# Uncovering pharmacological opportunities to target the drug resistance factor SAMHD1

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The treatment of acute leukaemias relies heavily upon a class of cytotoxic chemotherapy called antimetabolites. These drugs are synthetic mimics of naturally occurring metabolites, such as DNA precursors like nucleosides, that compete with their endogenous counterparts in metabolic processes to exert their anticancer effects. Despite high clinical impact, resistance to these therapies, either acquired or intrinsic, is a major obstacle to achieving cures, and knowledge gaps remain about the underlying molecular mechanisms and the design of therapeutics that can overcome it (*1*).

Our previous research identified the dNTP hydrolase SAMHD1 as a major resistance factor for antimetabolite chemotherapies in acute leukaemias, in particularly for standard-of-care therapy cytarabine in acute myeloid leukaemia (*2*). Thus, one of our research interests is to identify and develop strategies to inactivate this enzyme in cancer cells, and thereby provide a mechanism to overcome chemoresistance, and we have employed several orthogonal approaches. In a targeted approach, we developed a biochemical assay and screened chemical libraries to identify small molecules capable of directly inhibiting SAMHD1 (*3*), and currently have several series under evaluation with distinct inhibitory mechanisms. In parallel, we conducted a phenotypic screening approach and identified that a class of clinically used anticancer drugs can be re-deployed to indirectly supress the chemoresistance activity of SAMHD1 (*4*), which currently forms the basis of a clinical study, and we continue to build upon this finding. Here, both approaches will be discussed and compared with regards to what we have learned about SAMHD1 and its role in chemoresistance, and the potential mechanisms available to pharmacologically disrupt the activity of this enzyme.

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2. Herold et al. *Targeting SAMHD1 with the Vpx protein to improve cytarabine therapy for hematological malignancies*. ***Nature Medicine*** (2017). PMID: 28067901
3. Zhang et al. *Identification and evaluation of small-molecule inhibitors against the dNTPase SAMHD1 via a comprehensive screening funnel*. ***iScience*** (2024). PMID: 38318365
4. Rudd et al*. Ribonucleotide reductase inhibitors suppress SAMHD1 ara-CTPase activity enhancing cytarabine efficacy*. ***EMBO Molecular Medicine*** (2020). PMID: 31950591