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Novel insights into PepT1 transporter mediated dipeptide functionalized PLGA nanoparticles for docetaxel oral delivery

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Oral delivery of anticancer drug gained tremendous prominence in recent years owing to its good patients compliance and administration convenience. However, the severe irritation to gastrointestinal tract and the absorption barriers such as pH variation and enzymatic degradation and the low permeability across the intestinal epitheliums. To overcome these difficulties, we attempted to establish a PLGA based nanoplatform targeting the wide distributed oligopeptide transporter 1 (PepT1). PepT1 is a striking prodrug- designing target [1], for it plays an important role in the oral absorption of di-and tripeptides from the diet. At present, PepT1involved pharmaceutical strategies only restricted to peptidomimetic prodrugs [2]. However, no correlational studies based on nanoparticles were reported.

Firstly, we constructed functional copolymers with various ligand flexibility by synthesizing dipeptide with polyethylene glycol monostearate of different chain length (n=25, 40). To avoid the harsh environment of the GI tract, we selected PLGA as the main drug carrier and inserted the functionalized copolymer into the core. The docetaxel-loaded PLGA nanoparticles were prepared by a modified emulsion solvent-evaporation method. Particle size and zeta potential of nanoparticles were determined using laser diffraction (LD) method. The drug encapsulation efficiency was determined by HPLC. The morphology of the nanoparticles was visualized by transmission electron microscopy (TEM), and the status of docetaxel in nanoparticles was analyzed by X-ray powder diffraction. An *in vitro* release study was conducted by the dialysis method. Docking of the active ligand and the transporter was conducted to evaluate the binding

affinity for PepT1. Furthermore, the biodistribution of the modified nanoparticles was determined using coumarin 6 as the fluorescence probe.

The results of X-ray powder diffraction indicated that docetaxel was encapsulated in the nanoparticle mostly in the molecular or amorphous state. The docking experiments of the dipeptide ligand with transporter indicated that the selected dipeptide had a tight interaction with the target protein. And the result of the biodistribution experiment showed that the modified nanoparticles had an improved absoption in intestine of rats after oral administration.

This work evaluates the effects of transporter mediated strategy in oral delivery of anticancer drugs with poor membrane permeability and low oral bioavailability.

Keywords; PepT1 transporters; Ligand flexibility; PLGA nanoparticles; Docetaxel

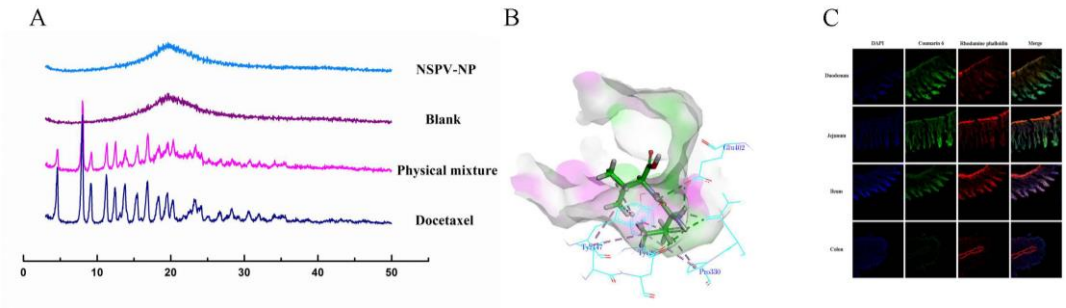

Fig.1. X-ray powder diffraction photograph (A), protein-ligand docking simulation (B) and biodistribution of the dipeptide decorated nanoparticles (C).

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