Targeting and Treating Bone Metastases using Layer-by-Layer functionalized Nanoparticles

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Statement of Purpose: Many cancer types, including the most common – lung, breast, and prostate, have a high proclivity towards development of metastases that localize in bone, characteristic of terminal-stage cancer.[1] This redistribution of cells from the primary tumor presents a significant drug delivery challenge that has yielded few promising systems.[2,3] Utilizing bisphosphonates, which are materials that have a high affinity for mineralized bone surfaces and inhibit bone resorption, this work seeks to develop a new approach towards targeting and treating bone metastases via systemically-administered, alendronate-targeted layer-by-layer functionalized nanoparticles.

Methods: Nanoparticles were functionalized using layer-by-layer assembly. Briefly, materials with complementary functionality are sequentially adsorbed on the surface of the nanoparticles. Targeting was achieved by incorporating poly(acrylic acid)-alendronate functionalized polymer as the anionic film component and terminal layer.

Results: Functionalized quantum dots were synthesized and shown to bind bone (coordinate calcium) both *in vitro* and *in vivo*, as shown in Figure 1.

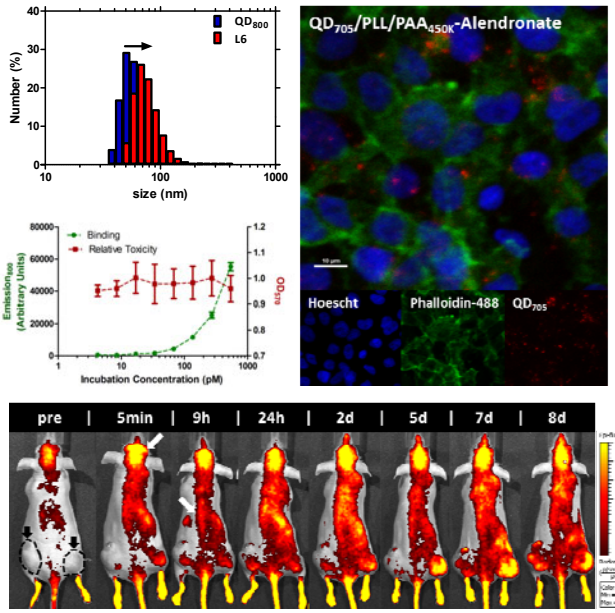

Figure 1. (A) Sizing pre- and post-functionlization. (B) Confocal microscopy of nanoparticle internalization. (C) *in vitro* binding and cytotoxicity. (D) *in vivo* targeting and localization in osteosarcoma xenografts.

Consistent with these results, blank liposomal systems functionalized with the same film constitutents exhibited significant levels of cell binding and uptake *in vitro* and *in vivo*, as shown in Figure 2. Current efforts are focused on incorporating cytoxotic agents in these systems for evaluation of therapeutic efficacy in addition to targeting capabilities.

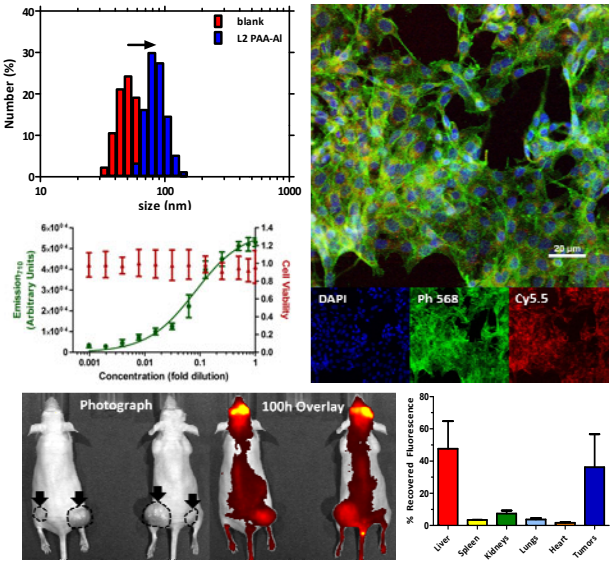

Figure 2. (A) Sizing pre- and post-functionalization. (B) Confocal microscopy of nanoparticle internalization. (C) *in vitro* binding and cytotoxicity. (D) *in vivo* binding and localization in osteosarcoma xenograft. (E) Biodistribution data, based on fluorescence recovery.

Conclusions: This work demonstrates alendronate-functionalized nanoparticles as having high affinity for bone, appreciably accumulating in bony regions and osteosarcoma xenografts over the course of several days *in vivo*. As such, this system is a promising technology for the potential targeted treatment of bone metastases.

References:

[1]Mundy, G.R. *Nature Reviews*. 2002 (2), 584-593.
[2]Torres Martin de Rosales, R. et al. *Bioconjugate Chemistry*. 2011 (22), 455-465.
[3]Ramanlal Chaudhari, K. et al. *Journal of Controlled Release*. 2012 (158), 470-478.

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