EXPANSILE NANOPARTICLES: SYNTHESIS, CHARACTERIZATION, AND IN VIVO EFFICACY

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Statement of Purpose: Nanoparticles are finding increased uses in drug delivery applications as a means to improve patient care.[1,2] These particles, depending on the application, are composed of hydroxy acid polymers, lipids, proteins, or carbohydrates. For example, nanoparticles composed of poly(lactic-glycolic acid), PLGA, are well studied for drug delivery and represent the prototypical polymer particle. We are interested in designing new nanoparticle compositions that possess an alternative delivery mechanism whereby a hydrophobic to hydrophilic transition is triggered, resulting in a swelled or expanded polymeric structure. As our clinical interest lies in the prevention of tumor recurrence following resection, we have evaluated these nanoparticles in models mimicking microscopic disease, akin to residual occult tumor that can remain at the resection margin following surgery, and a true recurrence model.
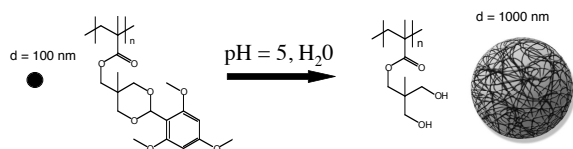

Figure 1. Proposed mechanism for the expansile nanoparticles

Methods: The expansile nanoparticles (eNP) were prepared by first creating a miniemulsion by sonication and then photopolymerizing to crosslink the polymer in the presence of a photoinitiator.[3] The resulting polymeric nanoparticles were then dialyzed against 5 mM, pH 8.5 phosphate buffer over two days to remove excess surfactant and salts. Dynamic light scattering (DLS) measurements revealed suspensions of small monodisperse nanoparticles ≈100 nm in diameter.

Results: Exposure of the nanoparticles to buffered aqueous solutions of pH 4, 5, or 7.4, over 24 hours at 37 °C followed by particle sizing using DLS showed that NPs swell to ≈ 1000 nm at mildly acidic conditions but not at pH 7.4 (Figure 2). Next, we used freeze-fracture TEM (FF-TEM) to observe the morphological changes that occur when the eNP swell in response to a low pH environment and as shown in Figure 2, a swollen structure was observed. Expansile nanoparticles were then loaded with paclitaxel, a poorly water-soluble anticancer drug, and were cytotoxic to a number of different cancer cell lines – LLC, A549, MSTO, etc. Finally, paclitaxel loaded expansile nanoparticles (Pax eNP) were evaluated in lung and mesothelioma *in vivo* animal models and were
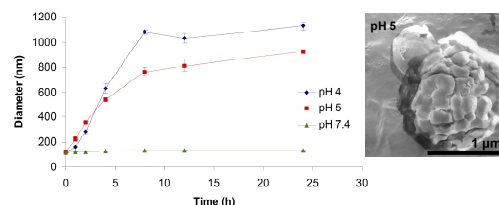

Figure 2. (left) Swelling of the eNP as a function of pH and time at 37 °C. Data displayed as mean ± SD; n=3. (right) FF-TEM images of eNP after exposure to pH 5 solution.

superior in performance to the conventional drug delivery method for paclitaxel using Cremophor EL/ethanol.

Conclusions: Polymeric nanoparticles that expand in response to a mildly acidic pH have been synthesized, characterized, and evaluated *in vivo*. The hydrophobic anti-cancer drug, paclitaxel, was encapsulated within these nanoparticles and was released upon this pH triggered hydrophobic to hydrophilic transition. The paclitaxel loaded expansile nanoparticles were superior over the standard-of-care method for paclitaxel delivery using Cremophor EL/ethanol in two animal models. This new delivery approach and vehicle allow localized delivery of drug with low systemic exposure and high efficacy.

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