

**SBC2013-14531****TARGETING THE TUMOR-DRAINING LYMPH NODE WITH ADJUVANT NANOPARTICLES FOR CANCER IMMUNOTHERAPY****Susan N. Thomas**Georgia Institute of Technology  
Atlanta, GA 30332  
USA

**Introduction:** Immunotherapy-based approaches for cancer treatment are of increasing clinical interest. Principles of drug delivery and the emerging field of material design for immunomodulation might hold significant promise for novel approaches in cancer immunotherapy since biomaterials engineering strategies enable enhanced delivery of immune modulatory agents to tissues and cells of the immune system<sup>1</sup>. One tissue of significant clinical interest in a cancer setting is the tumor-draining lymph node (TDLN), which participates in cancer progression by enabling both metastatic dissemination as well as tumor-induced immune escape. Hence, the TDLN represents a novel target for drug delivery schemes for cancer immunotherapy. We hypothesize that targeted delivery of adjuvants (Adjs) to the TDLN using a biomaterials-based approach might promote antitumor immunity and hinder tumor growth.

**Materials and Methods:** To deliver immune stimulatory adjuvants to the TDLN, we implemented poly(propylene) sulfide (PPS)-core nanoparticles (NPs) that target immune cells within the TDLN in an *in vivo* murine melanoma model when administered in the limb ipsilateral (i.l.) but not contralateral (c.l.) to the tumor (Figure 1A-B). NPs are composed of the polymer polypropylene sulfide (PPS) to form the hydrophobic

core, surface stabilized with Pluronic<sup>2</sup>. We incorporated either of two immune modulatory Adjs into the NPs by solvent dispersion or pyridyl disulfide covalent conjugation. First, we explored the use of paclitaxel (PXL), a widely used chemotherapeutic, that has more recently been described to enhance vaccine efficacy and function as a toll-like receptor (TLR) 4 ligand. Second, we implemented unmethylated DNA oligonucleotides (CpG) that induce robust inflammatory immune reactions via TLR9 ligand activity. We assessed the effect of targeted delivery of immunomodulatory Adjs using the NP technology to the TDLN and their induced immune response and resulting affect on tumor progression.

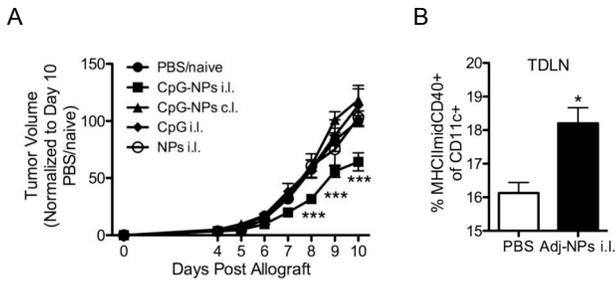
**Results and Discussion:** Both types of Adj-NPs, PXL-NPs and CpG-NPs, were capable of inducing immune reactions *in vitro*, as indicated by CD11c<sup>+</sup> cell maturation and inflammatory cytokine IL-12 production. When applied to the limb of mice i.l. to the tumor daily after tumor establishment at low doses (~0.5 mg/kg and 2.5 µg/mouse for PXL and CpG, respectively), Adj-NPs slowed tumor growth (Figure 1A) and reshaped the immune milieu inside both the TDLN and tumor (Figure 1B and data not shown). Specifically, treatment of the TDLN via administration of Adj-NPs in the i.l. limb induced CD11c<sup>+</sup> cell maturation within the TDLN,

increased the frequency of activated and antigen-specific CD8<sup>+</sup> T cells within the tumor, and reshaped the T cell distribution within both the TDLNs and tumor towards an inflammatory T<sub>H</sub>1 phenotype. Furthermore, reduced tumor growth required Adj delivery to the TDLN via the NP technology because application of Adj-NPs to the c.l. limb (targeting non-tumor draining LNs) or free Adj in the i.l. limb failed to slow tumor growth. No effect on tumor growth was observed with treatment of the i.l. limb with plain NPs or Adj mixed with NPs (Figure 1A). Hence reduced tumor burden results from the ability of the NPs to deliver Adj to immune cells in to the TDLN which in turn inhibits tumor-induced immune suppression.

**Conclusions:** Together, this work implicates the TDLN as a novel drug delivery target for immunotherapy of solid tumors. Moreover, these data indicate that biomaterials engineering strategies can enhance the potential of Adjs in the effective activation of immune reactions against tumors for cancer immunotherapy applications.

**References:** <sup>1</sup>Hubbell JA, Thomas SN, Swartz MA. Nature. 2009; 462:449-60.

<sup>2</sup>Rehor A, et al. Langmuir 2005; 21, 411-417



**Figure 1.** **A**, B16F10 melanoma tumor growth is slowed by treatment in the i.l. but not c.l. limb with Adj-NPs. **B**, CD11c<sup>+</sup> maturation within the TDLN is enhanced by treatment in the i.l. limb with Adj-NPs, indicating that Adj-NPs retain their immune stimulatory activity *in vivo*.