haematologica
Journal of the Ferrata Storti Foundation

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by Bradley Rockwell and Marina Konopleva

Received: February 18, 2025.
Accepted: March 6, 2025.

Citation: Bradley Rockwell and Marina Konopleva.
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Haematologica. 2025 Mar 13. doi: 10.3324/haematol.2024.287142 [Epub ahead of print]

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Bradley Rockwell, Marina Konopleva

Montefiore Einstein Comprehensive Cancer Center, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

Contributions: BR wrote and edited the manuscript. MK reviewed and edited the manuscript

Disclosures: BR has nothing to disclose. MK has received research funding from AbbVie, Allogene, AstraZeneca, Genentech, Gilead, ImmunoGen, MEI Pharma, Precision, Rafael, Sanofi, Stemline; advisory/consulting fees for AbbVie, AstraZeneca, Auxenion, Bakx, Boehringer, Dark Blue Therapeutics, F. Hoffman La-Roche, Genentech, Gilead, Janssen, Legend, MEI Pharma, Redona, Sanofi, Sellas, Stemline, Vincerx; stock options or royalties from Reata Pharmaceutical (IP), Patent: Novartis, Eli Lilly, Reata Pharmaceutica.

Corresponding Author: Bradley Rockwell (brockwel@montefiore.org)

Acute myeloid leukemia (AML) is a malignant neoplasm of the bone marrow with diverse genetic etiologies. For decades AML has been treated with cytotoxic chemotherapy, specifically cytarabine and anthracycline combinations. The small molecule venetoclax, an inhibitor of Bcl-2, was FDA approved for AML in 2018 starting a revolution of small molecule research.

Menin, a tumor suppressor scaffolding protein, has gained particular interest in the past few years given its well know biology for leukemogenesis through its interaction with KMT2A, particularly in mixed lineage leukemia (MLL) and AML with KMT2A translocation[1]. AML with KMT2A rearrangement secondary to prior treatments with chemotherapy and granulocyte-monocyte progenitors-like AMLs are of particular concern due to their known resistance to standard cytotoxic chemotherapy[2]. Menin and its interaction with KMT2A is thought to be leukemogenic through interactions with transcription factors, the DNA damage/stress response system, as a signaling pathway modulator, and through epigenetic changes[1]. Many small molecule menin inhibitors are gradually coming to market, such as ziftomenib and revumenib, but are still in the phase I or II stage with no drug in phase III testing as of February 2025. Revumenib recently received FDA approval for use in relapsed and refractory AML with KMT2A translocation. With that, over 90% of patients in the AUGMENT-101 study experienced ≥ grade 3 treatment associated adverse events, making off target effects an issue[3]. In this issue of *Haematologica*, Hogeling et al help uncover possible mechanisms by which the drug JNJ-75276617 (bleximenib) prevents proliferation of AML cells and possibly drives differentiation preclinically using patient samples, with limited effects on healthy CD34+ cells[4].

First and foremost, they show that bleximenib is effective preclinically against KMT2A-rearranged and NPM1-mutated leukemic cells, but less toxic to healthy CD34+ cells. This is

consistent with the clinical data from trials on revumenib[3,5] and ziftomenib[6] showing efficacy without prolonged cytopenias. Notably, there were KMT2A^{wt} and NPM1^{wt} patient samples that did respond. These included CEBPA, a regulator of stem cell differentiation, mutations and NUP98-rearranged AML. This shows possible use of menin inhibition outside of KMT2A-rearranged or NPM-1 mutated AML.

Next, they set out to determine whether this effect resulted from preventing the proliferation of malignant cells or from effects on differentiation. Ultimately, it was found to be either, both, or neither. Some cells are treated through prevention of proliferation and induction of differentiation. Some are just from proliferation. Some are just from induction of differentiation. Some are neither. This shows that we have just scratched the surface, but likely bleximenib works through multiple mechanisms.

To further characterize how the KMT2A-menin interaction causes AML through epigenetic changes, they next performed chromatin immunoprecipitation sequencing on 3 patient samples. Here they found downregulation of histone modification H3K4me3 on the important transcription factor MEIS-1 and the post-transcription gene regular IGF2BP2. While they note the heterogeneity in patient samples, there seems to be a clear epigenetic role of menin-inhibition that requires further investigation.

Not only did they discover a potential mechanism for impaired proliferation and induced differentiation, but they also suggest menin inhibition with bleximenib causes an immunogenic response with reactivation of antigen presenting mechanisms, specifically upregulation of MHC class I and class II expression. It is now well established that the immune system plays a key role in the development of AML. Impressively they show that HLA expression is upregulated after

treatment with bleximenib and, importantly, that this is independent of MEIS-1, a known leukemogenic hemeobox transcription factor[7].

To augment this understanding of the immune system response, they next treated cells with bleximenib and then exposed them to activated T cells from healthy donors. Half of the samples were noted to have an increase in sensitivity to allogeneic T cells. This should happily be expanded upon in the clinical setting, especially in KMT2A-AMLs. Given that these types of AMLs are often secondary from previous treatments with chemotherapy and themselves often resistant to chemotherapy, allogeneic (allo) stem cell transplant (SCT) is an essential part of the treatment paradigm. If this preclinical response to bleximenib and allogeneic T cells is true clinically, then augmenting the graft versus leukemia effect in alloSCT needs to be assessed either prior to alloSCT or as maintenance post-allo. T cell activity in an autologous setting was also assessed but unfortunately to this date, autologous T cell therapies in AML, autoSCT and CAR-T cell therapy, have been underwhelming.

Determining resistance mechanisms will be a crucial next step in search for a successful menin inhibitor. Recent studies have suggested loss of polycomb repressive complex 1.1 subunits, independent of the menin-MLL target, to be an important mechanism of resistance. This leads to epigenetic reactivation of noncanonical targets. Interestingly, these cells are sensitive to venetoclax, showing that combination therapy may be beneficial[8]. Here, they note that the MEIS locus is downregulated by menin inhibition and note their plans to further explore if this is dependent on polycomb proteins. We will eagerly await these future results.

In all, targeting menin shows promise through the many small molecule inhibitors that have recently been developed. While it is clear we are still uncovering the many mechanisms by which menin inhibition works and resistance occurs, Hogeling et al have laid the groundwork for

future preclinical and clinic studies with bleximenib. Recently, attempts have been made to preclinically determine which patients will respond to the small molecule venetoclax with rapid ex vivo sensitivity testing[9,10]. Applying this same rationale to menin inhibition could help differentiate those AML cell lines that do and do not respond in specific patients. With all the recent developments of small molecular inhibitors playing a role for the treatment of AML, it is hard to see menin inhibition not being a major player.

References:

1. Dhiman S, Dhillon V, Balasubramanian SK. Targeting Menin in Acute Myeloid Leukemia: Therapeutic Advances and Future Directions. Cancers. 2024;16(22):3743.

2. Issa GC, Zarka J, Sasaki K, et al. Predictors of outcomes in adults with acute myeloid leukemia and KMT2A rearrangements. Blood Cancer J. 2021;11(9):1-10.

3. Issa GC, Aldoss I, Thirman MJ, et al. Menin Inhibition With Revumenib for KMT2A-Rearranged Relapsed or Refractory Acute Leukemia (AUGMENT-101). J Clin Oncol. 2025;43(1):75-84.

4. Hogeling SM, Lê DM, Rose NL, et al. Bleximenib, the novel menin-KMT2A inhibitor JNJ-75276617, impairs long-term proliferation and immune evasion in acute myeloid leukemia. Haematologica. xxx

5. Issa GC, Aldoss I, DiPersio J, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. Nature. 2023;615(7954):920-924.

6. Wang ES, Issa GC, Erba HP, et al. Ziftomenib in relapsed or refractory acute myeloid leukaemia (KOMET-001): a multicentre, open-label, multi-cohort, phase 1 trial. Lancet Oncol. 2024;25(10):1310-1324.

7. Garcia-Cuellar M-P, Prinz A, Slany RK. Meis1 supports leukemogenesis through stimulation of ribosomal biogenesis and Myc. Haematologica. 2022;107(11):2601-2616.

8. Zhou X, Zhang L, Aryal S, et al. Epigenetic regulation of noncanonical menin targets modulates menin inhibitor response in acute myeloid leukemia. Blood. 2024;144(19):2018-2032.

9. Waclawiczek A, Leppä A-M, Renders S, et al. Combinatorial BCL2 Family Expression in Acute Myeloid Leukemia Stem Cells Predicts Clinical Response to Azacitidine/Venetoclax. Cancer Discov. 2023;13(6):1408-1427.

10. Kytölä S, Vänttinen I, Ruokoranta T, et al. Ex vivo venetoclax sensitivity predicts clinical response in acute myeloid leukemia in the prospective VenEx trial. Blood. 2025;145(4):409-421.