Hypoxia-Activated Floxuridine Oligomers via Bioreduction of Nitro and/or Azo Functionalities

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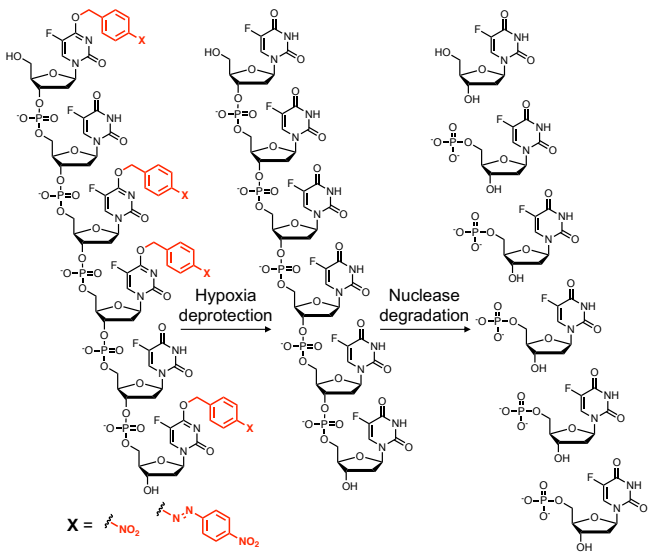
Chemotherapy is one of the most frequently used methodology for cancer treatment. Although many types of anticancer drugs have been developed and used, their side effects still decrease the therapeutic utility. To overcome this problem, prodrug strategy has been applied. Prodrugs are masked derivatives of drug molecules that undergo enzymatic or chemical transformations to release the active parent drugs, which can exert the therapeutic activity. The cancer specific microenvironment can be used as a trigger of selective prodrug activation and hypoxia is a distinctive feature of various diseased cells including cancer.[1)]

We designed and synthesized three types of floxuridine prodrug monomers **FdU^{NO2}**, **FdU^{Azo}**, and **FdU^{NA}** bearing a nitrobenzyl group, 4-(dimethylamino)azobenzyl group, and 4-nitroazobenzyl group, respectively. **FdU^{NO2}** and **FdU^{Azo}** are directly reduced to the aniline intermediate and subsequent 1,6-elimination gives floxuridine. On the other hand, **FdU^{NA}** requires a two-phased reduction; the nitro group should be reduced at first because 4-nitroazobenzyl moiety is not a substrate of azoreductases. Only after the reduction of nitro group to amino group, the azo moiety of **FdU^{NA}** is reduced to give the aniline intermediate. As we expected, all three floxuridine prodrug monomers showed cytotoxicity only under hypoxia conditions (O_2 = 1%). We also synthesized and evaluated floxuridine prodrug oligomers and will discuss in vitro and in vivo results (Figure).



1) J. Liu, W. Bu, J. Shi, *Chem. Rev.* **2017**, *117*, 6160.