeda. M.A. received research funding from Daiichi Sankyo, and consultancy honoraria from Jazz, Celgene, Amgen, AstaZeneca, Dimensions Capital, and equity ownership from Reata, Aptose, Europics, Senti Bio, Chimerix, Oncolyze.

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