Worm-like and Spherical Micelles Made from the Same PEO-PCL:
Advantages of Paclitaxel Delivery Using Worm-like Micelles

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Statement of Purpose: Encapsulation of extremely hydrophobic drugs such as paclitaxel (taxol ®) using diblock polymer based micelles for delivery has been extensively studied. Currently most spherical micelle-encapsulated taxol cannot stably circulate for long time after administration. Using worm-like micelles with extended length may help resist the blood stream shear stress, delay the phagocytic clearance, and extend the taxol circulation to allow less frequent dosing and enhanced dose tolerance.

Methods: Both worm-like and spherical micelles were prepared from the diblock polymer poly (ethylene oxide)-poly (ε-caprolactone) (PEO-PCL, or OCL3). Taxol was loaded and the loading capacity and efficiency were determined using HPLC. Micelle stability and degradability were also evaluated. Human lung carcinoma A549 cells were used for *in vitro* cytotoxicity studies, with currently used Cremophor EL taxol formulation as a benchmark. Maximum tolerated dose (MTD) was determined in mice followed by tumor shrinkage studies in mice implanted with A549 tumor and administered with micelle-encapsulated taxol at MTD. Circulation and biodistribution after 24 hrs were performed for blood and several organs.

Results/Discussion: Worm-like micelles have an average extended length of 6-7 μm, and similar radius to spherical micelles made from the same OCL3 copolymer. Loaded with taxol, OCL3 micelles in both morphologies showed comparable anticancer activities against A549 cells *in vitro*, both of which showed 3-4 fold lower IC_{50} than Cremophor EL taxol and 12-13 fold lower IC_{50} than free taxol, while the empty micelles showed 6-7 fold less toxicity than Cremohpor EL. Both types of taxol-loaded micelles were stable for 1 month, and longer storage could be attained by freezing. In addition, worm-like micelles demonstrated a 50-100% higher taxol loading capacity than spherical micelles, and also a higher maximum tolerated dose (MTD) in mice than spherical micelles, which allowed the improved tumor shrinkage with higher administered taxol doses in *in vivo* studies. Circulation and biodistribution studies showed the extended taxol circulation in blood and the enhanced taxol accumulation in tumor associated with encapsulation in worm-like micelles compared to spherical micelles.

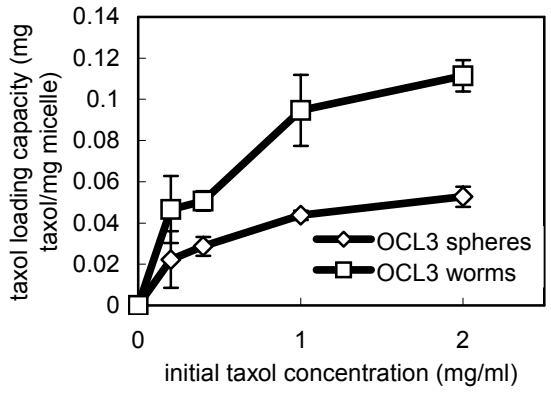

Figure 1. the loading capacity of taxol encapsulated into OCL3 spherical and worm-like micelles

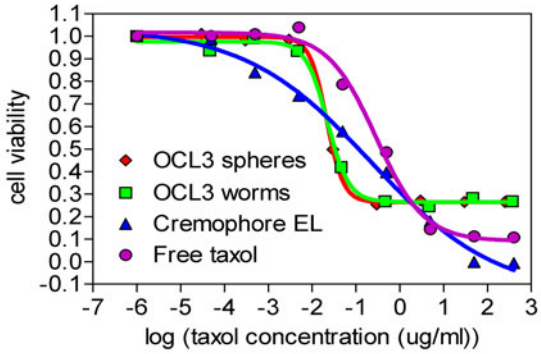

Figure 2. Cytotoxicity of taxol in different formulations against A549 celles. IC_{50} of taxol in OCL3 micelles were 3-4 fold lower than in Cremophor EL.

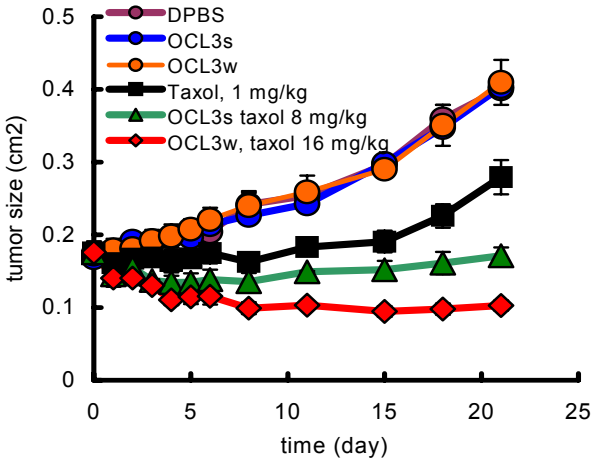

Figure 3. tumor shrinkage with taxol administered at MTD (free taxol 1 mg/kg, spherical micelles 8 mg/kg, worm-like micelles 16 mg/kg)

Conclusions: OCL3 polymeric micelles could be used as a better paclitaxel carrier with enhanced drug potency and reduced toxicity compared to Cremophor EL. Especially, OCL3 worm-like micelles have shown greater potential than spherical micelles of their ability to increase drug loading capacity, MTD, circulation in blood and accumulation in the tumor site.