Targeting the Undruggable: PROTAC-Based Approaches to Transcription Factor Degradation in Acute Myeloid Leukemia

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-Acute myeloid leukemia (AML) remains a challenging malignancy with 5-year survival rates below 30% in older adults.

-Despite advances in targeted therapy, many critical oncogenic drivers in AML—particularly transcription factors such as MYC, RUNX1-ETO, and AML1-ETO—have been considered "undruggable" due to their lack of enzymatic active sites or well-defined binding pockets.

-Proteolysis-targeting chimeras (PROTACs) represent an emerging therapeutic modality that enables selective protein degradation, potentially overcoming limitations of traditional small molecule inhibition.

Objective

Systematically review the current literature on PROTAC-based targeting of transcription factors in AML, evaluate preclinical evidence, assess clinical translation potential, and identify knowledge gaps for future research directions.

References

- A comprehensive literature search was conducted using PubMed, Embase, and Web of Science databases from January 2015 to July 2025. Search terms included "PROTAC," "protein degradation," "transcription factor," "acute myeloid leukemia," "MYC," "RUNX1," and "fusion protein." Studies were included if they reported on PROTAC design, synthesis, or biological evaluation targeting transcription factors relevant to AML pathogenesis. Review articles, case reports, and studies not available in English were excluded.

Preclinical studies demonstrated successful degradation of target proteins with DC50 values ranging from 10-500 nM across different AML cell lines.

Key findings include:

(1) CRBN-based PROTACs showed superior degradation efficiency compared to VHL-based compounds

(2) Selectivity indices favoring malignant over normal hematopoietic cells ranged from 5-50 fold.

(3) Combination approaches with venetoclax or hypomethylating agents showed synergistic effects in vitro

(4) Resistance mechanisms included E3 ligase mutations and target protein overexpression.

Clinical translation remains limited, with only three PROTAC compounds (ARV-471, ARV-766, and KT-333) entering phase trials for hematologic malignancies, though none specifically in AML.

-PROTAC technology offers unprecedented opportunities to target previously undruggable transcription factors in AML, with robust preclinical evidence supporting therapeutic potential.

-Significant challenges remain including optimization of pharmacokinetic properties, minimization of off-target effects, and development of biomarker strategies for patient selection.

-The field would benefit from standardized assessment methodologies, deeper understanding of resistance mechanisms, and accelerated clinical translation.

-Future research should focus on next-generation PROTAC designs with improved tissue selectivity and combination therapeutic strategies

Figure 1

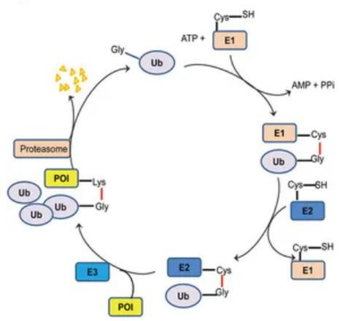

FIGURE 1. Schematic representation of the ubiquitination process. Ubiquitin is first activated by an E1 ubiquitin-activating enzyme, then transferred to an E2 ubiquitin-conjugating enzyme. An E3 ubiquitin ligase facilitates the transfer of ubiquitin to the target protein. Ubiquitin-tagged proteins are subsequently recognized and degraded by the proteasome.

Figure 2

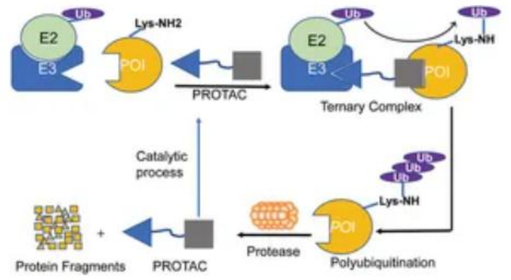

FIGURE 2. Mechanism of PROTAC-induced ubiquitination and proteasomal degradation of the protein of interest (POI). A PROTAC molecule consists of two ligands connected by a linker—one binds to an E3 ubiquitin ligase, and the other to the target protein. This proximity promotes polyubiquitination of the target protein, leading to its degradation by the proteasome within the cell.