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Targeted Degradation of MYB as a Novel Therapeutic Strategy for Acute Myeloid Leukemias

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Abstract: This study examines targeted degradation of the transcription factor MYB as a novel therapeutic avenue in acute myeloid leukemias. Its relevance stems from the limited efficacy of existing treatment regimens and the emergence of drug-resistant disease forms. The work's novelty lies in the integrated comparison of genetic models for MYB destabilization, chemical dTAG approaches, and the repurposing of low-molecular-weight compounds mebendazole and vitaferin A. Data are synthesized on MYB's transformational properties critical for leukemic-clone maintenance, and experimental findings are reviewed on the suppression of transcriptional programs and induction of blast-cell death following complete factor elimination. Special attention is devoted to prospects for developing PROTAC degraders and molecular glues capable of catalyzing ubiquitin-dependent proteolysis of MYB at low compound doses. The research aims to construct a comprehensive assessment of the efficacy and safety of MYB-degradation strategies and to identify directions for further preclinical investigation. Methods include comparative analysis of peer-reviewed literature, critical appraisal of in vitro and in vivo data, and synthesis of pharmacodynamic profiles of the repurposed agents. The overall evaluation highlights the approach's potential to overcome therapeutic resistance and improve patient survival. The findings will interest pharmacologists, oncologists, clinical researchers, and specialists in chemical biology.

Keywords: acute myeloid leukemia, MYB, proteasomal degradation, PROTAC, mebendazole, vitaferin A, targeted therapy, ubiquitin, molecular glue, drug resistance

INTRODUCTION

Acute myeloid leukemia (AML) remains a challenging disease to cure: escalating chemotherapy regimens no longer improve outcomes, prompting researchers to focus on selectively suppressing factors that sustain blast proliferation. The transcription factor MYB, which governs self-renewal and differentiation of hematopoietic stem cells, becomes hyperactivated in certain contexts—particularly in MLL-rearranged leukemias—forming pathogenic expression networks that block maturation and drive unchecked growth. In experimental models, MYB elimination induces leukemic-cell death, designating this protein as a high-priority target for novel therapeutic development.

Early intervention strategies aimed to disrupt the MYB–CBP/P300 complex: natural triterpenoids celastrol and plumbagin, alongside synthetic naphthol derivatives, impeded coactivator recruitment, weakened the transcriptional program, and inhibited blast proliferation. A more radical approach employed the cell-penetrating peptidomimetic MYBMIM, designed on the basis of the crystal structure of the interaction interface; MYBMIM displaces MYB from its complex, downregulates MYC and BCL2 expression, and triggers apoptosis. In mice bearing human AML xenografts, this compound slowed disease progression and extended survival. Despite these encouraging outcomes, MYB remains present in the nucleus under this strategy, limiting the depth of the antitumor effect.

The concept of induced proteolysis ultimately enables complete MYB removal: heterobifunctional PROTAC molecules simultaneously bind the target and an E3 ubiquitin ligase, initiate polyubiquitination, and shuttle the protein to the proteasome, acting repeatedly in a catalytic fashion. Such kinetics promise profound and durable remissions at low doses by eradicating the source of the transformational signal and bypassing resistance mechanisms that arise from partial inhibition. Consequently, targeted degradation of MYB is regarded as the most promising avenue for creating fundamentally new AML therapies.

The urgency of this topic is driven by the critical need for treatments against chemoresistant AML variants and the emergence of initial encouraging data on MYB suppression in disease models. The aim of this article is to analyze the current literature on targeted MYB degradation as an AML treatment strategy, to evaluate the scientific findings to date, and to outline prospects for its application. The specific objectives are:

1. To synthesize data on MYB's role in AML pathogenesis and on prior therapeutic attempts targeting MYB;
2. To describe key experimental discoveries demonstrating the feasibility of induced MYB degradation and its effects on leukemia;
3. To discuss the therapeutic potential of proteasomal-degradation technologies in comparison with conventional treatment modalities;
4. To assess the outlook for integrating MYB-degradation approaches into preclinical research and clinical practice.

METHODS AND MATERIALS

Z. Anwar [1] delivered a systematic review of degrader prospects in leukemia, underscoring the catalytic mechanism inherent to the PROTAC approach. M. Bekesh [2] examined the evolution of the PROTAC platform and its target-selection criteria, identifying transcription factors as the most promising candidates. K. Klesham [3] experimentally validated the efficacy of vitaferin A in eliminating MYB within AML cell models. T. Harada [4] developed a dTAG system for rapid degradation of endogenous MYB and assessed the transcriptomic consequences of factor removal. F. Modman [5] described mebendazole's anti-MYB effects, demonstrating its potential in preclinical studies. K. Ramaswami [6] engineered the peptidomimetic MYBMIM and proved that displacing MYB from its p300 complex triggers blast-cell apoptosis. R. G. Ramsey [7] investigated MYB's roles in normal hematopoiesis and oncogenesis, thereby substantiating its therapeutic appeal. V. Walf-Vorderwülbecke [8] showed that drug-induced degradation of MYB suppresses leukemia progression in vivo.

In preparing this article, comparative and analytical methods were employed, coupled with a critical synthesis of data from peer-reviewed publications, bibliographic searches in PubMed and Web of Science, and conceptual modeling of PROTAC technologies' potential for clinical translation.

RESULTS

Accumulating evidence confirms that AML cells are

critically dependent on sustained MYB expression. Genetic deletion or silencing of MYB induces rapid leukemic-cell death, as demonstrated in both classical knockout models and modern induced-degradation systems. In a recent study, researchers employed the chemical-degron technology (dTAG system) to selectively eradicate endogenous MYB in AML cells. By fusing the FKBP12^F36V degron domain to the C-terminus of MYB in the MV4-11 cell line, subsequent treatment with the selective ligand dTAGV-1 triggered rapid, ubiquitin-dependent proteolysis of the tagged MYB protein. Within one hour of degrader addition, cellular MYB levels had plummeted to near zero. Predictably, such acute depletion of MYB resulted in a dramatic loss of viability among leukemic cells, mirroring the effects seen in genetic MYB knockouts [4].

Simultaneously, transcriptome analysis via SLAM-seq revealed that removal of MYB altered transcription rates of hundreds of genes, with predominant suppression of those directly regulated by MYB. Notably, transcripts of MYC, BCL2, and other MYB-dependent proto-oncogenes were significantly reduced following MYB degradation [6].

Thus, the in vitro induced-degradation experiment vividly demonstrated that the oncogenic program in AML cells collapses upon MYB elimination, leading to clonal demise. These results substantiate the rationale for identifying compounds capable of effecting selective MYB degradation as a therapeutic avenue (Figure 1).

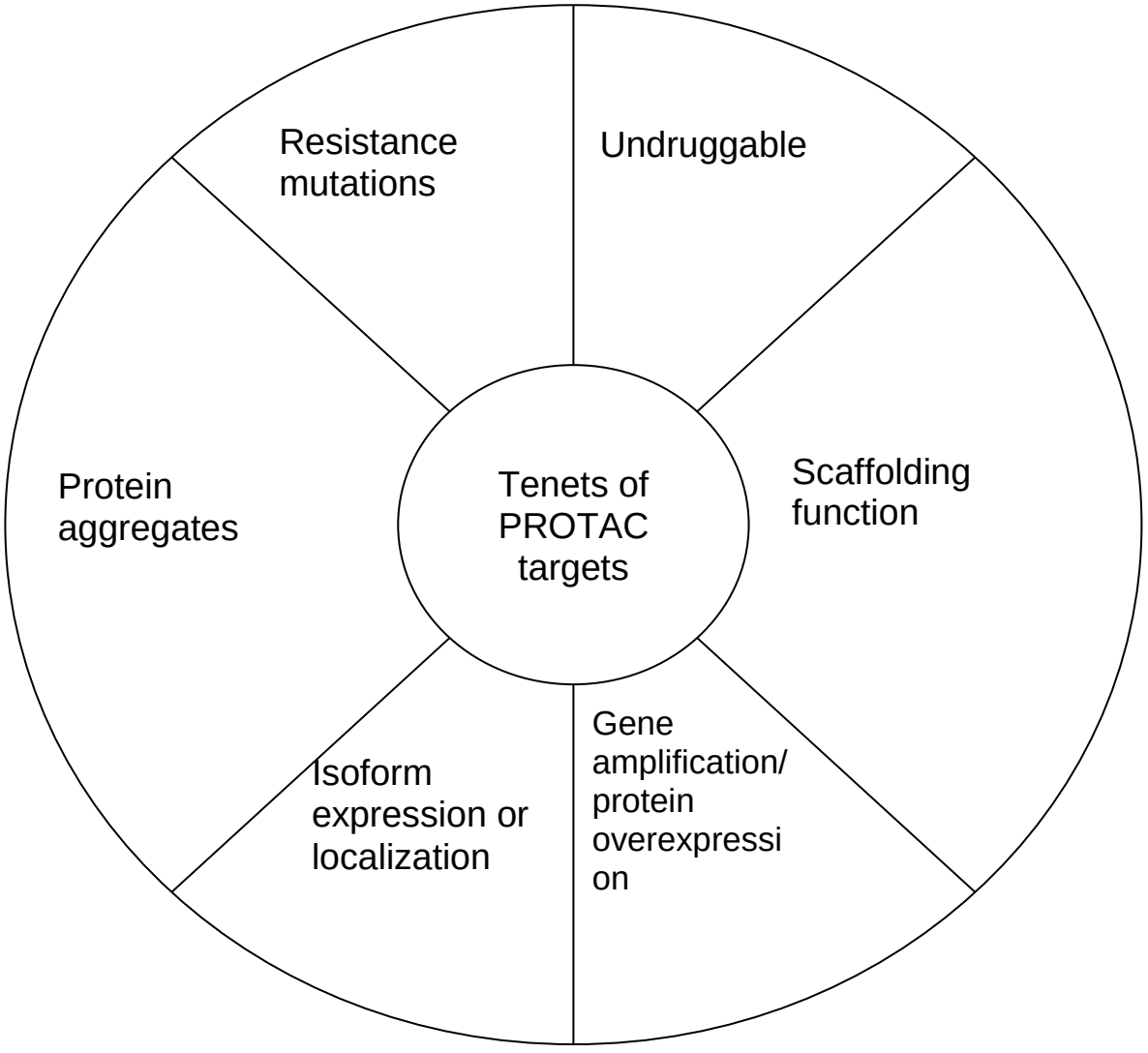

Figure 1. Major categories of proteins for which the PROTAC strategy demonstrates the greatest therapeutic efficacy [2]

Figure 1 illustrates six classes of targets that are optimal for proteasomal degradation. MYB falls into two of these groups—“undruggable” transcription factors and scaffold (platform) proteins. Such positioning strengthens the case for choosing MYB as a therapeutic target and sets the stage for the development of selective degraders described below.

Induction of MYB proteasomal degradation by drug

repurposing. The first chemical breakthrough in targeting MYB arose from a drug-repurposing strategy. By comparing the gene-expression "signature" governed by MYB against transcriptomic profiles in the Connectivity Map, researchers identified compounds capable of dampening the MYB signature. One of the strongest "hits" was mebendazole, a long-standing benzimidazole antihelminthic. In AML cells, mebendazole unexpectedly reduced c-Myb protein levels, effectively inducing its degradation via the proteasome. Mechanistically, mebendazole disrupts the HSP70/HSC70 chaperone system required for MYB stability, triggering ubiquitination and proteasomal clearance of c-Myb [8].

Notably, this effect occurs with only transient exposure: even brief mebendazole treatment markedly impaired leukemic-blast colony formation, while normal hematopoietic progenitors from cord blood remained largely unaffected. This suggests a therapeutic window in which leukemic cells are more susceptible to MYB loss than their normal counterparts. In vivo experiments in a human AML xenograft model further validated mebendazole's promise: treated mice exhibited significantly slower disease progression compared with untreated controls [8]. Moreover, given mebendazole's extensive, well-tolerated use in humans for parasitic infections, these data support induced MYB degradation by mebendazole as a novel and potentially safe AML therapy [8].

Another repurposed agent that elicits targeted MYB loss is withaferin A (WFA), a steroidal lactone derived from the plant Withania known for its antitumor properties. WFA emerged as a top hit alongside mebendazole in the Connectivity Map screen for MYB-suppressive activity. Recent work has shown that WFA induces rapid and pronounced ablation of c-Myb in AML cells [3]. Within hours of treatment, MYB protein levels fall to nearly undetectable levels and transcription of MYB-target genes is suppressed. WFA treatment mirrors mebendazole's effects, triggering blast-cell death and inhibiting colony formation. Its mechanism likewise involves proteostasis stress: WFA activates the unfolded-protein response, destabilizing the HSP70/HSC70 complex and leading to c-Myb ubiquitination and degradation. Crucially, expression of a degradation-resistant MYB mutant partially rescues cells from WFA-induced death, confirming the specificity of this pathway [3].

Thus, WFA's antileukemic action is largely mediated through MYB depletion. In vivo, WFA treatment of AML-bearing mice slowed disease progression and reduced leukemic burden. Given WFA's historical use in traditional medicine and established human exposure, its repurposing for AML therapy represents a highly attractive direction [3].

A distinguishing feature of the MYB-degradation strategy is the complete removal of the oncoprotein from the cell, whereas traditional approaches merely block its function while leaving the protein intact. Experience with direct MYB inhibitors shows their limited efficacy due to incomplete target suppression and off-target effects. For instance, small molecules that disrupt the MYB–p300 interaction (celastrol, plumbagin, etc.) and the peptidomimetic MYBMIM partially inhibit MYB's transcriptional activity and slow leukemic-cell growth [6]. However, a recent comparative analysis of these agents revealed significant drawbacks: purported MYB inhibitors exhibit only partial specificity and induce substantial collateral effects on the expression of unrelated genes. Moreover, some of these compounds were unexpectedly found to act in a dual manner—alongside inhibiting certain MYB functions, they paradoxically stimulate the expression of other MYB-regulated genes, functioning as mixed agonist–antagonists. These unforeseen activities complicate the clinical use of direct MYB inhibitors [6].

In contrast, targeted degradation eliminates MYB as a factor, theoretically obviating the risk of residual protein exerting excessive or compensatory activity. Indeed, in the described models, treatment with degraders (mebendazole, WFA) yielded unequivocal suppression of MYB-driven transcriptional programs and rapid cell death, with no signs of paradoxical oncogenic pathway activation [3; 8]. These findings suggest that a degradation-based strategy may be both more effective and more specific than traditional MYB inhibitors.

Different pharmacological paradigms vary in their specificity and clinical applicability. Comparing the approaches reported in the literature allows an assessment of the potential gains from adopting targeted-degradation technologies (Table 1).

Table 1 – Comparative analysis of therapeutic approaches in AML (compiled by the author based on [1–8])

Approach	Target	Mode of Action	Selectivity	Advantages	Limitations
Chemotherapy	DNA synthesis	Cytotoxicity	Low	Effective against rapidly dividing cells	Myelosuppression; resistance
FLT3 inhibitors	Activated kinase	Enzymatic blockade	Medium	Subtype-specific activity	Secondary mutations
MYB–p300 interaction inhibitors	Protein–protein	Coactivator disruption	Medium	Disrupts transcriptional complex	Partial MYB suppression; off-target effects [6]
Mebendazole/WFA repurposing	MYB	Induced degradation	High	Uses approved drugs; known safety profiles	Dose-dependent off-target activity [3; 8]
PROTAC degraders targeting MYB	MYB	Proteasomal degradation	Very high	Catalytic action at low doses	Requires pharmacokinetic optimization

Comparison shows that MYB removal outperforms traditional regimens both in selectivity and depth of tumor-clone suppression. This advantage stems from the leukemic cell's inability to compensate for loss of a central transcriptional node, whereas kinase inhibition often leads to escape signaling.

In summary, the review of experimental data demonstrates the practical feasibility and high efficacy of targeted MYB degradation in AML models. Induced proteasomal elimination of MYB—whether via dedicated chemical degraders or repurposed agents—triggers collapse of the oncogenic program and eradication of leukemic cells in vitro and in vivo. These findings lay the groundwork for developing a new class of therapeutics aimed at eliminating MYB in resistant AML forms.

DISCUSSION

The findings presented here must be viewed in the context of developing novel antileukemic therapies. Targeted degradation of MYB represents a fundamentally different strategy, aimed at the root of the oncogenic process—the pathological transcriptional network sustained by MYB. Unlike traditional cytotoxic agents, which nonspecifically target dividing cells, or kinase inhibitors that block individual signaling pathways, eradication of a key transcription factor promises simultaneous suppression of multiple oncogenic gene targets. In the case of MYB, these include critical drivers of proliferation and survival (such as MYC and BCL2) as well as factors that inhibit cellular differentiation. Consequently, MYB removal can induce both differentiation and apoptosis of leukemic blasts, as experimentally evidenced by mitochondrial apoptotic markers and signs of cellular maturation upon MYB suppression. This multi-targeted impact on the gene network renders MYB degradation a potent weapon against leukemia, potentially surpassing traditional modalities in depth of effect.

Thus, MYB degradation effectively "knocks out" the central hub upon which the malignant clone depends, a scenario fundamentally distinct from the action of narrowly focused agents (e.g., FLT3 or IDH mutation inhibitors), whose efficacy is confined to tumor subpopulations and often wanes with the emergence of secondary mutations. By contrast, MYB elimination

theoretically leaves leukemic cells no compensatory route, as it concurrently disrupts multiple oncogenic pathways.

From a practical standpoint, the targeted-degradation platform is advancing rapidly and already moving beyond the confines of the laboratory. PROTAC technology, as noted, has given rise to numerous experimental degraders against various oncoproteins [1]. Notably, the first examples are now appearing in oncohematology: PROTACs targeting the proto-oncogene STAT3, oncogenic kinases, and epigenetic regulators are under development, with several progressing through preclinical evaluation. Although no MYB-specific PROTAC has yet been disclosed, all the elements for its design are in place. As a "warhead"—the binding moiety—one might employ the peptidomimetic MYBMIM or another small molecule that disrupts the MYB–p300 interaction. By linking such a ligand to an appropriate linker and an E3-ligase recruiting moiety (for example, CRBN or VHL), it would be possible to craft a bifunctional degrader capable of recruiting the E3 ligase to MYB and marking it for proteasomal destruction. Given the success of PROTACs in other models, a parallel approach against MYB is anticipated to yield a potent antileukemic agent.

The PROTAC system has opened the door to the selective elimination of nuclear oncoproteins once considered "undruggable" by conventional small-molecule inhibitors. A chimeric PROTAC simultaneously engages the target factor and an E3 ligase, forming a transient ternary complex that initiates polyubiquitination and subsequent proteasomal degradation (Figure 2).

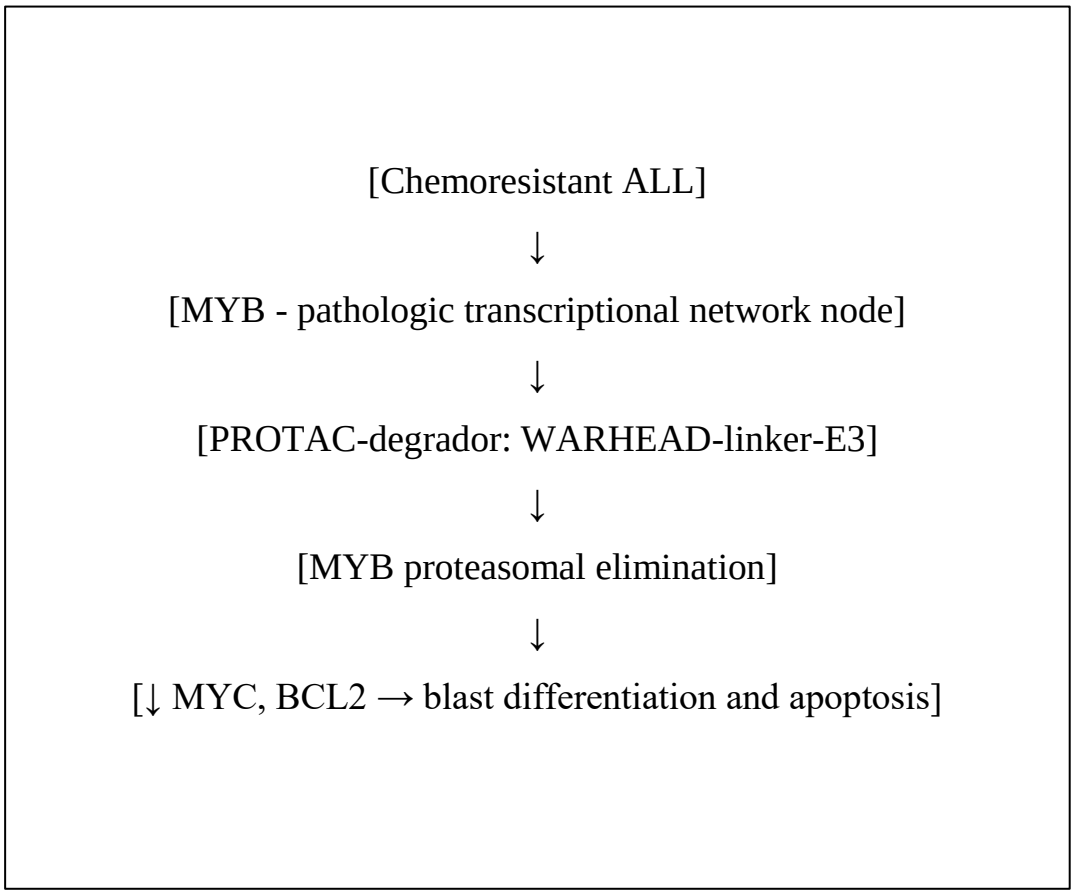

Figure 2. Sequence of events in PROTAC-induced MYB degradation: disease → target → tool → proteasomal removal → blast differentiation and apoptosis (compiled by the author based on [2])

Comparing the proposed strategy with conventional AML treatments highlights several aspects. Standard chemotherapy—based on antimetabolites and cytotoxins—lacks molecular specificity: it attacks all rapidly dividing cells, causing severe side effects and failing to guarantee eradication of the leukemic clone, particularly when the tumor harbors stem cells with low proliferative activity. Allogeneic bone-marrow transplantation can achieve radical cure through graft-versus-leukemia immunity but entails high mortality and serious complications. Targeted agents against mutant tyrosine kinases (for example, FLT3 inhibitors) and

epigenetic enzymes (IDH1/2 inhibitors) benefit only the corresponding patient subgroups and, while they often induce remission, do not prevent relapse when used as monotherapy. Against this backdrop, the MYB-degradation strategy distinguishes itself by universality—MYB is active across many AML subtypes, including cases without "druggable" mutations.

Moreover, it directly targets the fundamental mechanism sustaining leukemia. Of course, risks must be acknowledged: MYB is essential for normal hematopoiesis, so systemic MYB suppression may lead to myelosuppression and aplastic states. However, hematologists are accustomed to this challenge—intensive chemotherapy likewise ablates bone marrow, and clinicians manage the effect via transplantation or growth-factor support.

From the standpoint of in vivo efficacy and clinical translation, the first positive signals have already emerged. Mebendazole repurposing advanced rapidly to clinical evaluation thanks to its prior approval for other indications. In particular, clinical trials combining mebendazole with low-dose cytarabine in elderly and refractory AML patients are being initiated [5]. This regimen is designed to harness synergy: mebendazole both directly undermines blast survival through MYB (and other factor) degradation and increases residual cells' sensitivity to chemotherapeutics.

PROTAC platform technologies are already in early clinical studies for a variety of targets—such as androgen-receptor degraders in prostate cancer and estrogen-receptor degraders in breast cancer [2]. In oncohematology, efforts are also underway: for example, a PROTAC against BCL-XL, intended to treat leukemias without platelet toxicity, and degraders of fusion oncoproteins have been announced. Although specific data on a MYB-targeting PROTAC have not yet appeared, successes in related fields make the development of such molecules highly likely. Preclinically, they could be evaluated in human AML xenografts in immunodeficient mice (PDX models), where MYBMIM, mebendazole, and WFA have already demonstrated proof of concept.

CONCLUSION

The advancement of a targeted MYB-degradation strategy heralds a new chapter in acute myeloid leukemia therapy. Existing studies compellingly demonstrate the scientific merit of this approach: they confirm MYB's central role in maintaining the malignant AML phenotype and show that MYB elimination halts proliferation and induces leukemic-cell death. From a practical standpoint, MYB degradation offers an innovative solution to overcome drug resistance. In cases where tumors fail to respond to chemotherapy, direct removal of the transcriptional oncogene may deliver a "knockout" blow from which cancer cells cannot recover. This is especially relevant in refractory AML subtypes, where alternative targets may be absent or play only secondary roles.

In vitro and in vivo data indicate that proteasomal clearance of MYB achieves selective eradication of the leukemic clone while sparing normal hematopoietic progenitors to a large extent. These findings provide strong justification for continued development of this approach. Repurposing existing agents (such as mebendazole) accelerates the transition to clinical evaluation, while emerging platforms (PROTACs, molecular glues) expand the toolkit for directing the proteasome against MYB. Integration of MYB-degradation strategies into the preclinical pipeline is already underway: advanced animal studies are in progress, and combination regimens with chemotherapy are being optimized. In the near term, initial clinical trial results can be expected to clarify the feasibility and efficacy of this approach in patients.

In summary, targeted MYB degradation has established itself as a promising AML treatment modality capable of complementing and potentially surpassing conventional regimens in resistant disease forms. If subsequent trials confirm the safety and effectiveness of MYB degradation, this strategy may assume a prominent place in the antileukemic armamentarium—paving the way to more durable remissions and cures for patients who have exhausted existing options.

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