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Light induced drug release from a folic acid-drug conjugate

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ABSTRACT

A major area of cancer research focuses on improving the specificity of therapeutic agents by engineering drug-delivery vehicles that target overexpressed receptors on tumor cells. One of the most commonly used approaches involves targeting of folate receptors using folic acid conjugated to a drug-containing macromolecular cargo. Once internalized via endocytosis, the drugs must be released from these constructs in order to avoid being trapped in the endosomes. Here, we describe the synthesis of a small-molecule conjugate that couples folic acid to doxorubicin via a photocleavable linker. Using HPLC we show that the doxorubicin can be released with light rapidly and with high efficiency. This approach has advantages over macromolecular systems due to its simplicity and efficiency.

Targeted therapeutics promise to greatly reduce the adverse side effects associated with current cancer chemotherapeutics.[1] Targeted therapies typically act either by interfering with upregulated oncogenic pathways or through enabling cancer cell selective delivery by binding to an overexpressed receptor on the cell membrane of cancer cells.[2-5] In the latter approach, a receptor targeting ligand is covalently coupled to a cytotoxic agent, which is then selectively delivered to the tumor cells.

Folic acid (FA-vitamin B9) is a precursor to tetrahydrofolate, 1-carbon donor which is essential for the synthesis of nucleotide bases. Commonly prescribed as nutritional supplement, FA has high affinity towards folate receptors (FRs), which facilitates its internalization. Two independent and mechanistically different systems mediate cellular uptake of FA in mammalian cells. The Reduced Folate Carrier (RFC) is a low affinity (Kd ~ 10^{-6} M), high-capacity membrane-spanning anion transport protein that delivers reduced FAs across the plasma membrane in a bidirectional fashion. Folate Receptor (FRα) is a high affinity (Kd ~ 10^{-10} M), single chain FA-binding protein which internalizes FA through active-receptor mediated endocytosis.[6,7] FRα is frequently overexpressed in epithelial tumors, particularly in ovarian cancer where 90% of patients have elevated FRα levels.[8,9] For this reason, FR targeting is being pursued for imaging and therapeutic purposes by conjugating FA with imaging or drug molecules.[10-13] Folate-containing conjugates bind to FRα and are internalized via endocytosis. Once internalized the cargo needs to be released in order to prevent endosomal entrapment.[14]

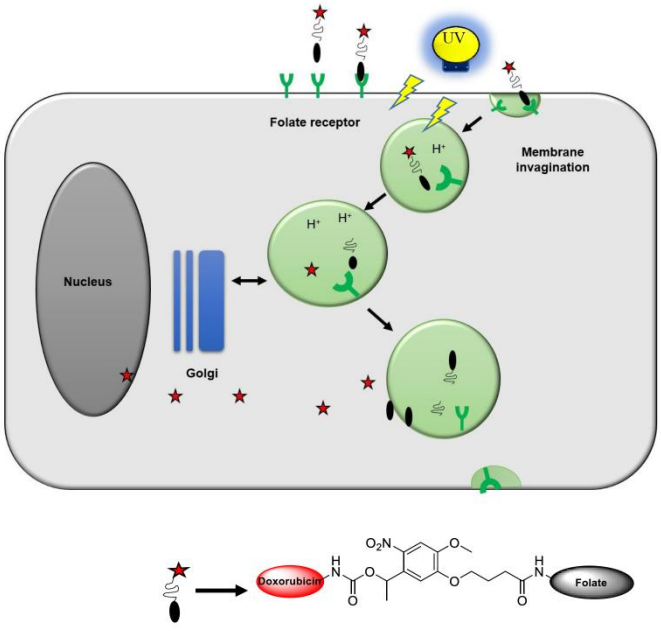

Figure 1: Schematic representation of targeted delivery of photocaged drug (Adapted from Hilgenbrink *et al.*[13])

Endosomal escape can be facilitated through cleavage of the bond between folate and a cell permeable drug, enabling it to pass through the endosomal membrane. A common