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POSTER ABSTRACTS

604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

REM-422, a Potent, Selective, Oral Small Molecule mRNA Degrader of the MYB Oncogene, Demonstrates Anti-Tumor Activity in Mouse Xenograft Models of AML

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The c-MYB (MYB) oncogenic transcription factor is a key regulator of hematopoietic cell differentiation and proliferation. Recurrent genetic lesions or dysregulation of MYB have been identified in a variety of cancers, including adenoid cystic carcinoma (ACC), acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-ALL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), pediatric low-grade glioma (pLGG), and others. AML is characterized by multiple oncogenic abnormalities and high MYB mRNA expression. Evidence from *in vitro* and *in vivo* animal studies suggests that MYB may be a key downstream effector of these oncogenic abnormalities through the direct regulation of genes such as BCL2, MYC and FLT3. Functional genomics studies reveal MYB dependencies in human leukemia cell lines and mouse models of leukemia. Together, these data suggest that MYB is an attractive therapeutic target for AML and other hematological malignancies.

Therapeutic agents that directly target MYB have yet to be developed, presumably due to the challenges of targeting this intrinsically disordered transcription factor, which lacks tractable ligand binding pockets. Here, we describe the mechanism of action and biological activity of REM-422, a potent, selective, oral small molecule messenger RNA (mRNA) degrader of MYB. REM-422 was identified through screening and medicinal chemistry efforts directed towards identifying small molecules that induce the inclusion of a normally unused 'poison exon' (PE), which contains a premature termination codon, into the MYB pre-mRNA transcript. Poison exon inclusion activates the nonsense-mediated decay pathway and promotes the degradation of MYB mRNA.

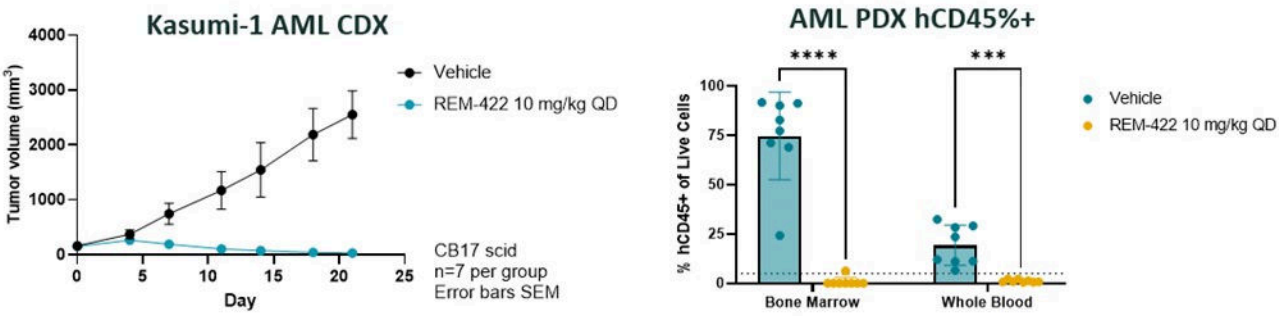
We demonstrate in a cell-free assay that REM-422 acts by selectively facilitating the binding of the U1 snRNP spliceosome complex, which governs exon usage by recognizing 5′ splice sites, to oligonucleotides containing the MYB PE 5′ splice site sequence. REM-422 treatment of human leukemia cell lines promotes poison exon inclusion, leading to degradation of MYB mRNA and subsequent reduction in MYB protein levels (Figure 1A). In a panel of AML cell lines, REM-422 demonstrated preferential anti-proliferative activity in cell lines with high MYB expression, and in those shown to be MYB-dependent through functional genomics studies.

To understand the pharmacokinetic (PK) and pharmacodynamic (PD) effects of MYB in vivo, Kasumi-1 AML cells were implanted subcutaneously in CB17 scid immunocompromised mice and REM-422 was dosed by oral gavage after the formation of established tumors. QD PO administration of REM-422 demonstrated dose-dependent effects in tumors on MYB mRNA levels, with induction of the MYB poison exon leading to reductions of MYB functional mRNA. In a 21-day study, REM-422 demonstrated significant anti-tumor activity, including tumor regressions at well tolerated dose levels (Figure 1 left).

To further investigate the activity of REM-422, AML patient cells were injected into NOG immunocompromised mice and allowed to engraft. After successful engraftment, mice were dosed by oral gavage once daily with REM-422 at 10 mg/kg or vehicle for 24 days. Flow cytometry analysis of bone marrow and peripheral blood samples demonstrated that REM-422 led to the eradication of human leukemia cells from both compartments (Figure 1 right).

Together, these data demonstrate that REM-422 treatment leads to degradation of MYB mRNA in preclinical models of AML and supports the therapeutic potential for REM-422 in AML patients.

Disclosures No relevant conflicts of interest to declare.



Legend: (left) Kasumi-1 AML cells were established as subcutaneous tumors in NOD scid mice, followed by PO administration of REM-422 or vehicle for 21 days. (right) Human AML cells were engrafted in NOG mice and vehicle or REM-422 was administered PO for 24 days. Flow cytometry was used to assess a pan-leukocyte marker, CD45, in the bone marrow or peripheral blood; the percentage of human CD45+ cells are shown.

Figure 1

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