Self-immolative phosphoramidates with cleavable dipeptides to expand the payload scope in antibody-drug conjugates by delivery of hydroxy-containing drugs.

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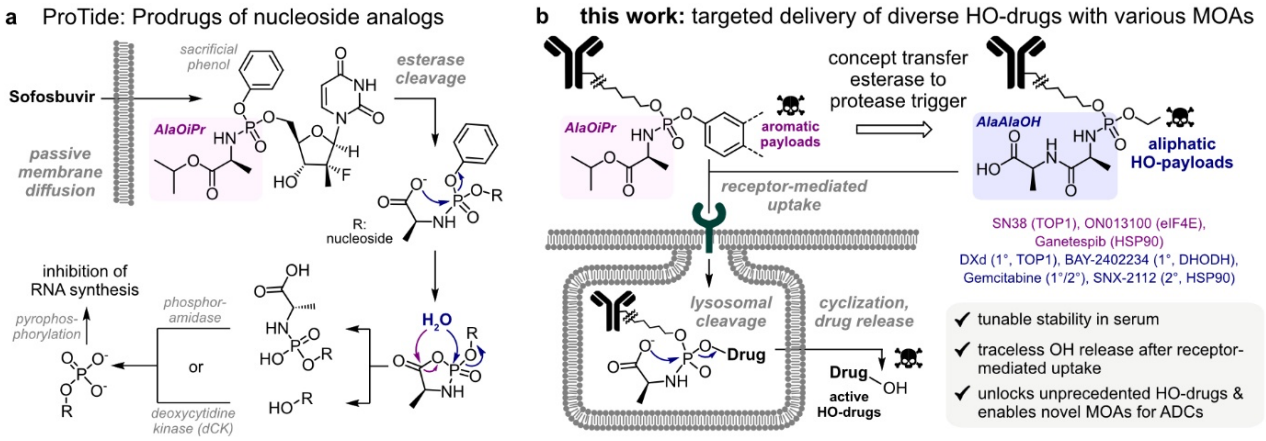
Despite recent advances in targeted drug delivery to improve current treatment options in oncology, approved Antibody-Drug-Conjugates (ADCs) are still limited by the delivery of a restricted set of payloads with limited modes of action (MOA).[1] Versatile linkers, applicable to functional groups prevalent across diverse pharmacophores are needed to expand this space.[2] To address this, we developed the Alco5 technology: A phosphoramidate-based self-immolative linker system that facilitates stable attachment in serum and traceless drug release in the target cell from aliphatic and aromatic alcohols.[3] Studies with camptothecins conjugated via Alco5 showed that stability and release are tunable by incorporating marginal chemical modifications in the phosphoramidate structure. Moreover, various intracellular trigger events can be exploited to ensure traceless drug delivery. Most importantly, protease-cleavable dipeptides, turned out to be superior release triggers for the Alco5 technology.
Excellent stability, in vivo efficacy, and pharmacokinetics (PK) compared to approved ADCs has been demonstrated. Most importantly, we were able to unlock novel payloads for targeted drug delivery by conjugating 10 different hydroxy-containing cytotoxins with different intracellular MOAs, many of them without prior precedence in drug delivery. In vivo studies with gemcitabine showed excellent PK and efficacy, unlocking gemcitabine's full potential and illustrating the ability of the phosphoramidate-based linker system to expand the payload space for ADCs.



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