ARTICLE

ACUTE MYELOID LEUKEMIA

# Targeting leukemia-specific dependence on the de novo purine synthesis pathway

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Acute myeloid leukemia (AML) is a devastating disease, and clinical outcomes are still far from satisfactory. Here, to identify novel targets for AML therapy, we performed a genome-wide CRISPR/Cas9 screen using AML cell lines, followed by a second screen in vivo. We show that PAICS, an enzyme involved in de novo purine biosynthesis, is a potential target for AML therapy. AML cells expressing shRNA-PAICS exhibited a proliferative disadvantage, indicating a toxic effect of shRNA-PAICS. Treatment of human AML cells with a PAICS inhibitor suppressed their proliferation by inhibiting DNA synthesis and promoting apoptosis and had anti-leukemic effects in AML PDX models. Furthermore, CRISPR/Cas9 screens using AML cells in the presence of the inhibitor revealed genes mediating resistance or synthetic lethal to PAICS inhibition. Our findings identify PAICS as a novel therapeutic target for AML and further define components of de novo purine synthesis pathway and its downstream effectors essential for AML cell survival.

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## INTRODUCTION

Clinical outcomes of acute myeloid leukemia (AML) vary depending on a patient's age, antecedent hematologic disorders, and genetic background [1–3]. For example, AML cases with *TP53* mutations with complex karyotype exhibit extremely poor prognosis, while those harboring the *PML/RARA* or *CBFB-MYH11* fusion generally exhibit favorable outcomes [1, 2]. Overall, long-term survival is nearly 40% in adult patients 60 years old or younger, while only 10% of patients older than 60 years achieve long-term survival [1, 3]. The last few decades have seen progress in defining its molecular pathogenesis as a consequence of advances in cancer genomics [4]. While sequencing studies now provide a near-complete picture of the AML genome, functional studies, such as phenotype-based target screens are necessary to devise therapies [5–7].

The efficiency and flexibility of the CRISPR-Cas9 genome editing system make it ideal for use in genome-wide recessive genetic screens [8–11]. In fact, recent proof-of-principle studies indicate the potential of this technology to identify genes essential for survival of mammalian cells [12–15]. Using such a screen, we recently identified the mRNA decapping enzyme scavenger, which encodes a mRNA 5′ cap binding protein implicated in mRNA decay, as a new target for AML therapy [16]. Furthermore, CRISPR screens in the presence of small molecules such molecularly targeted drugs enable identification of genes functioning in drug resistance and those whose combined loss results in synthetic lethality [17, 18].

Although a conventional 3 + 7 chemotherapy regimen (anthracycline + cytarabine) remains the standard induction therapy for AML, novel targeted drugs, such as inhibitors of FLT3 [19, 20], IDH1/2 [21, 22], or BCL2 [23], have changed clinical practice in AML. However, molecular-targeted therapies are unavailable for more than half of AML patients, leaving them few treatment options. Thus, identifying more widely expressed targets remains necessary.

Here, using CRISPR screens, we identified PAICS (Phosphoribosylaminoimidazole carboxylase and 5-aminoimidazole-4-(N-succinylcarboxamide) ribonucleotide (SAICAR) synthase), an enzyme functioning in de novo purine biosynthesis, as essential for AML cell survival. Our findings indicate that PAICS could be a novel therapeutic target and expand our knowledge of components of the de novo purine synthesis pathway essential for AML cell survival.

## METHODS

### Mice

C57BL/6 mice were purchased from Jackson Laboratory. C57BL/6. *Rag2*$^{null}$*Il2rg*$^{null}$NOD-*Sirpa* (BRGS) mice were developed in our laboratory as previously described [24]. Mice were bred and maintained in individual

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