PRODRUG APPROACHES FOR ANTICANCER DRUGS

- Cancer is still a major cause of death in the world thus the urge to discover novel and effective therapeutic agents continues.

- Only 20% of the cancer patients can benefit from surgical or radiation based therapies, and that's why chemotherapy is the primary choice for cancer treatment.

- However, current therapeutics may suffer from low bioavailability, high toxicity and drug resistance.

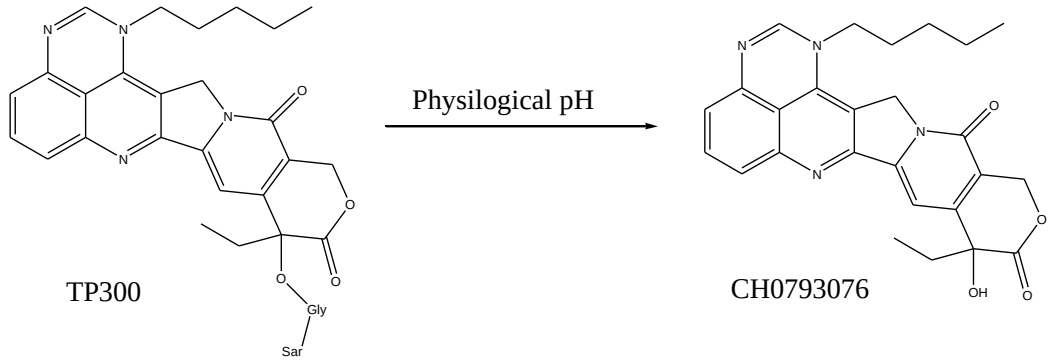
- Prodrugs provide possibilities for overcoming drug delivery challenges, such as poor aqueous solubility, formulation, insufficient oral absorption, chemical instability, inadequate brain penetration, toxicity and local irritation.

- Irinotecan`s clinical utility is limited due to the drawbacks such as poor bioconversion to the active drug SN-38, severe toxicities and the function of SN-38 as a substrate of the breast cancer resistance protein efflux pump.

- Ohwada and coworkers reported the syntheses and biological activities of water-soluble prodrugs of hexacyclic camptothecin analog, CH0793076, that exhibits pH-dependent convertion to parent compound and showed better anticancer activity than irinotecan.

- Among the prodrugs synthesized, TP300 is highly water-soluble and rapidly generates CH0793076 at physiological pH *in vitro*.

- TP300 showed a broader antitumor spectrum and more potent antitumor activity than irinotecan in various human cancer xenograft models[71].



- To enhance therapeutic index, and reduce the toxicity issues of cytotoxic chemotherapy, targeted prodrug approaches are new directions in the treatment of cancer.

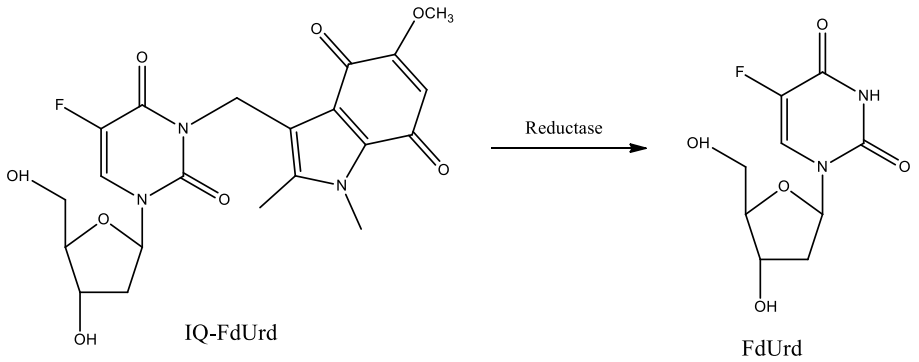
- These directions are receiving big attentions for adjustment of physical properties of drugs such as the charges, lipophilicity or reactivity by alteration leads to the selective delivery of the drugs to cancer cells and tissues. Therefore, prodrugs concentrate at their target cells, and show their activities there in a selective way.

- Significant strategies to accomplish the local activation of prodrugs including enzymatic activation of prodrugs in hypoxic cells, the use of pH sensitive conjugates, antibody-drug conjugates , hydrophobic drug self-delivery systems (HDSDSs), and integration of prodrugs with nanotechnology based drug delivery strategies etc…

- Jiho and his co-workers recognized an enzymatic one-electron reduction as a useful reaction that can be applied in the design of tumor hypoxia-targeting drugs.

- The enzymatic reaction of 5-fluorodeoxyuridine (FdUrd) prodrug bearing an which is a substrate of reductases had been characterized by them.

- Releasing of FdUrd under hypoxic conditions after treatment with cytochrome NADPH P450 reductase had been activated by IQ-FdUrd. They also confirmed that IQ-FdUrd showed selective cytotoxicity in hypoxic tumor cells.



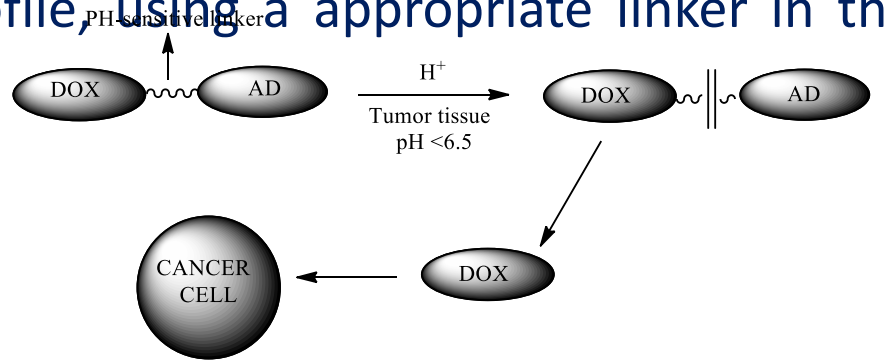
- Doxorubicin is a potent anti-cancer drug, but it causes dose-dependent cardiotoxicity.

- To overcome this problem, Gonzalez-Mendez and his co-workers designed pH sensitive prodrugs for improving its selectivity and reducing the toxic effects of the free drug.

- They optimized the synthesis of Dox attached to adamantane (Ad) by using three different pH sensitive linkers; ester, amide and hydrazone to reduce the toxicity of free drug.

- Kinetics of the *in vitro* hydrolysis of the three proposed linkers was evaluated at pH values, considering the acid microenvironment that characterizes tumors.

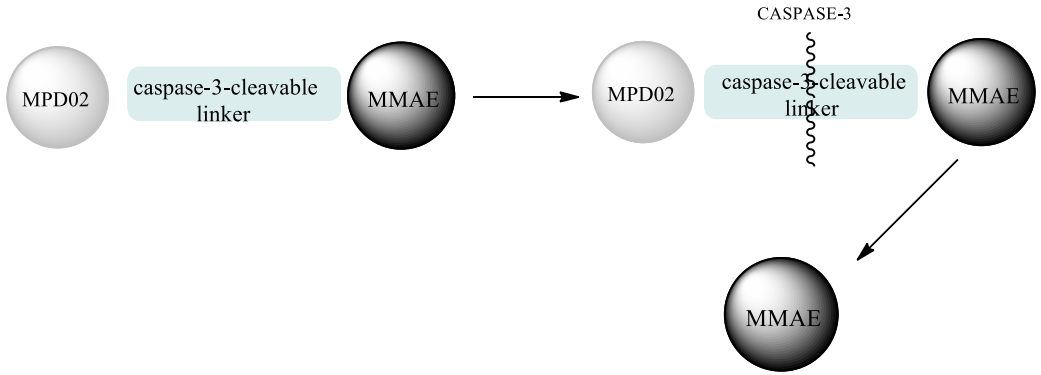
- The cytotoxic activity of the prodrug displayed a similar behavior to the free drug with the best release profile, using a appropriate linker in the design of pH sensitive Dox prodrugs.



- A novel strategy named radiation-induced apoptosis-targeted chemotherapy (RIATC), that could specifically deliver cytotoxic agents to the tumor guided by radiotherapy was proposed by Chung et.al.

- They synthesized a novel albumin-binding prodrug MPD02 by conjugating cytotoxin monomethyl auristatin E (MMAE) to the C-terminus of the KGDEVD peptide via self-eliminating linker and introducing a maleimide group to the Lys side chain of the peptide.

- They found that MPD02 metabolized into a highly potent MMAE on caspase-3-mediated activation, showing a highly potent anticancer effect with good safety profile in two different TNBC xenograft models.



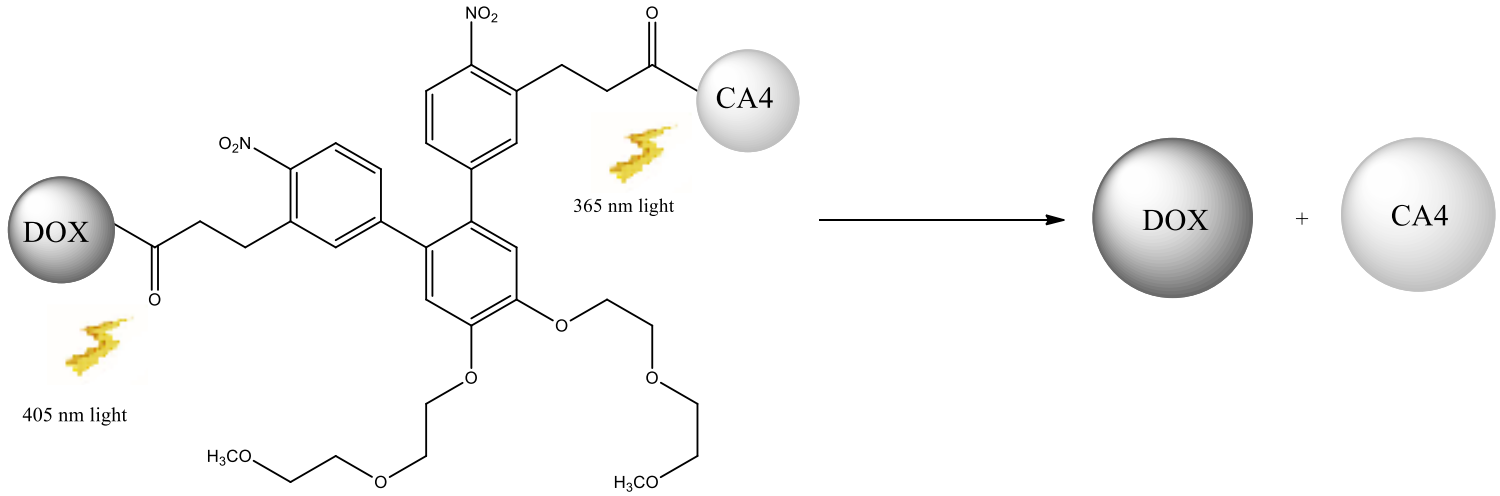
- Since the lights are non-invasive external stimuli and can be easily manipulated, photoremovable protection groups (PPGs) have received much attention in recent years for clinical applications.

- Inactive prodrugs were prepared by conjugation of active drug to PPGs with covalent bonds to achieve maximum activity and minimum toxic effects by controlled release of active drug in the target region by light irradiation.

- Liu and his co-workers synthesized a photoresponsive hybrid prodrug that has both doxorubicin (DOX) and combretastatin A4 (CA4) to explore the application of photoremovable protecting groups (PPGs) in the field of combination chemotherapy.

- They found that DOX release was achieved with 405 nm light and CA4 release with mostly 365 nm light.

- Cell viability assessment confirmed that the prodrug had greater toxicity to MDA-MB-231 cells compared to individual drugs and a synergistic effect was achieved.



- A prodrug of 5-fluorouracil (5FU) covalently conjugated to low molecular weight chitosan (LMWC) via a photocleavable linker have been synthesized by Horo et.al to improve hydrophilicity as well as increase the retention time of the drug.

- Then, they used ionic gelation technique to the LMWC-5FU conjugate into nanoparticles for effective penetration into cells. The conjugate was designed to be cleaved under 365 nm UV-A radiations.

- The conjugate has been found to exhibit greater water solubility compared to LMWC and forms hydrogel and DMSO gel.