analysis of an open-label, randomised, phase 3 trial. *Lancet*. 2022;399(10343):2294-2308.

5. Hoffmann MS, Hunter BD, Cobb PW, Varela JC, Munoz J. Overcoming barriers to referral for chimeric antigen receptor T cell therapy in patients with relapsed/refractory diffuse large B cell lymphoma. *Transplant Cell Ther*. 2023;29(7):440-448.
6. Glatzer M, Panje CM, Sirén C, Cihoric N, Putora PM. Decision making criteria in oncology. *Oncology (Williston Park)*. 2020;98(6):370-378.
7. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2020;38(27):3119-3128.
8. Jacobson CA, Locke FL, Ma L, et al. Real-world evidence of axicabtagene ciloleucel for the treatment of large B cell lymphoma in the United States. *Transplant Cell Ther*. 2022;28(9):581.e1-581.e8.
9. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med*. 2022;28(10):2145-2154.
10. Ram R, Grisariu S, Shargian-Alon L, et al. Toxicity and efficacy of chimeric antigen receptor T-cell therapy in patients with diffuse large B-cell lymphoma above the age of 70 years compared to younger patients - a matched control multicenter cohort study. *Haematologica*. 2022;107(5):1111-1118.
11. Obaisi O, Fontillas RC, Patel K, Ngo-Huang A. Rehabilitation needs for patients undergoing CAR T-cell therapy. *Curr Oncol Rep*. 2022;24(6):741-749.
12. SEER*Explorer: An interactive website for SEER cancer statistics. Surveillance Research Program, National Cancer Institute. Accessed 8 June 2023. https://seer.cancer.gov/statistics-network/explorer/

https://doi.org/10.1182/blood.2023021094

MYELOID NEOPLASIA

Comment on Carter et al, page 1056

Targeting the epichaperome to combat AML

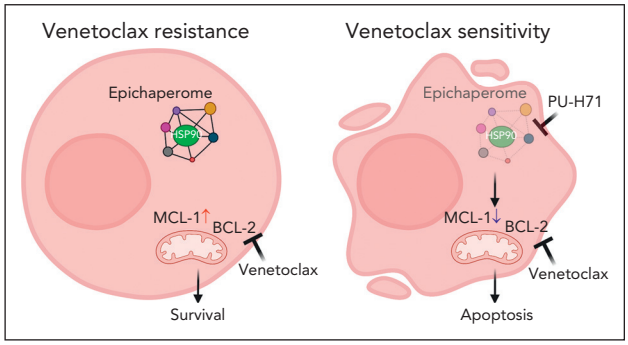
Sha Li and Peter D. Adams | Sanford Burnham Prebys Medical Discovery Institute

In this issue of *Blood*, Carter et al[1] report that targeting the epichaperome boosts the effectiveness of venetoclax in treating acute myeloid leukemia (AML), and it also inhibits the outgrowth of venetoclax-resistant *TP53*-mutant AML.

Venetoclax, an inhibitor of anti-apoptotic protein B-cell lymphoma-2 (BCL-2), has emerged as a promising treatment for AML and is currently considered the standard of care when combined with azacitidine for newly diagnosed patients with AML who are not eligible for induction chemotherapy.[2] However, the issue of resistance poses a significant impediment in care of patients undergoing venetoclax treatment, persistently frustrating patients, clinicians, and researchers. The development of resistance is frequently linked to mutations in *TP53*, *RAS*, or *FLT3* pathways.[3] Addition of venetoclax to azacitidine does not confer any significant advantages in *TP53*-mutated AML cases with poor-risk cytogenetics.[4] The article by Carter et al focuses on this critical area, where there is a substantial gap in meeting the medical needs of patients with *TP53*-mutant AML. After conducting a high-throughput drug screen, they suggest targeting epichaperomes whose inhibition would prevent the outgrowth of venetoclax-resistant cells.

The epichaperome is a sophisticated interconnected network consisting of chaperones and cochaperones found within various tumors. This network promotes the survival of malignant cells.[5] Heat shock protein 90 (HSP90) and heat shock cognate protein 70 act as key nucleating sites for these physically and functionally interconnected complexes.[5] PU-H71 is a novel epichaperome inhibitor that selectively targets HSP90 in cancer cells expressing the epichaperome.

Through an extensive series of experiments, using human leukemia cell lines, primary AML cells in vitro and in xenografts, and patient-derived xenograft (PDX) models, the authors demonstrate the presence of epichaperomes in *TP53*-mutant AML and AML stem/progenitor cells. Inhibition of the epichaperome using PU-H71 affects *TP53*-mutant AML and leads to cell death in AML cells and *TP53*-mutant stem/progenitor cells. Notably, normal bone marrow cells do not exhibit the epichaperome and are, thus, unaffected by its inhibition. On the basis of these data, Carter et al evaluated combination therapy of PU-H71 and venetoclax. They found these 2 agents synergistically induce cell death in AML cells and stem/progenitor cells in both *TP53* wild-type and *TP53*-mutant cells. The study also reveals that PU-H71 decreases myeloid cell leukemia-1 (MCL-1) and increases Bcl-2-interacting mediator of cell death (BIM), thereby enhancing venetoclax activity (see figure). In addition, several other signaling proteins, such as phosphorylated STAT3, phosphorylated protein kinase B, phosphorylated extracellular signal-regulated protein kinase, v-Myc avian myelocytomatosis viral oncogen homolog (c-MYC), heat shock transcription factor-1 (HSF-1),



Targeting the HSP90 epichaperome synergized with BCL-2 inhibition to effectively eliminate TP53-mutant AML cells. (Left) Exposure to venetoclax over longer time, MCL-1 expression is elevated. (Right) Addition of PU-H71 decreases MCL-1 expression and induces apoptosis. Figure created with BioRender.com.

and hypoxia inducible factor-1a (HIF-1a), are downregulated with PU-H71 treatment.

Another study that examined samples from patients with de novo and relapsed/refractory primary AML also reported a high level of epichaperomes in nearly 50% of the samples.[6] Furthermore, there was a recent report of a patient with a novel *PML-SYK* fusion AML who achieved durable complete remission after PU-H71 treatment.[7] Phase 1 clinical trials evaluating PU-H71 in metastatic breast cancer, lymphoma, and myeloproliferative neoplasms have been completed in recent years (clinicaltrials.gov identifiers NCT03166085 and NCT01393509). The findings by Carter et al suggest that AML with mutant *TP53* should also be added to the list of target malignant cancers for exploration with PU-H71 given alone or in combination with venetoclax. However, further work is needed to optimize the dosage for combination therapy, as PU-H71/venetoclax did not extend the survival of nonobese diabetic severe combined immunodeficiency gamma SGM3 (NSGS) mice in the PDX model, despite effectively reducing disease burden. In addition, combination therapy needs to be explored in the laboratory in the 17% of patient samples with AML that are resistant to PU-H71.[6] Last, evaluating the abundance of the epichaperome in each patient before treatment would be recommended for effective personalized treatment.

Overall, the exciting study by Carter et al presents compelling evidence that combining the epichaperome inhibitor PU-H71 with the BCL-2 inhibitor venetoclax is a potent and synergistic drug combination. This discovery opens up new avenues for therapeutic intervention in AML, particularly for patients with *TP53* mutations.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Carter BZ, Mak PY, Muftuoglu M, et al. Epichaperome inhibition targets *TP53*-mutant AML and AML stem/progenitor cells. *Blood*. 2023;142(12):1056-1070.
2. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.
3. DiNardo CD, Tiong IS, Quaglieri A, et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. *Blood*. 2020;135(11):791-803.
4. Pollyea DA, Pratz KW, Wei AH, et al. Outcomes in patients with poor-risk cytogenetics with or without TP53 mutations treated with venetoclax and azacitidine. *Clin Cancer Res*. 2022;28(24):5272-5279.
5. Rodina A, Wang T, Yan P, et al. The epichaperome is an integrated chaperome network that facilitates tumour survival. *Nature*. 2016;538(7625):397-401.
6. Tavakkoli M, Kaner JD, Sahil S, et al. Epichaperome abundance predicts response to the epichaperome inhibitor, Puh-71, in acute myeloid leukemia. *Blood*. 2019;134(suppl 1):5145.
7. Sugita M, Wilkes DC, Bareja R, et al. Targeting the epichaperome as an effective precision medicine approach in a novel PML-SYK fusion acute myeloid leukemia. *NPJ Precis Oncol*. 2021;5(1):44.

https://doi.org/10.1182/blood.2023021386

THROMBOSIS AND HEMOSTASIS

Comment on Jiang et al, page 1071

New targeted therapy for hemophilia

Roger J. S. Preston | Royal College of Surgeons in Ireland University of Medicine and Health Sciences and Children's Health Ireland Crumlin

In this issue of *Blood*, Jiang et al[1] describe the development of a new monoclonal antibody that binds with very high affinity to activated protein C (APC) and selectively inhibits its anticoagulant activity to restore hemostasis in preclinical models of hemophilia.

Maintenance of hemostasis is central to the prevention of thrombosis and bleeding. Diminished thrombin generation and clot formation arising from clotting factor deficiencies, such as hemophilia, disrupt this delicate balance and promote bleeding. Factor replacement is the standard of care for people with hemophilia in wealthy countries, but alternative hemostatic products are required if inhibitors to replacement factors develop. Although the factor VIII (FVIII) mimetic bispecific antibody emicizumab has enhanced the treatment of patients with hemophilia A with inhibitors, the need for alternative therapies for individuals with hemophilia B and other rare bleeding disorders has stimulated the generation of a plethora of new prohemostatic agents that target different facets of the coagulation system. Of these, novel therapies that can safely attenuate endogenous anticoagulant pathways may represent a solution to "rebalance" hemostasis in individuals with inherited or acquired bleeding disorders. To this end, antibody-mediated inhibition of tissue factor pathway inhibitor or aptamer-mediated suppression of antithrombin has already demonstrated positive outcomes in clinical trials with patients with hemophilia.

Inhibition of the protein C pathway also represents an attractive target based on its central role in the dynamic regulation of thrombin generation.[2] Plasma protein C is activated by thrombin bound to its anticoagulant receptor, thrombomodulin, which is abundantly expressed on the vessel wall. This complex, in turn, converts protein C into its activated form, APC, in a process accelerated by protein C binding to the endothelial protein C receptor. APC with its cofactor protein S then degrades activated procoagulant cofactors FVa and FVIIIa to restrict further thrombin generation (see figure). APC also exists in minute quantities in plasma (~40 pM), and attenuation of its anticoagulant properties may help promote thrombin generation in individuals with bleeding disorders. Several creative approaches have already been developed to achieve APC inhibition. SerpinPC, a recombinant α1-antitrypsin variant with enhanced specificity for APC, promotes hemostasis by inhibiting APC anticoagulant activity and is currently being evaluated in phase II