SWEET TARGETS: A BIOCATALYTIC METHOD TO GLYCOSYLATE NUCLEOSIDE ANALOGUES

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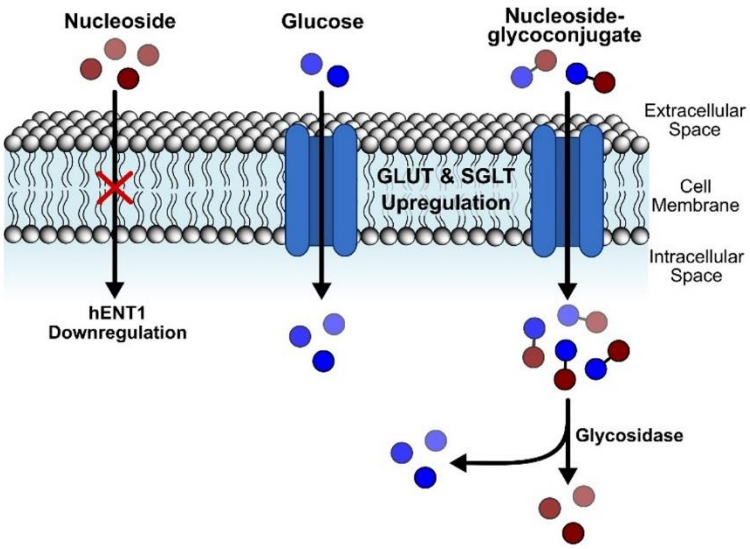
Nucleoside analogue therapeutics have a proven capability within drug discovery as antiviral and anticancer agents [1,2]. However, their efficacy can be limited by poor cellular uptake caused by the down regulation of nucleoside transporters [e.g., human equilibrative nucleoside transporter 1 (hENT1)], off target toxicity and poor bioavailability. Prodrugs of such analogues contribute to an improved pharmacokinetic profile, exemplified by the ProTide therapeutics Sofosbuvir and Tenofovir. Herein, we explore biocatalytic glycosylation of nucleoside analogues as a means towards an alternative prodrug strategy, highjacking glucose transport. In cancerous tissues, an upregulation of hexose transporters (GLUTs) is observed, leading to enhanced glucose uptake and this has led to targeting GLUTs as a method of increasing the selectivity of antitumour therapeutics [3].



Building upon our previous work targeting biocatalytic synthesis of nucleoside analogues and novel gemcitabine glycoconjugates for GLUT1,[4,5] the activity of the nucleoside-specific 3'-*O*-glycosyltransferase AvpGT from *Streptomyces sp. AVP053U2* is investigated against a panel of both natural and clinically relevant purine and pyrimidine nucleoside analogues. AvpGT demonstrates broad substrate promiscuity, with 16 of 22 nucleosides tested showing glycosylation by HILIC-MS. Of these, 13 nucleosides were successfully glycosylated on 25 µmol scale in 39-91% yields, including four current nucleoside analogue therapeutics. The resulting conjugates were screened for their antitumor activity and selectivity against metastatic PC3, LNCaP & AML cell lines.[6] Furthermore, a novel β-glucosidase, AvpGS, was identified from the same *Streptomyces sp.* strain, heterologously expressed, purified and shown to display high substrate promiscuity in subsequently removing glucose from the glycoconjugates. Notably, the human cytosolic glucosidase, GBA3, was inactive here and such orthogonal activity of AvpGS to GBA3 posits an opportunity to explore target specific drug delivery systems, similar to those reported for lectin- and antibody-directed prodrug therapies.

References:

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