27O-ISMS23 **DFP-11207, a Novel Promising Antimetabolite by Using the Technology of Module Drug Discovery**

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For over 50 years, 5-fluorouracil (5-FU) has played a critical role in the systemic chemotherapy of various gastrointestinal cancers. Although systemic cytotoxics such as 5-FU can modestly prolong overall survival, but at the cost of unpleasant toxicities. Therefore better drug formulations are desirable by using the module drug-discovery technology. We developed a new conceptual fluoropyrimidine, DFP-11207 was engineered to reduce toxicity without loss of antitumor activity as well in addition to providing sustained concentrations of the active anti-cancer moiety. DFP-11207 contains three components in one formulation: 1-ethoxymethyl-5-fluorouracil (EM-FU) as a prodrug of 5-FU, 5-chloro-2,4-dihyroxypyridine (CDHP) as a potent inhibitor of 5-FU degradation and cytrazinic acid (CTA) as a gastrointestinal regulator of 5-FU phosphorylation. In in vitro studies using rat plasma, homogenates from rat liver and human tumor xenografts or intact tumor cells, DFP-11207 was rapidly hydrolyzed to 3 components and subsequently EM-FU was specifically converted to 5-FU by liver microsomes, and CDHP and CTA strongly inhibited 5-FU degradation and phosphorylation, respectively. Following consecutive oral administration to human tumor-bearing nude rats, DFP-11207 attained favorable antitumor efficacy and unique PK profiles with lack of toxicities such as diarrhea, thrombocytopenia and H&F syndrome and so on. In early clinical data, DFP-11207 was suggested that it was a promising compound and caught overcome the shortcomings of all other oral fluoropyrimidines.