Towards targeted drug delivery using click-to-release chemistry

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Targeted drug delivery is an attractive tool that facilitates higher efficacy while simultaneously decreasing side effects and thus, is of great interest in biomedical research.

In this work we present an elegant way to trap and cleave a drug on an intracellular level by exploiting bioorthogonal click-to-release chemistry between tetrazines and trans-cyclooctenes (TCOs) that was first introduced by Versteegen et al.[1]

A TCO-drug conjugate is accumulated in the cytosol by binding to an intracellular target. This accumulation process allows the use of non-toxic concentrations of highly potent drugs such as Monomethyl auristatin E (MMAE) that otherwise could not be used as drug itself due to its high toxicity.

Addition of a suitable tetrazine leads to addition ("click") followed by spontaneous elimination and thus release of the formerly caged drug (Fig.1). The latter can move to its site of action where it can unfold its full potential.

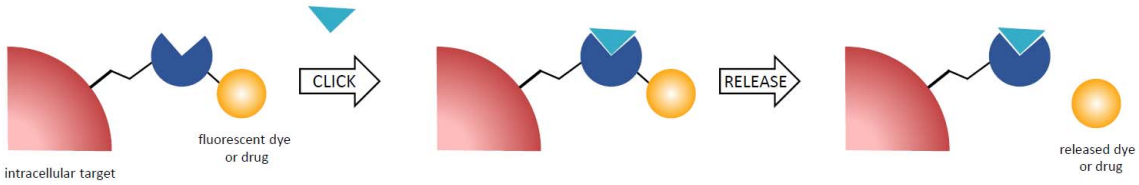

Figure 1: Intracellular click-to-release reaction

In vitro experiments were carried out using a BTK (Bruton's Tyrosine Kinase) overexpressing cell line and Ibrutinib, a small molecule drug that binds covalently to this enzyme. Preliminary work was carried out using a fluorescent dye in place of a drug to monitor release via fluorescence microscopy.

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[1] Angew. Chemie Int. Ed. 52, 14112–14116 (2013)