Biodegradable Self-Assembled Nanoparticles for Targeted Delivery of Paclitaxel to Tumor Cells

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Statement of Purpsoe: Tumor vasculature has enhanced permeability and the clearance of macromolecules from the interstitial compartment is seriously compromised. Biodegradable nanoparticles (NPs) are especially attractive as a delivery system because they can be degraded by hydrolysis or enzymatic pathways to reduce their accumulation. Our laboratory has developed novel bioresorbable PLEOF macromers that self-assemble into NPs. PLEOF contains short lactide-co-glycolide and ethylene oxide blocks linked by fumaric acid units. After self-assembly, these nanoparticles can be crosslinked or grafted with cell-responsive biomolecules for targeted delivery of antitumor drugs. The purpose of this work was to determine uptake and biodistribution of NPs.

Methods: PLEOF macromers were in DMSO and self-assembled into NPs by dialysis against water. NPs were imaged by SEM and distribution was measured by light scattering. HCT116 cancer cells were cultured in McCoy's Medium supplemented with 10% FBS and harvested with trypsin/EDTA. For uptake experiments, HCT116 cancer cells were cultured in media containing NPs loaded with FITC-Dextran. Cells were stained with phallotoxin and DAPI and imaged by confocal laser scanning microscopy. Tumor cell cytotoxicity was determined by exposing the HCT116 cells to Paclitaxel-loaded nanoparticles in basal media and measuring cell viability by MTT assay with time.

Results and Discussion: The size of the NPs depended on the ratio of LG to EO blocks, as shown by SEM images of PLEOF90/10 (90% LG and 10% EO) and PLEOF70/30 in Figure 1. Size can be varied from 500 to 15 nm to tailor to a specific application by adjusting the LG to PEO ratio.

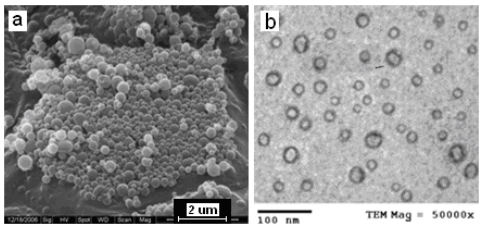

Figure 1. Images of PLEOF90/10 (a), PLEOF70/30 (b) NPs.

The time for complete degradation of the PLGEOF nanoparticles can be varied from 3 to >36 weeks simply by changing the lactide to glycolide ratio in the macromer and release profile was consistent with their degradation. The images of the HCT116 cell nucleus (blue) cytoskeleton (red), FITC (green; fluorescence of nanoparticles), and the composite image (all three colors) are shown in Figures 4. These images demonstrate that nanoparticles are internalized by tumor cells (green fluorescence of the nanoparticles coincides with red fluorescence of cytoskeleton).

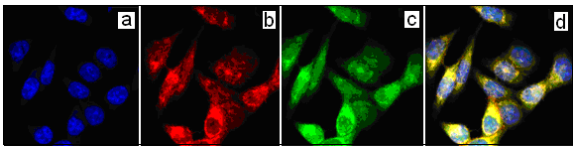

Figure 2. Image of tumor cells incubated with FITC-Dextran PLEOF NPs for 2 h: (a) cell nucleus, (b) cytoskeleton, (c) NPs, and composite image (d).

Figure 3 compares viability of HCT116 cells incubated with 10 and 40 ug/ml Paclitaxel (light and dark blue) with those incubated with the same concentration of in PLGEOFNPs (orange and red). Light (low dose) and dark (high dose) green curves show cells viability incubated with NPs alone. Clearly, tumor cell cytotoxicity is lower when Paclitaxel is delivered with NPs.

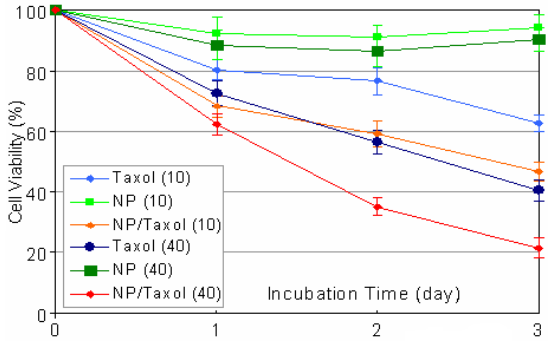

Figure 3. Cell viability of tumor cells incubated with Paclitaxel Loaded NPs.

Near-infrared image (800 nm wavelength) of the ApcMin/+ mouse injected with 500 µl of the PLAF/PLEOF NPs encapsulated with IRDye 800RS Carboxylate dye (peak absorption at 786 nm) is shown in Figure 4. The NPs suspension was injected in the mouse tail vein and scanned 4 h after injection. The intensities are displayed in pseudo colors to isolate regions of interest. The infrared intensity in the intestinal region was at least 100 times higher than the other regions.

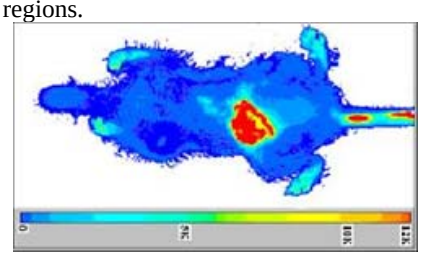

Figure 4. Near infrared scan of the ApcMin/+ mouse injected with NPs encapsulated with the IRDye dye.

Conclusion: Results demonstrate that NPs facilitate the uptake of Paclitaxel by tumor cells.

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