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Commentary

Methionine adenosyltransferase 2A (MAT2A) inhibitors as single agents or in combination strategy for cancer therapy

Yi Kuang[1,2], Zhiyong Yu[1,2], Feng Zhou[1,2,*]

[1]State Key Laboratory of Neurology and Oncology Drug Development, Shanghai, China

[2]Simcere Zaiming Pharmaceutical Co., Ltd., Shanghai, China

*Author for correspondence:
Email: zhoufeng2@simcere.com, fengz504@icloud.com

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Abstract

Methylthioadenosine phosphorylase (*MTAP*)-deletion occurs in about 15% of all cancers. The metabolic enzyme methionine adenosyltransferase 2A (MAT2A) was found to elicit synthetic lethality in *MTAP*-deleted cancers. Here, we commented on a novel MAT2A inhibitor SCR-7952, and discussed the potential of MAT2A inhibitors as single agents or in combination for cancer therapy, including solid tumors and hematologic malignancies. Several MAT2A inhibitors with high efficacy and selectivity have been discovered. And MAT2A inhibitors synergize strongly with protein arginine N-methyltransferase 5 (PRMT5) inhibitors, taxanes, platinum, topoisomerase inhibitors, and antibody-drug conjugates (ADC). A MAT2A inhibitor IDE397 and the combination strategies with chemotherapies or other targeted therapies are under investigation in clinical. The promising preliminary clinical results demonstrate the potential of MAT2A inhibitors for the treatment of *MTAP*-deleted tumors.

Keywords: MAT2A inhibitor, PRMT5, *MTAP*-deleted cancer, Drug combination

Introduction

Methionine adenosyltransferase 2A (MAT2A), one of the rate-limiting enzymes in the methionine cycle, primarily catalyzes methionine into *S*-adenosylmethionine (SAM) [1,2]. SAM is the global methyl-donor for transmethylation and biosynthesis reactions, which protein arginine N-methyltransferase 5 (PRMT5) utilizes for symmetric dimethylarginine (SDMA) posttranslational modifications [3]. MAT2A and PRMT5 participate in a series of regulatory pathways that underlie cancer development, progression, and therapy-response. Recent studies have found MAT2A as a synthetic lethal target in methylthioadenosine phosphorylase (*MTAP*)-deleted cancers [4]. The deletion of *MTAP* leads to an accumulation of methylthioadenosine (MTA), which is a natural selective inhibitor of PRMT5. This inhibition by MTA results in an increased sensitivity of PRMT5 on the reduction of its substrate SAM. Therefore, silencing or inhibition of MAT2A reduces intracellular SAM and promotes selective cell death in *MTAP*-deleted cancers. Considering that *MTAP*-deletion occurs at high frequency in almost 15% of all human cancer types [5], synthetic lethality emerges MAT2A as a potential target for cancer treatment.

Recently, a potent and specific allosteric MAT2A inhibitor SCR-7952 was discovered, exhibiting promising MAT2A inhibition and anti-tumor effects on *MTAP*-deleted cancers both *in vitro* and *in vivo* [6]. SCR-7952 binds at the same allosteric pocket as other MAT2A inhibitors AG-270 and PF-9366 [7], but shows higher potency in enzymatic assay and higher selectivity against HCT116 WT cells. A comparison of SCR-7952 with other MAT2A inhibitors is shown in **Table 1**. PF-9366 is the first commercial MAT2A inhibitor, discovered by Pfizer, but the inhibition of MAT2A is not as potent, with an IC_{50} value of 420 nM [7]. Then, another MAT2A inhibitor, AG-270 is developed by Agios, exhibiting selectivity on *MTAP*-sufficient cells [8]. The selectivity of SCR-7952 is higher

Table 1. The comparison between SCR-7952 and other MAT2A inhibitors.

	MAT2A enzyme (nM)	Cellular SAM levels (nM)	Anti-proliferation (nM)		Reference
			HCT116 *MTAP*$^{-/-}$	HCT116 WT	
SCR-7952	18.7	1.9	34.4	487.7	[6]
PF-9366	420	1200	-	-	[7]
AG-270	68.3	5.8	300.4	1223.3	[8]
AZ9567	-	1.4	~100	~1000	[10]
Compound 28	26	-	75	>10000	[9]
IDE397	~ 10	7	15	>20000	[11]

compared with AG-270, indicating a higher safety window and a viable therapeutic approach to MTAP naturally deleted cancer cells. Other MAT2A inhibitors such as AZ9567 and compound 28 also exhibit similar potency on MAT2A activity, but weaker anti-proliferation effects [9,10]. SCR-7952 shows potent anti-tumor effects at lower therapeutic dosages compared with other MAT2A inhibitors, presumably a result of the high enzyme activity and good pharmacokinetic profiles.

Similar to other MAT2A inhibitors, the mechanism of SCR-7952 is via a selective impairment of PRMT5 and PRMT5-dependent spliceosome activity, such as FANCA splicing perturbations. The same mechanism and downstream of MAT2A and PRMT5 hint at a combination strategy of SCR-7952 with PRMT5 inhibitors. Remarkable synergistic interactions are observed between SCR-7952 and the SAM-competitive or the MTA-cooperative PRMT5 inhibitors, but not substrate-competitive ones [6]. Other studies also reported the combination of MAT2A inhibitors, GH31 and IDE397 with multiple MTA-cooperative PRMT5 inhibitors in *MTAP*-deleted glioblastoma, lung, and pancreas cancers [12,13]. The combination treatment leads to more reduction of SDMA levels and a greater extent of PRMT5 inhibition as compared to either agent alone, thus further enhancing the efficacy of MAT2A inhibitors.

Several MAT2A and PRMT5 inhibitors are under investigation in clinical. IDE397 showed encouraging clinical activity in a phase 2 clinical trial in *MTAP*-deletion urothelial cancer and NSCLC (ClinicalTrials.gov NCT04794699). The overall response rate (ORR) and disease control rate (DCR) were 39% and 94%, respectively. The adverse event (AE) profile was favorable at the 30 mg once-a-day expansion dose, with 5.6% grade 3 or higher drug-related AEs and no drug-related serious adverse events (SAEs). The most common grade 3 AE was asthenia, and all grade AEs were nausea and peripheral neuropathy. No discontinuations due to drug-related adverse events made long-term dosing feasible. In preclinical toxicity evaluation, we observed strong toxic reactions in animals. This discrepancy may imply differences in the toxic responses of animals and humans to MAT2A inhibitors. The MTA-cooperative PRMT5 inhibitors AMG 193 and MRTX1719 also showed promising preliminary clinical activity in MTAP-null solid tumors, with 5/31 and 6/18 PR, respectively (ClinicalTrials.gov NCT05094336, NCT05245500) [14]. In a phase 1 study of AMG 193, 5 patients were observed dose-limiting toxicities (DLTs) in the escalating cohorts. Any-grade and grade 3 treatment-related AEs in the dose-expansion phase occurred in 83.9% and 18.4% of patients, respectively. In a phase 1/2 study of MRTX1719, patients were well tolerated with no DLT or grade 4/5 TRAEs observed at dose levels up to 400 mg once a day. The most frequent treatment-related adverse events (TRAEs) of AMG 193 and MRTX1719 were nausea, vomiting, and fatigue. These promising clinical results further demonstrate the potential of MAT2A and PRMT5 inhibitors for the treatment of *MTAP*-deleted tumors. Although, MAT2A and PRMT5 inhibition demonstrated promising clinical efficacy as monotherapy, the combination therapy may lead to better efficacy based on preclinical observation. Further, MAT2A and PRMT5 inhibitors have different clinical AE profiles, suggesting a low probability of additive toxicity produced by that combination strategy in clinical. Notably, decreased appetite in low frequency was observed in both MAT2A and PRMT5 inhibitor treatment patients, suggesting this target-related toxicity could be more serious in combination. Actually, a phase 1/2 study is evaluating the combination of IDE397 with PRMT5 inhibitor AMG 193 in participants with metastatic or locally advanced *MTAP*-null non-small cell lung cancer (NSCLC) and other *MTAP*-null solid tumors (ClinicalTrials.gov NCT05975073).

Besides PRMT5 inhibitors, MAT2A inhibitors also exhibit synergistic effects with chemotherapies and other targeted therapies, such as antimitotic taxanes. AG-270 exhibits synergistic antiproliferative effects with docetaxel and paclitaxel in *MTAP*-deleted pancreatic cancer and NSCLC, both *in vitro* and *in vivo* [5]. The mechanism is via the downregulation of the FA DNA repair pathway by MAT2A inhibitors. MAT2A inhibitors cause significant upregulation of FANCA DI-containing transcripts and in turn, reduction of the total level of FANCA [5,6]. The FA complex has mitotic roles, including the resolution of R loops and the formation of DNA repair structures during the S phase via homologous recombination [15,16]. The deficiency of FA activity via DI-mediated downregulation upon MAT2A inhibition generates exacerbated DNA damage and mitotic defects downstream, and eventually the hypersensitivity to the antimitotic therapeutics [15]. Treatment with another MAT2A inhibitor IDE397 also generates perturbations in pre-mRNA splicing, DNA damage repair, and mitotic spindle assembly across diverse cancer models [17]. A high-throughput combination screen of over 400 drugs reveals that IDE397 synergizes with taxanes, platinum, topoisomerase inhibitors, splicing inhibitors, and anti-folates in *MTAP*-deleted models [17]. The combination results provide effective clinical strategies. Taxanes such as paclitaxel and docetaxel are widely used as chemotherapy agents, and several clinical trials are investigating the combination of MAT2A inhibitors with taxane-based chemotherapies. AG-270 and IDE397 are under evaluation in phase 1 studies as a single agent and in combination with taxane-based chemotherapy (docetaxel, paclitaxel) in participants with *MTAP*-deleted advanced solid tumors or lymphoma (ClinicalTrials.gov NCT03435250, NCT04794699). There is also a phase 1/2 trial investigating a MAT2A inhibitor

S095033 in combination with paclitaxel in participants with advanced or metastatic esophageal squamous cell carcinoma (ESCC) (ClinicalTrials.gov NCT05312372). IDE397 also exhibits durable benefit and synergistic effect with topoisomerase inhibitor irinotecan, in challenging RT112/84 urothelial cancer xenograft mice model indicates a novel combination and dual payload antibody-drug conjugate (ADC) strategy, which topoisomerase inhibitors are widely conjugated to as the payload [17]. A phase 1 study is evaluating the combination of IDE397 with Sacituzumab govitecan, which is a Trop-2-directed ADC conjugated with a topoisomerase inhibitor SN-38 (ClinicalTrials.gov NCT04794699). A case report in a patient with urothelial cancer and *MTAP*-deletion and FGFR-TACC3 fusion shows the combination benefit, with partial response (PR) of -31% after 12 weeks. 2 of 2 patients with *MTAP*-deleted urothelial cancer on combination observed molecular response with ctDNA reduction of more than 95% at first evaluation. There is speculation that MAT2A and ADCs conjugated with topoisomerase inhibitors will exhibit synergistic effects on *MTAP* wild-type cancers. Further study is needed, and if the speculation is demonstrated, the indications for MAT2A inhibitors may be expanded. Given that nearly all MTAP-deleted pancreatic cancers have a co-occurring RAS mutation, Tango Therapeutics indicated that they have entered into a clinical collaboration with Revolution Medicines to conduct the combination trials of TNG462, an MTA-cooperative PRMT5 inhibitor with two RAS(ON) inhibitors, RAS(ON) multi-selective inhibitor RMC-6236 and RAS(ON) G12D-selective inhibitor RMC-9805 [18]. It suggests that the combination of MAT2A inhibitors and RAS inhibitors also deserves further investigation.

Except for solid tumors, MAT2A is also reported as the key regulator and therapeutic target in hematologic malignancies, such as multiple myeloma, lymphoma, and leukemia. The expression of MAT2A is the highest in brain cancer, leukemia, and lymphoma compared to other cancers, and significantly higher than healthy controls [19]. The high level of MAT2A is associated with an unfavorable prognosis in patients with hematologic malignancies, for instance, multiple myeloma (MM) and acute myeloid leukemia (AML) [20,21]. Silencing MAT2A or inhibition by FIDAS-5 restrains cell cycle progression and induces cell apoptosis via reduction of intracellular SAM level and inactivation of the mTOR-4EBP1 pathway in MM cell lines, both *in vitro* and *in vivo* [20]. Another study found that the MAT2A inhibitor PF-9366 reduces the proliferation of MLL and sensitizes MLL cells to chemotherapy, by reducing global histone methylation [19]. PF-9366 acts synergistically with cytarabine, telomeric silencing 1-like (DOT1L) inhibitor EPZ004777, and PRMT5 inhibitor EPZ015666. Recently, DOT1L and PRMT5 have been identified as suitable targets for leukemia treatment [22], indicating a beneficial combinational treatment of MAT2A inhibitors with these targeted therapies. In the meantime, AG-270 is undergoing a phase I clinical trial in patients suffering from lymphoma or solid tumors (ClinicalTrials.gov NCT03435250), further supporting the rationale to target MAT2A in hematologic malignancies.

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