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Menin: from molecular insights to clinical impact

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REVIEW

Menin: from molecular insights to clinical impact

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ABSTRACT

Menin, the protein product of the *MEN1* gene, is essential for development and has been implicated in multiple different cancer types. These include leukemias and several different solid tumors, including neuroendocrine tumors. Menin interacts with many different protein partners and genomic loci in a context-dependent manner, implicating it in numerous cellular processes. The role of Menin varies across tumor types as well, acting as a tumor suppressor in some tissues and an oncogenic co-factor in others. Given the role of Menin in cancer, and particularly its oncogenic role in acute myeloid leukemia, the development of Menin inhibitors has been an expanding field over the past 10–15 years. Many inhibitors have been in clinical trials and one has recently received approval from the Food and Drug Administration (FDA). In this review, we explore the role of Menin in multiple cancer types, the development of Menin inhibitors and their clinical applications and what the focus of the field should be in the next 5–10 years to expand the use and efficacy of these drugs.

PLAIN LANGUAGE SUMMARY

The protein Menin is vital for normal human development and growth. However, changes in Menin, or in proteins that bind to Menin, can lead to tumor formation in various tissues. This is common in blood cancer (acute myeloid leukemia or AML) and solid tumors (neuroendocrine tumors or NETs), such as those found in the pituitary and parathyroid glands, and pancreas cells. In some cases of AML, an important Menin-binding partner, called MLL1, is altered and promotes cancer growth. In NETs, Menin itself is altered, and its normal function is impaired. Because of the role of the Menin-MLL1 interaction in AML, scientists have developed inhibitors to block it. This review discusses Menin's involvement in different cancer types, the generation and development of Menin inhibitors, and the clinical use of these medications.

1. Introduction

Menin is a unique chromatin adaptor protein that is encoded by the *MEN1* gene. Menin has multiple isoforms, but the two most prevalent encode for proteins of 610 and 615 amino acids. The only annotated regions of Menin are two nuclear localization signals (NLSs) that flank an intrinsically disordered region (IDR) of the protein (Figure 1) [1]. Menin lacks homology to any other known eukaryotic protein, making it hard to infer function from its sequence or structure.

However, Menin is known to interact with many proteins involved in different cellular functions including gene regulation and DNA repair, and is known to play an important role in development and disease, as its loss leads to embryonic lethality [2–17]. Menin was initially found to act as a transcriptional repressor through its interactions with the transcription factor JunD and the histone deacetylase (HDAC) mSin3A [5,18]. However, soon after, it was found to also be involved in transcriptional activation by recruiting and stabilizing the MLL1 and MLL2 histone methyltransferase (HMT) complexes to transcriptional start sites (TSS) [3,4]. The genomic localization of the Menin-MLL complex at TSSs of the *HOX* gene locus implicated Menin in organismal development, helping to explain its embryonic lethality and role in disease.

The main focus of Menin's role in disease has been in the field of cancer biology. In this context, Menin has paradoxical roles, acting both as an oncogenic co-factor and a tumor suppressor depending on the cellular context [17,19,20]. Germline inactivating mutations in *MEN1* lead to the genetic disorder Multiple Endocrine Neoplasia Type 1 (MEN1 syndrome), in which somatic mutations of the remaining allele lead to the formation of tumors derived from neuroendocrine tissues [21–25]. Menin has also been found to be an oncogenic co-factor in acute myeloid leukemia (AML), as it is the chromatin adaptor subunit of the MLL1/2 histone methyltransferase complex and the MLL1-fusion proteins [7,17]. More recently, Menin has been found to also play a role in a variety of solid tumors including breast, prostate and lung cancers [26–31].

Several studies have contributed to the development of Menin-MLL small molecule inhibitors, which are being explored and clinically tested as potential treatments for AML and other Menin-related cancers [32–39]. Multiple independent groups have developed various classes of Menin inhibitors. For the most part, these have been developed to treat *MLL1*-rearranged (*MLL1*-r) AML. However, it has been

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found that they are also efficacious for other malignancies including AML driven by other mutations (non *MLL1*-r), acute lymphoblastic leukemia (ALL), and a variety of solid tumors. Several inhibitors are currently in clinical trials as both single agents and in combination therapies, with the first approval from the Food and Drug Administration (FDA) having just occurred in November 2024 [40].

In this review, we will discuss the development, characterization, and use of Menin inhibitors to treat cancer. We will begin by discussing the cellular roles of Menin and how those contribute to its context-specific role in various cancer types. The discussion will continue with the history of Menin inhibitors development, how these are being used in the clinic and emerging evidence of resistance mutations. We will also share our perspectives on future avenues in the role of Menin, *MEN1* mutations and Menin inhibitors in solid tumors and non-cancer diseases/disorders.

2. History of Menin

The gene *MEN1*, which encodes for the protein Menin, was originally cloned and identified as the causal gene of the human MEN1 syndrome in 1997 [41]. *MEN1* is located on chromosome 11q13, contains 10 coding exons and is ubiquitously expressed across tissues (Figure 1). Menin contains two NLSs and is predominantly found in the nucleus of cells [1]. Menin is a highly conserved protein from sea anemone (*Nematostella vectensis*) through humans (*Homo sapiens*). However, it contains no regions of homology to any other eukaryotic proteins and no annotated functional domains, aside from two NLSs in the C-terminal half of the protein (Figure 1) [1,41]. These structural features (or lack thereof) indicate that Menin plays a unique and essential cellular role, yet it has been a challenge to study given that there are no biochemical clues from the amino acid sequence or 3D protein structures.

Soon after the identification and cloning of *MEN1*, *Men1* null mouse models were developed, leading to the discovery that loss of *Men1* is lethal between embryonic stages 11.5–13.5 [9,10]. These embryos were found to have abnormal nervous system development and heart hypotrophy [9]. Mice harboring heterozygous deletions of *Men1* have a developmental trajectory that mimics that of human MEN1 syndrome. These mice develop pancreatic islet lesions and parathyroid adenomas at nine months, and then larger tumors of the pancreatic islets, parathyroid, thyroid, adrenal cortex and pituitary gland at 16 months [10]. The tumors that form in these mice have undergone loss of heterozygosity at the *Men1* locus. To study the role of Menin in various tissues while circumventing the lethality of a full *Men1* deletion, many groups have developed mouse models of conditional, tissue-specific *Men1* deletion. These generally use a homozygous whole-body floxed *Men1* allele crossed to Cre recombinase that is expressed under a tissue-specific promoter. Examples of tissues that have been targeted by this method include lung, gastrointestinal tract, breast and prostate [30,42–45].

The first functional studies of Menin revolved around transcriptional regulation. Multiple studies found that Menin can both activate and repress gene transcription
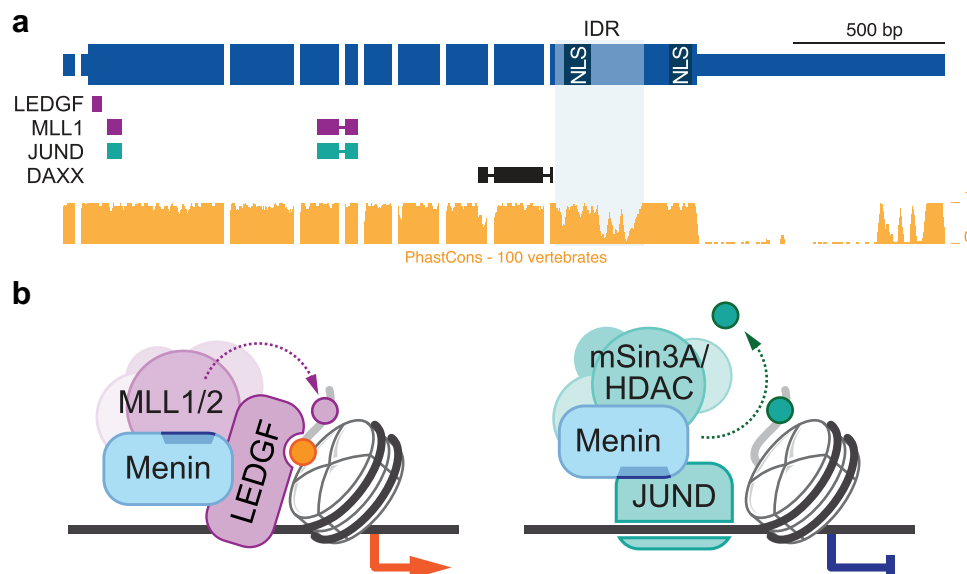

Figure 1. Menin as a scaffold for chromatin-associated factors. (a) Schematic of the *MEN1* gene, the binding locations of known Menin interactors and Menin sequence conservation in vertebrates. (b) The Menin protein has differential effects on gene expression depending on the complexes it is bound to. NLS – Nuclear localization signal; IDR – Intrinsically disordered region.

through its interactions with various protein partners. It was found that Menin is a transcriptional co-activator through interactions with SMAD3, the MLL1 and MLL2 histone methyltransferases, and Serine 5-phosphorylated RNA Polymerase II (S5P-Pol II) [4,15]. During development, these interactions are important for activating genes in the *HOX* locus where Menin binds, and loss of Menin in mouse embryos have shown a lower expression of *Hoxc6* and *Hoxc8* [4]. Simultaneously, it was found that Menin can repress transcription through interactions with JunD and NF-$_k$B [5,14]. The interaction surface of Menin with JunD is the same surface that MLL1/2 binds to, making these two interactions mutually exclusive. Finally, it was shown that Menin can bind double-stranded DNA in a sequence-independent manner through the positively charged residues that compose the NLSs at the C-terminus of the protein [46]. However, whether Menin is able to directly bind DNA on its own is a debated topic in the field.

Continued research in the role of Menin using various cellular systems has uncovered a wide variety of interacting partners and cellular processes that Menin helps control. These studies have centered Menin as a hub for many different molecular and cellular processes.

3. Menin as a hub for molecular and cellular processes

Just as Menin plays a variety of roles in disease, it is also known to interact with many different proteins and genomic loci in the cell, further implicating Menin in a wide range of cellular functions. These processes include: transcriptional activation, transcriptional repression, cell cycle/migration, DNA damage response, signal transduction and differentiation.

3.1. Transcriptional activation

Menin interacts with MLL1/2, acting as the chromatin adaptor subunit of this HMT complex and linking it with the transcriptional co-activator, LEDGF (Figure 2) [3,4,7]. This HMT complex trimethylates histone 3 on lysine 4 (H3K4) at the TSS of important developmental genes such as *HOX* locus genes and is a mark associated with active transcription [4,47]. Importantly, Menin retains binding to the MLL1 fusion proteins that drive a subset of AML, acting as an oncogenic co-factor in this setting [17]. Menin has also been found to interact with S5P-Pol II, the state of Pol II associated with transcription initiation [4]. This interaction further implicates Menin in transcriptional activation. While the interaction between Menin and MLL HMTs is probably the most well-understood role for Menin in activating gene expression, it can also contribute to transcriptional activation in H3K4 trimethylation (H3K4me3)-independent manners, including interacting with the nuclear receptor estrogen receptor alpha (ERα), and the oncogene MYC [8,26].

3.2. Transcriptional repression

Given the context-dependent nature of Menin, it is unsurprising that it also contributes to transcriptional repression. One of the
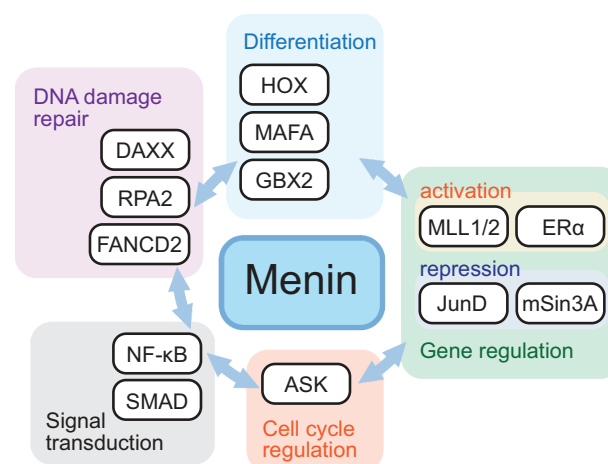

Figure 2. Menin's many interactions implicate it in multiple different cellular processes.

first identified interacting partners of Menin was the activating protein-1 (AP-1) transcription factor, JunD, and it was found that this interaction repressed JunD-mediated transcription (Figure 2) [5]. It was later found that JunD and MLL interact with the same binding pocket on Menin and these interactions are mutually exclusive (Figure 1) [6]. One proposed mechanism by which this transcriptional repression occurs is through the interaction of Menin and an mSin3A HDAC complex [18]. The deacetylation of histones leads to a more compact chromatin state and subsequently, less transcription. Further corroborating this HDAC-dependent mechanism, Menin was later found to interact with CHES1, a component of an mSin3A-HDAC complex, in the context of DNA damage-induced S-phase arrest [48]. Menin also represses NF-$_k$B mediated transcription through interactions with the p65 protein [14]. This mechanism was found to rely on Menin interacting with a different deacetylase, SIRT1. The acetylation of lysine 310 (K310) on p65 is an important post-translational modification (PTM) for NF-$_k$B mediated transcriptional activation, and Menin recruits SIRT1 to p65, leading to the deacetylation of K310 and subsequent transcriptional repression [49]. Menin is also known to recruit the methyltransferases SUV39H1 and PRMT5 to chromatin, where they place repressive methyl marks on lysine 9 of histone H3 (H3K9) and arginine 3 of histone H4 (H4R3), respectively [50,51]. The trimethylation of H3K9 is also enhanced by the interaction between Menin and Daxx, a transcriptional co-repressor and histone chaperone [52]. Finally, Soto-Feliciano et al. found that in the context of *MLL1*-r AML, Menin recruits the wild type (WT) form of MLL1 to tumor suppressor genes, repressing their expression in a mechanism that has yet to be characterized [53].

3.3. Cell cycle/migration

The subcellular localization of Menin is mainly nuclear, which is unsurprising given its role as a chromatin adaptor protein. However, during S and G2 phases of the cell cycle, Menin has been found to associate with intermediate filament proteins vimentin and GFAP in the cytosol [54]. It is unclear whether

there is a functional role for Menin in this interaction or if it is simply a sequestration mechanism during cell division. Consistent with its role as a tumor suppressor, Menin interacts with activator of S-phase kinase (ASK) and represses ASK-induced cell proliferation (Figure 2) [16]. Menin also binds to IQ motif containing GTPase activating protein 1 (IQGAP1), increasing its interaction with epithelial cadherin (E-cadherin) and β-catenin [55]. This same study found that cells overexpressing Menin had more E-cadherin and β-catenin localized to cell-cell contact sites and were inhibited in their ability to migrate [55]. Together, these results implicate Menin in helping to control cell proliferation and migration in its role as a tumor suppressor gene. Along with directly interacting with cell cycle-related proteins, Menin also regulates the expression of important cell cycle-related factors. Menin binds to the loci of *CDKN1B, CDKN2C* and *GAS1* and recruits histone methyltransferases to either activate or repress their transcription. At the *CDKN1B* and *CDKN2C* loci, Menin nucleates the MLL1 HMT complex to deposit H3K4me3, a mark associated with transcriptional activation [56]. The *CDKN1B* and *CDKN2C* protein products are cyclin-dependent kinase (CDK) inhibitors so the expression of these leads to the regulation of cell growth [57,58]. The loss of Menin expression/activity in this context leads to the decrease in expression of *CDKN1B* and *CDKN2C*, subsequently resulting in increased CDK activity and accelerated S-phase entry/cell growth [56,59]. The role of Menin in the context of *GAS1* has a similar output of decreased cell proliferation, but it occurs through the repression of the *GAS1* gene by scaffolding the HMT PRMT5 to place repressive dimethyl marks on H4R3 (H4R3me2) at the promoter [51]. The protein product of *GAS1* is an important cofactor for Hedgehog signaling, a pathway that impacts proliferation of pancreatic endocrine cells and is important for their development and function [60]. Therefore, repression of this gene by Menin leads to inhibition of cell proliferation.

3.4. DNA damage response

To ensure proper DNA repair, the cellular DNA damage response machinery requires accessibility to the damaged sites. Changes to the chromatin landscape are therefore important aspects of this process. Unsurprisingly, Menin is implicated in the DNA damage response in multiple different ways. It was found that the loss of Menin in mouse embryonic fibroblasts (MEFs) leads to increased DNA damage sensitivity [11]. Menin interacts with DNA repair protein FANCD2 as well as chromatin, and both of these interactions were found to increase in response to gamma-irradiation (Figure 2) [11]. Menin has also been found to bind with replication protein A subunit 2 (RPA2), a protein important for DNA repair, as well as replication and recombination (Figure 2) [12]. The interacting surfaces on these two proteins have also been recently computationally predicted [61]. However, the interaction between Menin and RPA2 had no impact on the ability of RPA2 to bind DNA, so the functional implications of this interaction remain unknown [12]. Menin has also been found to be important for the checkpoint pathway that arrests cells in S-phase in response to DNA damage [48]. Menin contributes to this arrest by interacting with the forkhead

transcription factor CHES1, a component of the mSin3A HDAC complex that leads to transcriptional repression [48]. This is a similar mechanism that has been suggested for the role of Menin in the transcriptional repression of JunD targets [18], indicating that a common mechanism of Menin-dependent transcriptional repression exists in multiple contexts.

3.5. Signal transduction

Many signal transduction pathways start with an extracellular signal that leads to a change in gene regulation via activated or repressed transcription. As a chromatin adaptor protein with important roles in both activating and repressing transcription, Menin plays an important role in multiple signal transduction pathways. The TGFβ pathway is one that culminates in the proteins SMAD3 and SMAD4 binding to DNA and, in some contexts, activating transcription of growth inhibitory programs, leading to the suppression of cell growth [62,63]. Menin is known to bind SMAD3 and loss of Menin has been found to antagonize the SMAD3-DNA interaction and block the downstream growth inhibition of the TGF-βpathway (Figure 2) [15]. These results indicate a tumor suppressive role for Menin as an adaptor protein of the SMAD3/4 proteins that is an important component of TGF-β induced cell growth inhibition. Other members of the SMAD family (SMAD1 and SMAD5) are involved in the BMP-2 pathway which controls the expression of osteoblast lineage genes *RUNX2* and osteocalcin (*OCN*) [64]. Menin is also known to bind SMAD1/5 and this interaction is important for the differentiation of mesenchymal stem cells into the osteoblast lineage, as the inactivation of Menin inhibits the commitment of cells to the osteoblast lineage (Figure 2) [65]. Hedgehog signaling is a pathway that has been found to be important for the development and function of pancreatic endocrine cells and Menin has been found to play a role in this [51,60]. Specifically, Menin acts as a chromatin adaptor for the protein arginine methyltransferase PRMT5 at the *GAS1* promoter, where it places repressive H4R3me2 marks [51]. The *GAS1* gene is important for the binding of the Sonic hedgehog ligand to its receptor, so repression of this gene leads to the subsequent repression of Hedgehog signaling, culminating in the inhibition of pancreatic islet cell proliferation. Menin has also been found to be involved in the NF-$_k$B pathway by binding to the transcription factor p65 and repressing its transcriptional activation (Figure 2) [14]. While Menin can act as both a transcriptional co-activator or co-repressor, the outcome is mainly to help control cell growth.

3.6. Differentiation

The role that Menin plays in gene regulation extends to genes that are important for development and differentiation in a variety of tissues. Menin plays a role in the development of pancreatic endocrine cells, but not pancreatic exocrine cells. It was found that *Men1* knockout in mice leads to irregular pancreatic endocrine development including a decrease in glucagon-positive cells as well as neurogenin 3 cells and altered pancreatic structure [66]. Since that study, it has

been found that part of Menin's role in pancreatic endocrine development comes from it binding to the promoter of *MAFA*, the master transcription factor for β-cell differentiation (Figure 2) [67]. It was also found that Menin knockdown leads to a decrease in β-cell differentiation markers including *MAFA* [67]. Menin is also known to play a major role in hematopoiesis. Multiple groups have demonstrated that the recruitment, by Menin, of the MLL1 HMT complex to *HOX* loci, including *HOXA9* and *MEIS1*, and subsequent transcriptional activation, is important for hematopoietic development [3,7,68,69] (Figure 2). Furthermore, loss of Menin expression leads to a decrease in *HOX* locus expression and defects in hematopoietic progenitor cells [68]. It has also been suggested that Menin is particularly important for hematopoietic response to stress and recovery [69]. Menin has also been found to repress the expression of *GBX2*, a transcription factor that contributes to the development of multiple different cellular lineages, via SUV39H1 interaction and H3K9 methylation [50]. Through its interactions with SMAD1/5 (described previously), Menin also plays an important role in osteoblast development [65]. Through the various roles that Menin plays in differentiation and development, it is unsurprising that any disruptions to Menin or its activities could significantly impact many cellular processes and identities and result in various disease states.

It is clear that Menin can play many different roles in the cell, yet not all of these are occurring at the same time. The context-specific nature of Menin is a very important aspect of its biology and this extends to the role that Menin plays in various diseases, particularly cancers.

4. Paradoxical roles in cancer

Menin is known to be important for the formation and maintenance of multiple forms of cancer. However, its specific role is tissue-dependent. In neuroendocrine tissues, Menin acts as a tumor suppressor and is highly mutated in tumors of these tissue types (Figure 3). These mutations include both germline and somatic mutations that are mostly missense or truncations. However, no genotype-phenotype associations have been determined for any identified *MEN1* mutations. In other cases, such as acute leukemia, Menin acts as an oncogenic co-factor of fusion proteins (e.g., MLL1-AF9) and is rarely mutated (Figure 3) [7].

4.1. MEN1 syndrome

Multiple Endocrine Neoplasia Type 1 (MEN1) syndrome is a familial cancer predisposition syndrome that is inherited in an autosomal dominant manner, with 100% penetrance [70]. It was first described in 1954 as an association of tumors of endocrine origin [71]. Due to its familial occurrence, it was presumed to have a genetic cause. MEN1 syndrome is known to affect the endocrine tissues including the parathyroid, pituitary gland, and islet cells of the pancreas.

The *MEN1* gene, which encodes for the protein Menin, was mapped and identified as the gene responsible for the MEN1 syndrome in 1988 and cloned in 1997 [41,72]. Loss of *MEN1* function results in multiple tumors of the parathyroid, pituitary gland and pancreatic islet cells (Figure 3). The loss of *MEN1*
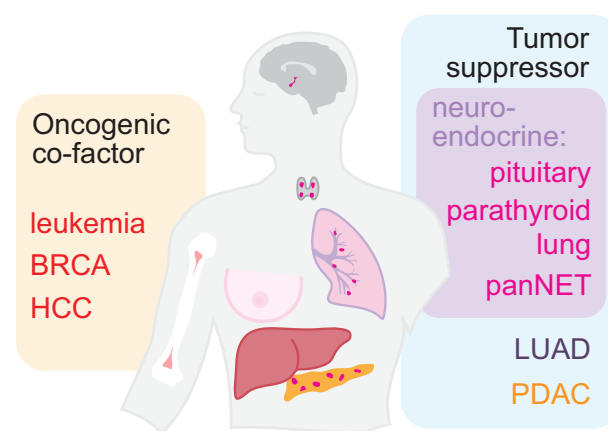

Figure 3. Menin has paradoxical roles in different cancer subsets. BRCA – Breast invasive carcinoma; HCC – Hepatocellular carcinoma; PDAC – Pancreatic ductal adenocarcinoma; LUAD – Lung adenocarcinoma.

function follows Knudson's 'two-hit hypothesis,' where an affected individual inherits a germline mutated allele of the *MEN1* gene, and through loss of heterozygosity (LOH), the second allele also becomes nonfunctional. While all MEN1 tumors are known to display LOH on chromosome 11, where the *MEN1* gene is located, the pattern of LOH can be different between lesions in a patient [22]. It was also found that MEN1 patients have intratumoral heterogeneity in terms of chromosomal deletions, indicating that MEN1 tumors harbor genomic and chromosomal instability.

The parathyroid is the most commonly affected tissue in MEN1 syndrome, leading to hyperparathyroidism [73,74]. Tumors of the endocrine pancreas are the second most common, leading to gastrinomas and insulinomas (40% and 10% of MEN1 patients, respectively) [73,74]. Other manifestations such as glucagonomas and somatostatinomas also occur, but infrequently. About 20–30% of endocrine pancreatic tumors are nonfunctioning, or do not secrete any hormones [73,75]. Pituitary tumors also occur in many MEN1 patients. The majority of these tumors are prolactinomas or growth hormone secreting tumors, or tumors that secrete both of these hormones. Adrenocorticotropin secreting tumors can also be found. These pituitary gland tumors can also cause symptoms due to mass effects on the brain including visual field anomalies and cranial nerve palsies [73]. Tumors in other tissues can also form due to MEN1 syndrome including adrenal tumors, foregut carcinoid tumors, thyroid and thymic tumors [73,74,76–78].

Current treatment options for MEN1 patients are dependent on the tumors that they present with and have been thoroughly reviewed [79,80]. Surgery is recommended for patients that present with hyperparathyroidism, as well as some patients with endocrine pancreas and parathyroid tumors. However, this treatment option is not a cure-all as conditions can continue to persist or recur, and other side effects have been reported as well. Somatostatin analogs (SSAs) can be used to treat pancreatic neuroendocrine tumors (NETs) as well as some parathyroid and pituitary tumors. However, these are only feasible if somatostatin receptors (SSTRs) are expressed in the tumor cells being targeted.

Similarly, peptide receptor radionuclide therapy (PRRT) can be used for some pancreatic and pituitary NETs, but these also require the expression of SSTR on tumor cells for efficacy. There are also some treatment options that are specific for certain tumor types as well as for symptomatic treatment. For example, proton pump inhibitors can be efficacious against gastrinomas, while drugs that inhibit insulin secretion can be used for insulinomas and dopamine agonists can be used to help control hormone secretion from parathyroid tumors.

Despite this variety of treatment options, people with MEN1 syndrome are still dying younger than the general population. Even though many options are available for treating hormone excess, patients are still dying due to this cause. The majority of MEN1 deaths are due to malignant pancreatic endocrine tumors (PETs) and thymic carcinoid tumors [25]. Poor prognostic factors for MEN1 patients include high hormone levels, large PETs and the presence of metastases [25].

4.2. Sporadic NETs

Somatic *MEN1* mutations also occur in sporadic NETs that form independently of a MEN1 syndrome diagnosis, further reinforcing its role as a tumor suppressor in this context. Multiple groups have reported on the role of Menin and somatic *MEN1* mutations in a variety of NETs including pancreatic endocrine tumors [81–83], gastroenteropancreatic NETs [84], and lung NETs [43]. These studies revealed that many different types of mutations can lead to loss of function of the Menin protein and subsequent tumorigenic phenotypes. These include missense mutations [19,81,83,84], insertion/deletions (indels) that cause truncations [81,82,84] and splice site mutations [81]. These mutations cause a variety of functional changes on the Menin protein product including loss of interaction with canonical binding partners [19,82,83], altered subcellular localization [81], and reduced protein stability [84]. Multiple studies have found that both mutant and wild type Menin are post-translationally degraded in the context of NETs and that stabilizing Menin in these contexts could have a therapeutic benefit [84,85].

4.3. Acute myeloid leukemia

The role that Menin plays in AML is as an oncogenic cofactor (Figure 3). Menin is known to interact with the MLL1 HMT and maintains this interaction with MLL1 fusion proteins, which are known to be oncogenic drivers of AML [86]. MLL1 fusion proteins drive AML through mediating the expression of *HOX* genes, especially *HOXA7* and *HOXA9*, as well as *MEIS1* [87–89]. The interaction between Menin and MLL1 fusion proteins is essential for leukemogenesis and AML maintenance, as Menin is the chromatin adaptor of the MLL1 HMT complex, helping it localize to the *HOX* gene locus [3,17]. Experiments showing that dominant negative inhibitors of the Menin-MLL1 interaction or knockout of Menin decreases *HOX* and *MEIS1* gene expression as well as AML proliferation both *in vitro* and *in vivo*, were the first indicators that targeting this complex could have therapeutic benefits [68,90]. *NUP98* fusion proteins and *NPM1* mutations also drive AML and result in aberrant *HOX* gene expression [91,92]. It has been found that both of

these classes of AML are also dependent on the Menin-MLL1 HMT and that Menin inhibitors can also be used in these cases to lead to lower *HOX* gene expression and upregulate markers of differentiation [93–95]. These studies increase the patient population that can potentially benefit from the use of Menin inhibitors, and clinical trials for Menin inhibitors are now including these patients as well.

4.4. Other solid malignancies

While a majority of the studies on the role of Menin in cancer have been performed in NET or leukemia systems, it has also been implicated in many other solid cancers. Again, Menin is able to act as both a cancer promoter or suppressor in solid tumors, depending on the tissue type (Figure 3).

Menin has been found to act in a pro-oncogenic fashion in breast cancer [26,27], hepatocellular carcinoma (HCC) [96,97], gastrointestinal stromal tumors (GIST) [98], endometrial cancer [99], castration-resistant prostate cancer [28,29], ovarian cancer [100], *PIK3CA*-mutant colorectal cancer [101], and Ewing sarcoma [102,103]. On the other hand, Menin has been found to act as a tumor suppressor in pancreatic ductal adenocarcinoma [104,105] and lung adenocarcinoma [30,31]. In many of these cases the mechanism of Menin's role is tied to it transcriptionally regulating various genes that play important roles in the specific cancer contexts. While pharmacological inhibitors of Menin have been mainly developed to target the role of Menin in AML, solid tumors in which Menin plays a role are also starting to reap the benefits of these inhibitors.

4.5. Tissue specificity

The different roles that Menin plays in NETs compared to AML paints a picture of tissue specificity. Menin is a tumor suppressor in neuroendocrine tissues yet an oncogenic cofactor in the hematopoietic system and has been found to not be an important factor in some other tissues such as the liver [106]. The paradox of Menin in cancer suggests a subsequent paradox for the treatment of these tumors. The literature summarized above suggests that Menin degradation would be the most efficacious in leukemia, yet in solid tumors, such as NETs, the stabilization of Menin would have a better outcome for patients.

As we turn our attention toward pharmacological inhibitors of Menin, it is important to keep in mind the multiple mechanisms that Menin is able to sample to contribute to transcriptional control. This continues to stress the importance of the context-specificity of this protein, something that needs to be considered when determining how to target Menin in different disease contexts.

5. Drugs/targets

Since Menin was identified as an oncogenic co-factor in some subsets of AML, disrupting this interaction has been a main draw as a potential therapeutic option for these patients. Many inhibitors have now been developed, combination therapies tried, and clinical trials started. Some inhibitors

have even shown promise for solid tumors and Menin-related disorders.

5.1. Structure

Many different studies have helped to structurally map important interaction surfaces on Menin. The first studies to map the Menin-MLL1 interaction did so by mapping the interacting surface on MLL1, determining which residues are important for its interaction with Menin [3,17,90]. It was initially found that the N-terminal portion of MLL1 (first ~1,400 amino acids) is important for binding Menin [3]. This was then further refined to the first 331 amino acids of MLL1 with the first 35–45 being the most important for high-affinity binding to Menin [17,90]. The first crystal structure of Menin was published in 2011 and demonstrated a clear binding pocket for MLL1, as Menin mutational sites known to disrupt the interaction were mapped to that pocket [107]. In 2012, the crystal structure of human Menin in complex with MLL1, as well as with JunD, was published [6]. This paper confirmed that the central pocket of Menin was indeed the MLL1 binding site and that this was also the site of binding to JunD, indicating that the two are mutually exclusive interactors with Menin. Most recently, the cryo-electron microscopy (cryo-EM) structure of Menin bound to a nucleosome has been published (3.2 Å) [108]. From the earliest papers mapping the interactions of Menin, especially those between Menin and MLL1, it has been suggested that this could be a potential therapeutic target. As the resolution of this interaction became more clear, that suggestion became more realistic, leading to the first development of Menin inhibitors.

5.2. Leukemia

5.2.1. Identification of Menin/MLL1 interaction as a druggable target

One of the first studies showing that the interaction of Menin and MLL1 is important came from purifying the MLL1 complex and the identification of other proteins in this complex. In this same study, they knocked down MLL1 and found that the expression of *HOXA9* was downregulated. They also found that Menin knockdown had the same effect on *HOXA9* expression, yet loss of the rest of the identified components in the MLL1 complex did not have this same effect [3]. This finding was confirmed by another study which further showed via chromatin immunoprecipitation that Menin and MLL1 directly bind to the *Hoxa9* locus in murine myeloid cells [68]. These authors went on to speculate that blocking the function of Menin could be a therapeutic option for leukemia patients since *HOX* genes are important for hematopoiesis and leukemic transformation. Finally, one of the first experiments that directly targeted the Menin-MLL1 interaction showed that using dominant negative mutants of MLL1 downregulates *Meis1* expression and leads to reduced cell proliferation in MLL1-AF9 transformed cells [90]. These authors also started to map the interaction surface between MLL1 and Menin and found that amino acids 5–44 on MLL1 are required for its interaction with Menin and for the oncogenic transformation by the MLL1-AF9 fusion protein.

Further structural insights helped to lay the foundation for the development of small molecule inhibitors of the Menin-MLL1 interaction. Grembecka, et al. used nuclear magnetic resonance (NMR) spectroscopy to map this interaction interface and found that MLL1 has two binding motifs for Menin [109]. These two motifs are composed of amino acids 4–15 and 23–40 of MLL1. They also found that a peptide corresponding to the sequence of binding motif 1 can dissociate the Menin-MLL1 complex. These interaction mapping experiments were critical for the development of the different inhibitors of this complex that will be discussed below.

5.2.2. Types of acute leukemia that can be targeted with Menin inhibitors

5.2.2.1. MLL1-rearrangements (MLL1-r) AML. This is the original subtype of leukemia that Menin inhibitors were designed to target [17,33]. In particular, many of the Menin inhibitors that are described in section 5.3 were developed to target the interaction of Menin and MLL1 fusion proteins for *MLL1*-r AML. Furthermore, many of the studies that initially determined the effects and mechanism of Menin inhibitors (discussed in section 5.4) were performed in *MLL1-r* AML cells. However, it has also been found that Menin inhibitors have efficacy in other subsets of Acute Leukemia.

5.2.2.2. NPM1-mutant AML. Similarly to *MLL1-r* AML, *NPM1*-mutant (*NPM1c*) AML is known to be associated with *HOX* and *MEIS1* gene upregulation [110]. This oncogenic transcriptional phenotype was found to be reliant on the Menin-MLL1 interaction and treatment of *NPM1c* AML with Menin inhibitors, both *in vitro* and *in vivo*, were found to reduce leukemia proliferation and deplete Menin from *HOX* and *MEIS1* loci [95,111]. While most *NPM1c* is ectopically localized to the cytoplasm, it has recently been found that the *NPM1c* that remains in the nucleus can cooperate with the Menin-MLL1 complex to regulate this oncogenic gene expression profile and that it is also evicted from chromatin upon treatment with Menin-MLL1 inhibitors [112]. *NPM1c* AML patients are mainly adults, and have been included in many of the clinical trials of Menin-MLL1 inhibitors (Table 2).

5.2.2.3. NUP98-fusion AML. MLL1 is also known to be a molecular dependency in *NUP98*-fusion leukemias, where it colocalizes at *HOX* gene promoters with NUP98 fusion proteins [93]. It was later found that Menin inhibitors (VTP-50469) are effective against *NUP98*-fusion driven leukemia cell lines and preclinical models of *NUP98*-fusion leukemia, including patient-derived xenograft (PDX) models [94].

5.2.2.4. UBTF tandem duplication AML. Studies of AML driven by *UBTF* tandem duplications (*UBTF*-TDs) found that these protein products occupy regions of chromatin that are co-occupied by MLL1 and Menin. It was further found that treatment of *UBTF*-TD leukemia cells are sensitive to Menin inhibitor (SNDX-5613) both *in vitro* and *in vivo* [113].

The commonality between each of these subsets of AML are their dependence on the expression of *HOXA* and *MEIS1* genes, which are activated by the Menin-MLL1 complex. In each of these AML types, treatment with various Menin

inhibitors leads to the downregulation of these leukemia-promoting genes and the upregulation of myeloid differentiation genes. This finding demonstrates a reliance on the Menin-MLL1 axis even in AML subtypes that are not driven by *MLL1*-rearrangements. This is a promising finding, as it expands the patient population that could benefit from these inhibitors. It has also been found that in *MLL1*-r and *NPM1*-mutant AML, the WT copy of MLL1 is localized to tumor suppressor genes, yet the transcription of these genes is repressed [53]. This mechanism is not fully understood and more research into this mechanism is needed in the context of all mentioned AML subtypes.

5.2.2.5. Acute lymphoid leukemia (ALL).

MLL1-rearrangements also occur in ALL (e.g., MLL1-AF4), and Menin inhibitors have been found to be efficacious in models of this disease as well [114]. Many of the inhibitors that will be further discussed below have shown promise in cell-based and PDX models of ALL including MI-derived compounds, VTP-50469, DS-1594, BAY-155 and JNJ-75276617 [33,35,37,115–119]. Many of the clinical trials for these drugs also include ALL patients (NCT-04065399, NCT05761171, NCT04752163, NCT-04988555, NCT-05153330 and NCT-06052813).

5.3. Types of Menin-MLL1 inhibitors

Since the identification of the Menin-MLL1 complex as a druggable target, many different iterations of Menin-MLL1 inhibitors have been developed. These can generally be classified into four categories: **MI**, **VTP/SNDX**, **covalent** and **others** (Table 1) [33–39,117–124]. The commercial drug based off the MI class of drugs is known as Ziftomenib and the commercial version of the VTP/SNDX class is Revumenib.

Grembecka, et al. developed the first small molecule to inhibit the Menin-MLL1 interaction using a small molecule screen [33]. Multiple modifications to the most potent molecule identified from the screen led to the development of **MI-2** and **MI-3** which bind to Menin with a K_d of 158 nM and 201 nM and inhibit with an IC_{50} of 446 nM and 648 nM, respectively [33]). The structure of Menin bound to MI-2 was also solved by the same group, demonstrating that this inhibitor binds to the same site on Menin that MLL1 binds [125] (Figure 4). This structure then led to the development of **MI-2-2** and the probe inhibitor **MIV-6**, which bind to Menin with a K_d of 22 and 85 nM and inhibit Menin-MLL1 with an IC_{50} of 46 and 56 nM, respectively [115,125]. These studies led to the development of a class of MI-derived Menin-MLL1 inhibitors by the Grembecka/Cierpicki Lab. MI-2 and MI-2-2 did not have very good activity in cells so **MI-503** was developed for *in vivo* use [117]. MI-503 binds to Menin with a K_d of 9.3 nM and inhibits with an IC_{50} of 14.7 nM. This compound was found to selectively kill *MLL1*-r driven leukemia cells and reduced MLL1-AF4 driven leukemia burden in mice [117]. Further improvement came with the development of **MI-538**, with a K_d of 6.5 nM and an IC_{50} of 21 nM, as well as improved cellular activity and enhanced selectively for *MLL1*-r driven leukemia [34]. These compounds were improved again, with the development of **MI-1481** (Kd: 9 nM; IC_{50}: 3.6 nM) [123]. However, this compound has lower oral bioavailability

compared to previously developed compounds. **MI-3454** (IC_{50}: 0.51 nM) was then developed to improve the translatable properties of Menin inhibitors and was found to be efficacious in mouse models of leukemia, including PDX models [116]. **Ziftomenib**, also known as **KO-539**, is an MI-based Menin inhibitor developed by Kura Oncology that is currently in clinical trials (Table 1). Phase 1a/1b of this First-in-Human study for patients with relapsed or refractory AML is now complete. Phase 1 showed promising results. Although some patients suffered from differentiation syndrome, ~25% of patients with *MLL1*-rearrangements or *NPM1* mutations showed complete remission [32]. Phase 2 of this trial is now underway.

VTP-50469 is another small molecule Menin-MLL1 inhibitor that was developed using structure-based design focused on the MLL1 binding pocket of Menin (Figure 4) [35]. This compound has an IC_{50} in the range of 13-37 nM for *MLL1*-r cell lines and leads to differentiation and apoptosis. It was also found to reduce leukemic burden in PDX mouse models of *MLL1*-r AML, as well as in a mouse model of *NPM1*-mutant AML [35,111]. **Revumenib**, also known as **SNDX-5613**, is a VTP analog that is also in clinical trials (Table 2). Phase 1 of the First in Human trial for patients with relapsed or refractory AML showed that 30% of patients treated with Revumenib achieved complete remission with a low frequency of treatment-related adverse events [36]. Phase 2 for patients harboring *MLL1*-rearrangements is also now completed for the trial and demonstrated that while there were some adverse events, there was also a 63% response rate, with a large proportion of patients with no detectable residual disease [120]. Revumenib achieved FDA approval for treatment of *MLL1*-r acute leukemia in November 2024 [40].

BMF-219 is the first covalent inhibitor of Menin (Table 1). This inhibitor entered clinical trials for adult patients with AML, ALL with *MLL1*-rearrangements or *NPM1* mutations, Diffuse large B-cell lymphoma (DLBCL), Multiple myeloma (MM) and Chronic/small lymphocytic lymphoma (CLL/SLL) in 2022 (Table 2). In an update on the acute leukemia arm (AML/ALL), it was shared that there were no treatment-related toxicities or deaths and that, while the cohort was small, 2/5 patients achieved complete remission [121].

Other small molecule Menin inhibitors include **BAY-155**, **DS-1594a**, **DSP-5336** and **JNJ-75276617** (Table 1). Brzezinka et al. developed the probe inhibitor **BAY-155** building off of the structure of MI-503. BAY-155 has a K_d of 75 nM and an IC_{50} of 8 nM, successfully inhibits proliferation of *MLL1*-r AML cell lines and reduces tumor volume and weight in AML-derived mouse xenograft models [119]. **DS-1594a** was developed through a high-throughput screen and derivatizing from scaffolds found in the screen (Figure 4) [37]. This group found that DS-1594a selectively inhibited the growth of *MLL1*-r and *NPM1*-mutant human leukemia cell lines with a GI_{50} of <30 nM, and did not inhibit the growth of leukemia cells without either of these alterations. DS-1594a also exhibits antitumor efficacy in preclinical PDX models of *MLL1*-r or *NPM1*-mutant leukemia. **Enzomenib**, also known as **DSP-5336**, is another small molecule inhibitor currently in clinical trials (Table 1). DSP-5336 was developed by Eguchi et al., binds to Menin with a K_d of 6.0 nM and inhibits the Menin-MLL1 interaction in

Table 1. Menin inhibitors. GIST – Gastrointestinal stromal tumor; NSCLC – Non-small cell lung cancer.

Molecule	Disease type	Inhibitor class	Trials	Reference
MI-2	Leukemia	MI-derived	N/A	[33]
MI-3	Leukemia	MI-derived	N/A	[33]
MI-2-2	Leukemia	MI-derived	N/A	[116]
MIV-6	Leukemia	MI-derived (Probe)	N/A	[126]
MI-503	Leukemia	MI-derived	N/A	[118]
MI-463	Leukemia	MI-derived	N/A	[118]
MI-538	Leukemia	MI-derived	N/A	[34]
MI-1481	Leukemia	MI-derived	N/A	[124]
MI-3454	Leukemia	MI-derived	N/A	[117]
KO-539 (Ziftomenib)	Leukemia; GIST	MI-derived	NCT-04067336; NCT-06655246; NCT-05735184; NCT-06001788	[133]
VTP-50469	Leukemia	VTP/SNDX	N/A	[35]
SNDX-5613 (Revumenib)	Leukemia	VTP/SNDX	NCT-04065399; NCT-06229912; NCT-05731947; NCT-06222580; NCT-06284486; NCT-05886049; NCT-05326516; NCT-05761171; NCT-06652438; NCT-05360160	[36]
BAY-155	Leukemia	Other (Probe)	N/A	[120]
DS-1594	Leukemia	Other	NCT-04752163	[37]
DSP-5336 (Enzomenib)	Leukemia	Other	NCT-04988555	[38]
JNJ-75276617 (Bleximenib)	Leukemia	Other	NCT-04811560; NCT-05453903	[39]
BN104	Leukemia	Other	NCT-06052813	
BMF-219	Leukemia; NSCLC; Pancreatic Cancer; Colorectal Cancer; Diabetes Mellitus (Type 1 and 2)	Covalent	NCT-05153330; NCT-05631574; NCT-05731544; NCT-06152042	[122]

human leukemia cells with an IC_{50} ranging from 10–30 nM, depending on the cell line [38]. This drug was found to specifically inhibit cell lines with *MLL1*-rearrangements or *NPM1* mutations and have antitumor effects in mouse xenograft models, reducing the expression of *MEIS1* and *HOXA9* [38]. A clinical trial was started in 2022 to look at this drug in relapsed/refractory AML or ALL (Table 2). In an update reported in 2024, it was shared that there had been no treatment-related deaths and that there was a response rate of 50–60% and complete remission rate of ~ 20% in patients with *MLL1*-r and *NPM1*-mutant AML [126]. **Bleximenib**, also known as **JNJ-75276617**, is the Menin-MLL1 inhibitor developed by Janssen R&D that is also currently in clinical trials (Table 2 / Figure 4). This drug was also found to have antiproliferative activity that is specific for *MLL1*-r or *NPM1*-mutant AML cell lines and reduce leukemic burden in AML preclinical models [39]. The trials for this drug are currently ongoing.

5.4. Effects/Mechanism of inhibitors

Since the introduction of Menin inhibitors there have been many studies looking into the downstream effects of Menin inhibition on transcription to further elucidate the mechanism by which these small molecules act. It was found that MLL1-fusion proteins (MLL1-FP) target different genes than WT MLL1/2 and that deletion of Menin or treatment with MI-2/MI-2-2 preferentially affects gene expression of MLL1-FP targets over MLL1/2 targets in MLL1-AF9 cells [127]. This study concluded that MLL1-FP may rely more on Menin for chromatin targeting than WT MLL1/2. Around the same time, it was also found that treatment of AML cells with MI-503 or MI-463 leads to ubiquitination of Menin and reduced protein stability that could be rescued by treatment with an E1 ligase inhibitor [128]. In this same study, the use of a proteasome inhibitor also rescued the levels of H3K4me3 and expression of

HOXA9, indicating that the loss of Menin stability is an important mechanism of Menin inhibitors. It was further found that the transcriptional effects of MLL1-AF9 loss from chromatin happen quite quickly. Within 15 minutes of dTAG treatment on MLL1-AF9-FKBP12 cell lines, they found a loss of transcriptional elongation at MLL1-FP target loci, including *MEIS1* and *HOXA9*, and a loss of histone PTMs associated with active transcription [129]. While the loss of expression of *MEIS1* and *HOXA9* has been appreciated as part of the response to Menin inhibition, it has also been found that treatment of AML cells with the Menin inhibitors MI-503 and VTP-50469 leads to an increase in expression of tumor suppressor genes and senescence-associated genes [53]. In this study, the authors identify a molecular switch that occurs upon Menin inhibitor treatment in which Menin-MLL1 gets evicted from chromatin and UTX-MLL3/4 binds at those same genomic sites. Many of these sites are tumor suppressor genes or senescence-associated genes and this switch leads to a transcriptional change from repression of these genes to activation [53]. This study expanded our understanding of the mechanism of Menin inhibitors beyond the silencing of AML-associated genes. Other studies have also found that changes to expression of other gene targets are important for the efficacy of Menin inhibitors. On one hand, it was found that upon Menin inhibition, MLL1/2 gets redistributed to bivalent genes, causing Menin-dependent MLL1 gene activation to decrease but Menin-independent MLL1 gene activation to be maintained at the bivalent sites [130]. On the other hand, a class of non-canonical Menin targets that include *MYC*, *LRP5* and *RUNX3*, and are bivalently occupied by Menin and the repressive histone mark H2A lysine 119 ubiquitination (K119Ub), which is regulated by PRC1.1, were also found [131]. This study found that this class of genes gets down regulated upon Menin inhibition. Finally, Menin inhibitors are also in clinical trials for forms of AML that are not MLL1-FP driven (*NPM1*-mutant and *NUP98*-FP driven). In the context of *NPM1*-mutant AML, it was found that mutant

Table 2. Menin inhibitor clinical trials. Clinical trial information was obtained from Clinicaltrial.Gov. R/R – Relapsed/Refractory; AML – Acute myeloid leukemia; CRC – Colorectal cancer; ALL – Acute lymphoblastic leukemia; DLBCL – Diffuse large B-cell lymphoma; MM – Multiple myeloma; CLL – Chronic lymphocytic leukemia; SLL – Small lymphocytic lymphoma; NSCLC – Non-small cell lung cancer; GIST – Gastrointestinal stromal tumor; MPAL – Mixed-phenotype acute leukemia; MRD – Minimal residual disease.

Trial	Molecule	Tumor type	Trial stage	Single agent/Combination
NCT-04067336	Ziftomenib	R/R AML	Recruiting	Single agent
NCT-04065399	Revumenib	R/R Leukemias	Recruiting	Single agent
NCT-06229912	Revumenib	Leukemia with upregulation of *HOX* genes	Recruiting	Single agent
NCT-05731947	Revumenib	CRC and other solid tumors	Active, not recruiting	Single agent
NCT-06575296	Revumenib	AML Post-Allogeneic Stem Cell Transplant	Recruiting	Single agent
NCT-05153330	BMF-219	AML, ALL (with *KMT2A*/MLL1r, *NPM1* mutations), DLBCL, MM, and CLL/SLL	Recruiting	Single agent
NCT-05631574	BMF-219	*KRAS*-driven NSCLC, Pancreatic Cancer and Colorectal Cancer	Recruiting	Single agent
NCT-05731544	BMF-219	Type 2 Diabetes Mellitus	Active, not recruiting	Single agent
NCT-06152042	BMF-219	Type 1 Diabetes Mellitus	Active, not recruiting	Single agent
NCT-04988555	DSP-5336	R/R AML or ALL	Recruiting	Single agent
NCT-04811560	Bleximenib	Acute Leukemia	Recruiting	Single agent
NCT-06052813	BN104	ALL/AML	Not yet recruiting	Single agent
NCT-06655246	Ziftomenib	GIST	Recruiting	Imatinib
NCT-05735184	Ziftomenib	AML	Recruiting	Venetoclax + Azacitidine; Venetoclax; 7 + 3
NCT-06001788	Ziftomenib	R/R AML	Recruiting	FLAG-IDA; low-dose cytarabine; gilteritinib
NCT-06448013	Ziftomenib	R/R AML or MPAL	Not yet recruiting	Venetoclax + Gemtuzumab
NCT-06376162	Ziftomenib	Pediatric R/R AML	Not yet recruiting	FLA
NCT-06397027	Ziftomenib	Pediatric R/R AML	Not yet recruiting	Venetoclax + Azacitidine
NCT-06222580	Revumenib	R/R AML with *FLT3* mutation and either *NPM1* mutation or MLLr	Recruiting	Gilteritinib
NCT-06284486	Revumenib	MRD-positive AML	Recruiting	Venetoclax
NCT-05886049	Revumenib	AML with *NPM1* or MLL mutation	Recruiting	Daunorubicin + Cytarabine
NCT-05326516	Revumenib	R/R AML with MLL rearrangement or amplification, *NUP98* rearrangement or *NPM1* mutation	Completed	Chemotherapy
NCT-05761171	Revumenib	Pediatric R/R MLL rearranged leukemia	Recruiting	Chemotherapy
NCT-06652438	Revumenib	*NPM1* mutant or MLL rearranged AML	Not yet recruiting	Azacitidine + Venetoclax
NCT-05360160	Revumenib	AML/MPAL	Recruiting	Decitibine/Cedazuridine + Venetoclax
NCT-06313437	Revumenib	*NPM1* and *FLT3* mutant AML	Recruiting	7 + 3 + Midostaurin
NCT-04752163	DS-1594	R/R AML or ALL	Completed	Azacitidine; Venetoclax; mini-HCVD
NCT-05453903	Bleximenib	AML with MLL or *NPM1* alterations	Recruiting	Venetoclax; Azacitidine; Cytaribine; Daunorubicin/Idarubicin
NCT-05521087	Bleximenib	R/R acute leukemia with MLL1, *NPM1* or *NUP98* alterations	Withdrawn	Chemotherapy

NPM binds to chromatin and cooperates with the MLL1 complex at similar target genes as MLL1-FP [112]. They also found that mutant NPM requires MLL1 to bind to those targets and that treatment with VTP-50469 evicts NPM from chromatin as well as Menin and MLL1. Therefore, Menin inhibition acts in a similar manner in these other subsets of AML as it does in MLL1-FP driven AML.

5.5. Combination treatment

Menin inhibitors have recently also started to be tested in combination with other therapies. There are currently multiple new and ongoing trials that combine Menin inhibitors with various chemotherapy regimens (Table 2). This includes multiple trials combining Revumenib (SNDX) with chemotherapy (NCT05326516, NCT05761171), as well as more specific trials to combine Revumenib with decitabine/cedazuridine (NCT05360160) and daunorubicin/cytarabine (NCT05886049). There has also been a trial with the Menin inhibitor DS-1594 in combination with the mini-HCVD regimen or azacitidine

(NCT04752163). Finally, Ziftomenib (KO-539) is in clinical trials with the FLAG-IDA regimen (NCT06001788) and will soon be recruiting for a trial in pediatric patients that combines Ziftomenib with chemotherapy (NCT06376162). Kinase inhibitors have also been a target for combination therapy with Menin inhibitors. Studies have shown that CDK6 and FLT3 are also important for AML and that targeting these in combination with menin inhibitors in *MLL1*-r, *NUP98*-rearranged or *NPM1*-mutant AML, leads to a synergistic effect [122,132]. These results have led to new clinical trials combining Revumenib with gilter-itinib, a FLT3 inhibitor, in *MLL1*-r or *NPM1*-mutant AML (NCT06222580). The combination of the Menin inhibitor Ziftomenib and kinase inhibitor Imatinib are also being tried in a new trial for GIST (NCT06655246). Bcl-2 is another critical factor for AML survival. Multiple studies have found that treatment with Menin inhibitors leads to lower Bcl-2 expression. These studies also found that combination treatment of various Menin inhibitors with the Bcl-2 inhibitor Venetoclax led to synergistic lethality [131–134]. Combination therapy of Venetoclax with Revumenib is now in a clinical trial (NCT06284486). There are also now many
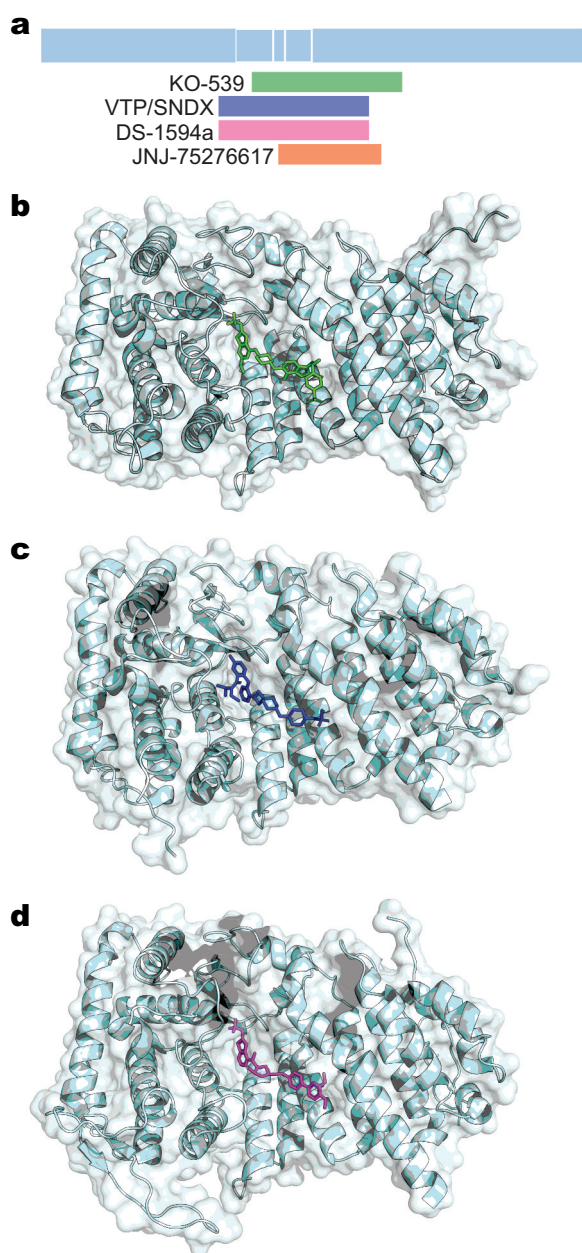
Figure 4. Interaction of small molecule Menin inhibitors with the Menin protein. (a) Depiction of the regions of Menin (blue) that Menin inhibitors interact with. Depicted here are only the inhibitors for which binding sites are published. (b) Model of KO-539 (green) binding in the MLL1 binding pocket of Menin (teal). (c) Model of VTP/SNDX (blue) binding in the MLL1 binding pocket of Menin (teal). (d) Model of DS-1594a (pink) binding in the MLL1 binding pocket of Menin (teal).

ongoing and new clinical trials combining Menin inhibition, Venetoclax, and other treatments. There is a new trial that is not yet recruiting to test the combination of Ziftomenib, Venetoclax and Gemtuzumab, an antibody-drug conjugate targeting CD33, in pediatric AML (NCT06448013). Finally, Venetoclax and Menin inhibitors are also being tested in combination with the chemotherapy Azacitidine. These include clinical trials with Revumenib (NCT06652438), Ziftomenib (NCT05735184 and NCT06397027) and JNJ-75276617 (NCT05453903) [118].

Aside from Venetoclax, other targeted therapies have been shown to have synergistic effects with Menin inhibitors.

IKAROS was identified as an essential transcription factor in MLL1-r AML and its degradation using Mezigdomide was found to be synergistic with the Menin inhibitor VTP-50469 [135,136]. It was also found that combining the Menin inhibitor MI-503 with the KDM4C inhibitor SD70 had a synergistic killing effect in MLL1-r AML [137]. Co-treatment of MLL1-r or NPM1-mutant AML with Ziftomenib and ATRA also had a synergistic effect to both slow growth and enhance proliferation into myeloid cells [134]. Another study further expanded the list of potential AML co-dependencies with Menin inhibitor treatment, identifying BRD4, EP300, MOZ and KDM1A via CRISPR screen and confirming synergy with inhibitors targeting each of these factors and Menin inhibitor [138]. Finally, knockout of IGF2BP3 was found to sensitize MLL1-r AML cells to MI-503, indicating that this is a potential therapeutic combination for patients [139]. While none of these combination treatments are yet in clinical trials, they demonstrate potential future directions to expand the therapeutic options for AML patients.

5.6. Emerging resistance

As with most small molecule inhibitors, cells developing resistance to Menin inhibitors is a concern. Studies of Menin inhibitor resistance have led to discoveries of two types of resistance: MEN1 mutations and non-MEN1 mutations.

A subset of patients in phase 1 trials for the Menin inhibitor Revumenib were found to have developed resistance after an initial response. One study analyzed the mutations found in those patients, which they also found in xenograft models and from a base editor screen of AML treated with Revumenib, and determined that they occur at the interface of Menin and the inhibitor. These mutations prevent the drug from binding to Menin but do not disrupt the Menin-MLL1 interaction, preventing the eviction of the Menin-MLL1 complex from chromatin [140]. Some of these MEN1 patient mutations were further characterized, including T349M, M327I, G331R and G331D. In this study, the crystal structure of these mutated Menin proteins bound to MLL1 peptides was solved and found that the mutations reside near the MLL1 binding site but not in the actual binding site so that they generate steric hindrance with Menin inhibitors but do not affect the interaction of Menin with MLL1 [141].

After discovering that the UTX/MLL3/4 complex contributes to the efficacy of Menin inhibition, one study found that a PDX model of AML that harbored an MLL3 mutation was resistant to VTP-50469 in vivo, demonstrating that Menin inhibitor resistance can be acquired through mutations of downstream pathways of Menin inhibitors [53]. Another study also found that clonal evolution of AML can contribute to Menin inhibitor resistance. Using PDX models treated with VTP-50469 or SNDX-5613, they found populations of resistant cells that still have on-target efficacy from the drug at the transcriptional level yet are still able to grow out [142]. Some examples of clonal mutations that they discovered were mutations in RAS, KMT2D, and TP53. They found that AML is less sensitive to Menin inhibition if it is later in the treatment course and is being used after multiple lines of previous therapy. This work

is very consistent with previously published work that Menin inhibitor resistance can be acquired independently of Menin mutations [53]. The authors speculate that as AML goes through more rounds of treatment, it will acquire more mutations and eventually become independent of the initial driver mutation. This will then allow the disease to persist even in the presence of on-target, efficacious Menin inhibition. As described above, repression of non-canonical Menin targets are important for the efficacy of Menin inhibitors. One study found that this repression is dependent on PRC1.1 and that resistance can occur via loss of PRC1.1 subunits [131].

5.6.1. Strategies to mitigate resistance

Some of the studies that demonstrated resistance due to non-MEN1 mutations also pursued combination treatment options that could overcome these resistance mechanisms. One study found that co-treatment with the CDK4/6 inhibitor Palbociclib and VTP-50469 can help overcome resistance due to MLL3 mutation [53]. Another also found that treatment with Venetoclax, the Bcl-2 inhibitor, can overcome Menin inhibitor resistance via PRC1.1 mutation [131]. This combination is already being tested in clinical trials. Finally, some of the reported MEN1 mutations that lead to resistance can be addressed by other forms of Menin inhibitors. For example, two mutations that are known to confer resistance to Revumenib, M327I and T349M, are unable to confer resistance to JNJ-75276617 as it has a slightly different mode of binding to Menin [118].

5.7. Other clinical indications

5.7.1. Solid tumors

Menin inhibition has also been studied in the context of solid tumors. In some models, Menin inhibitors have little activity or effects on proliferation and/or tumor formation [119,143]. However, many studies have shown promising results for treating some solid tumor types with Menin inhibitors. By using drug and CRISPR-based screens, Menin inhibitors have been found to be efficacious for GIST, endometrial tumors and gliomas [98,99,144]. However, in a subsequent study, MI-2 inhibition of H3K27M-driven glioma was found to be independent of targeting Menin [145]. The efficacy of Menin inhibitors in GIST and endometrial tumors has been validated both in vitro and in vivo using mouse modeling [98,99] and the Menin inhibitor Ziftomenib is now in a new clinical trial in combination with the kinase inhibitor Imatinib for treatment of GIST (NCT06655246) (Table 2). Menin inhibitors have also been found to be effective in tumors that have either enhanced Menin expression or MLL1 HMT activity in certain genes. These include HCC, castration-resistant prostate cancer, breast, ovarian and colorectal cancer [27–29,97,100,101]. Many of these studies found that the use of Menin inhibitors enhances or synergizes with other treatment options as well. In HCC, it was found that MI-503 treatment has antitumor activity in mouse xenograft models and that it enhances the current standard of care for HCC, the kinase inhibitor Sorafenib [97]. In breast cancer MI-136 and MI-503 were found to synergize with the DOT1L inhibitors EPZ004777/EPZ5676 to inhibit cell proliferation and a similar result was found in ovarian

cancer where MI-136 and MI-503 had additive effects with the DOT1L inhibitor EPZ5676 [27,100]. In colorectal cancer, it was found that the Menin inhibitor VTP50469 was effective in combination with the PI3K inhibitor Alpelisib [101]. The use of Menin inhibitors to treat colorectal cancer is now in two clinical trials, one using Revumenib (NCT-05731947) and one using BMF-219, a covalent Menin inhibitor, in KRAS-driven non-small cell lung cancer, pancreatic cancer and colorectal cancer (NCT-05631574) (Table 2). Finally, one study found that MI-503 treatment of cells expressing mutant Menin was able to stabilize the protein products of mutant Menin and rescue its nuclear expression [84]. This is a unique application for use of Menin inhibitors and suggests the potential of using these small molecules to treat patients with MEN1 loss-of-function (LOF) mutations in NETs.

5.7.2. Metabolic disorders

Menin inhibitors have also been found to be effective for non-cancer diseases. It was found that expression of Menin and MLL1 increases upon kidney injury and contributes to renal fibrosis [146]. They found that treatment with MI-503 attenuates renal fibrosis in vivo. Further, they found that MI-503 treatment reduces expression of Snail, Twist and TGFβ-1, indicating that Menin inhibition can reduce renal fibrosis through inhibiting the epithelial to mesenchymal transition (EMT) and fibroblast activation [146]. Finally, given the important role of Menin in neuroendocrine tissues, it is unsurprising that it is a relevant factor in β-cell proliferation and diabetes. It was found that BMF-219 treatment in rat models of type 2 diabetes led to a 50% decrease in blood glucose levels and reduced serum insulin levels [147]. This irreversible, covalent inhibitor of Menin is currently in trials for treatment of both type 1 and type 2 diabetes (NCT06152042/NCT05731544) (Table 2).

6. Future perspectives

The development of small molecule Menin inhibitors has been a major advancement for the treatment of Menin-related cancers, particularly AML. Over 15 iterations of Menin inhibitors have been introduced, including both reversible small molecules and covalent inhibitors [33,35,37–39,115–117,119,121,123,125]. These small molecules have led to almost 30 clinical trials and the first FDA approval (Table 2) [40]. While Menin inhibitors have led to large improvements in treatment options for AML, there are still areas that need more exploration in the next 5–10 years to expand the impact of these inhibitors beyond leukemia and cancer.

As Menin inhibitors have progressed through clinical trials, resistance has emerged [140,141]. Mutations in MEN1 that occlude binding of the small molecule to Menin have been found [140,141], as well as mutations in downstream pathways [53,131,142]. Further work needs to be done to predict, understand, and intercept resistance-associated mutations. Additionally, a better understanding of secondary treatment strategies for patients who become resistant to Menin inhibitors is required. This includes novel Menin inhibitors that evade resistance mechanisms, as well as treatment with combination therapies. There are already a number of clinical trials, both ongoing and recruiting, that are studying Menin inhibitors in

combination with other anti-cancer agents (Table 2). The results of these studies will address whether these treatment options evade or delay the emergence of Menin inhibitor resistance.

Furthermore, it will be important to follow up with patients who sustain durable responses to Menin inhibitors. Since LOF mutations in Menin have been shown to drive the formation of NETs, both in MEN1 syndrome and in sporadic tumors, patients with chronic inhibition of Menin could be at risk of forming sporadic NETs [22,41,72,81,82,84]. Tracking this relationship will be a critical aspect of understanding long-term patient responses to Menin inhibitors.

The *MEN1* gene was discovered in the context of MEN1 syndrome, yet the development of Menin inhibitors have disproportionately led to a better understanding of the role of Menin in AML and to more treatment options for that disease. Menin is known to have both tumor suppressive and promoting functions in various tumor types and more research is needed to understand if Menin inhibitors could be efficacious in any of these diseases [26–31].

Further, studying how *MEN1* mutations alter Menin's properties will be important for understanding the role of the mutant protein in various tumor types. LOF *MEN1* mutations are prevalent in NETs and one study has shown that treatment with Menin inhibitors can stabilize mutant Menin proteins [124]. Other Menin mutations are also prevalent in solid tumors. These include missense mutations and stable frameshift mutations [148]. Determining how these altered Menin proteins impact disease and whether Menin inhibitors are efficacious in these settings could lead to large therapeutic advancements for additional tumor types.

Finally, initial studies have indicated that Menin inhibitors can help in the context of non-cancer diseases including renal fibrosis and diabetes, and a covalent Menin inhibitor is in clinical trials for both type 1 and 2 diabetes (Table 2) [147]. In the United States, the rates of metabolic syndrome and obesity have been increasing consistently over the past few decades [149]. A better understanding of the role of Menin in endocrine and metabolic disorders will help expand the number of pathologies that Menin inhibitors can treat.

The development of Menin inhibitors over the last 10–15 years has contributed to great therapeutic advancements for AML. A focus on the role of Menin in solid tumors and endocrine disorders in the next 5–10 years will lead to similar advancements for these disease settings.

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Author contributions

Margaret R. Brown and Yadira M. Soto-Feliciano conceptualized the manuscript and the figures. Margaret R. Brown wrote the manuscript and created the figures. Yadira M. Soto-Feliciano revised the manuscript and the figures.

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