Catch & Release Drug Delivery System – Heterocycles, Bioorthogonal Chemistry and Implantable Biomaterials Optimize the Pharmacokinetics of Systemic Small Molecules

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Purpose: We present a heterocyclic-based drug delivery platform that optimizes the concentration of a systemic drug at a location of interest. As a therapeutic proof of concept, we apply the system to the construction of an antibiotic agent based on vancomycin.

Background: Our prior studies have shown that an area of the body pre-implanted with a biomaterial containing a bioorthogonal reaction partner (*trans*-cyclooctene, TCO) can increase by ten times the local concentration of a heterocycle (tetrazine, Tz) carrying a radioactive payload *in-vivo*. Now we present a platform that localizes and releases small molecules at the desired location (Fig. 1).

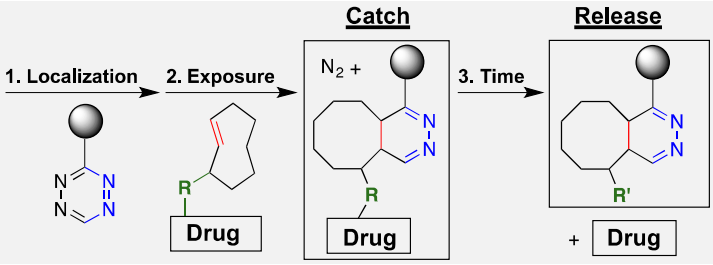

Figure 1. Catch & Release Drug Delivery. First a biomaterial covalently linked to tetrazines is placed at the area of interest. Then drugs linked to *trans*-cyclooctene moieties are injected. When the reagents come in close proximity, they react *in-situ* and the drug is released.

Methods/Results: We modified fluorophores and vancomycin with TCO and as well as synthesized an alginate biomaterial modified with tetrazine (Tz-gel). We tested them through *in-vivo* and *in-vitro* models over multiple days. The results indicate that the "Catch & Release" method can deliver an increased payload to a local area pre-implantated with the biomaterial. The *in-vitro* therapeutic efficacy of the releasable vancomycin was comparable to vancomycin when tested in the presence of the Tz-gel against luminescent methicillin sensitive Staph. aureus (MSSA, Xen 29, Perkin Elmer, MA).

Conclusions: We present a drug delivery system that enables medical practitioners to direct drug to specific locations of the body by pre-implanting a biomaterial. This system could have major implications to improve the therapeutic index of new and old drugs.