Deoxyguanosine analogues allosterically modulate the dNTPase activity of chemoresistance factor SAMHD1

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SAMHD1 is a deoxynucleotide hydrolase (dNTPase) that regulates cellular dNTP levels and has recently been implicated as a resistance factor to nucleoside analogue antimetabolite chemotherapy. Antimetabolites are important in the treatment of many cancer types, but tumour-specific factors can negatively affect therapy outcome. Nucleoside analogues enter the cell as prodrugs and, once activated, disrupt the cellular dNTP pool or cause direct damage to the genome. As a dNTPase, SAMHD1 cleaves the active metabolites of these drugs and is therefore an attractive target for the development of inhibitors to improve the effectiveness of nucleoside analogue therapy. Compounds that modulate SAMHD1 activity could also serve as experimental tools to further understand the enzyme's biological roles.

Catalytically competent SAMHD1 requires nucleotide binding at two distinct allosteric sites (AS1 and AS2) to induce tetramerization, with AS1 being specific for guanine nucleotides. Guanine nucleotide analogues, such as the triphosphate metabolite of the antiviral Acyclovir, act as allosteric activators of SAMHD1. Interestingly, in the absence of their triphosphate moiety, both Acyclovir and the endogenous nucleoside deoxyguanosine inhibit the dNTPase activity of SAMHD1 in vitro. However, the mode of inhibition was not yet described.

In the present study, we investigate these as yet unknown modes of SAMHD1 activity modulation by deoxyguanosine analogues. Using a pipeline of biochemical and biophysical studies including enzyme activity assays, competition binding and in-vitro protein crosslinking, we are studying the affinity of different nucleoside analogues for SAMHD1's allosteric sites, as well as their effect on the enzyme's dNTPase activity and oligomerisation status. Preliminary results suggest that deoxyguanosine analogues inhibit SAMHD1 by inducing an inactive dimeric state that is unable to progress to catalytically active homotetramer. The triphosphate metabolites of deoxyguanosine analogues, acting as allosteric activators, induce the formation of a tetrameric and catalytically competent SAMHD1 with inherently reduced hydrolase activity.

Altogether, this study aims to diversify the modes of inhibition towards the chemoresistance factor SAMHD1 and provide a starting point to rationally develop allosterically targeting molecules.