Rational design of pro-drug iterations of the small molecule inhibitor HEX for the collateral lethality targeting of ENO1-deleted glioblastoma

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Genomic deletions are ubiquitous in the cancer genome, often inactivating tumor suppressor genes. An unintended consequence of these deletions is the co-deletion of nearby chromosomal neighbors that are irrelevant to tumor progression. These co-deleted genes are known as “passengers”\(^1\). In demonstrating the pharmacological vulnerability conferred by deletion of these passenger genes, we have spearheaded a novel therapeutic strategy known as “collateral lethality”\(^{1,2}\). One promising passenger deletion is of the glycolytic enzyme ENO1 in glioma cells. Cancers harboring the deletion of ENO1 are dramatically sensitized to inhibition of its redundant paralog, ENO2\(^3\).

Our current endeavors towards bringing this concept to the clinic aim to improve our small molecule ENO2 inhibitor, HEX. HEX is substrate-competitive Enolase inhibitor with a Ki of 63 nM for ENO2 versus 250 nM for ENO1. Presently, we have developed our lead compound POMHEX, a carboxylesterase-activated pro-drug version of the HEX pharmacophore. Preliminary data indicate that POMHEX is effective in cell-based systems and eradicates ENO1-homozygously deleted tumors in intracranial xenografted mouse models in up to 40\% of cases\(^4\). Animals are effectively cured without tumor recurrence even after discontinuation of the drug\(^4\). However, its sub-optimal pharmacokinetic properties portend significantly lower concentrations of POMHEX in the brain relative to visceral organs. To amend this issue, we are applying retrometabolic drug design to examine alternative, more robust mechanisms of bioactivation. Central to this work is the design and synthesis of a pro-drug of HEX that that applies a similar mechanism of action as the prominent chemotherapeutic, cyclophosphamide.

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