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Induction of Endothelial Tightening to Limit Off-Target Deposition of Nanomedicines

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Introduction:

For decades now, nanomedicines have been billed as the future of cancer therapy. However, the field of tumor-targeted nanomedicine has failed to significantly advance toward becoming the gold standard of cancer treatment. The largest obstacle that has yet to be overcome is off-target accumulation of the nanoparticles. The truth about most nanomedicines, particularly chemotherapeutics, is that only ~1% of the dose will end up in the target tissue[1]. Even with engineered "stealth" formulations most of the dose will be taken-up by the liver, spleen, and other major organs. Today, chemotherapeutic nanomedicines are still highly dose limited due to off-target toxicities.

We propose a novel approach to "targeting" nanomedicines by focusing on decreasing off-target accumulation rather than directly increasing tumor delivery. Recent studies in the field of virology have revealed a novel anti-viral phenotype in epithelial cells that limits the spread of viruses. Changes induced by an anti-viral type III interferon (IFN-λ) lead to tightening of endothelial/epithelial junctions that limits the ability of viral particles to diffuse into tissues. We hypothesize that by harnessing this effect it will be possible to limit off-target accumulation and toxicity of nanomedicines. With a decrease in off-target deposition the nanomedicine will have an increased circulation time leading to greater tumor accumulation.

[1] S. Wilhelm, A.J. Tavares, Q. Dai, S. Ohta, J. Audet, H.F. Dvorak, W.C.W. Chan, Analysis of nanoparticle delivery to tumours, Nature Reviews 1(May 2016) (2016) 1-12.

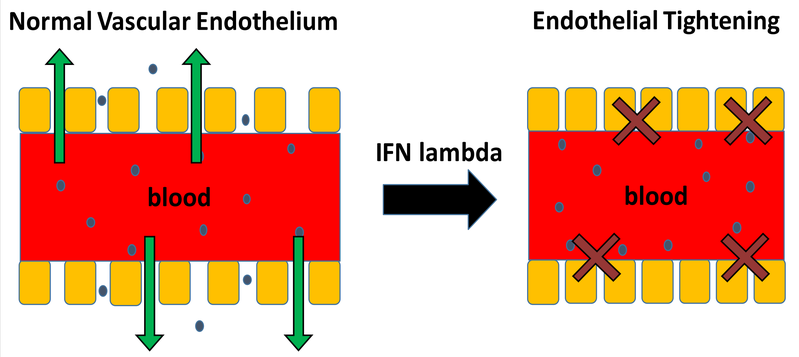

Figure 1. Diagram of endothelial tightening that prevents paracellular transport of viruses and nanoparticles.

Hypothesis:

Intravenous injection of a formulated virus-like nanoparticle will induce a systemic anti-viral endothelial "tightening" event. However, due to the dysregulation of the vasculature in the tumor microenvironment, tightening will not occur in the tumor endothelium. After endothelial tightening is engaged a subsequently administered nanomedicine will show a decrease in off-target deposition and increase in tumor accumulation.

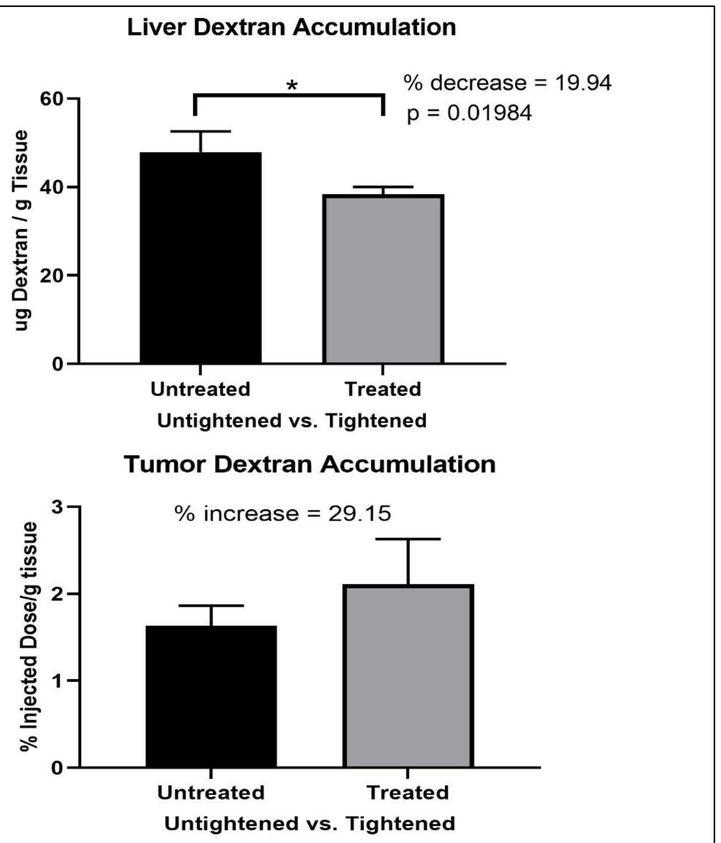

Figure 2. Quantification of FITC-labeled dextran per gram of tissue (150kD, 10mg/kg) with or without lipoplex pretreatment. (Untreated n = 4) (Treated n = 3). Mice were injected with PBS or lipoplexes followed by FITC-labeled dextran 24h later. Mice were sacrificed 24 h after dextran injection. Dextran was then extracted from the tissues and quantified using fluorescence analysis.

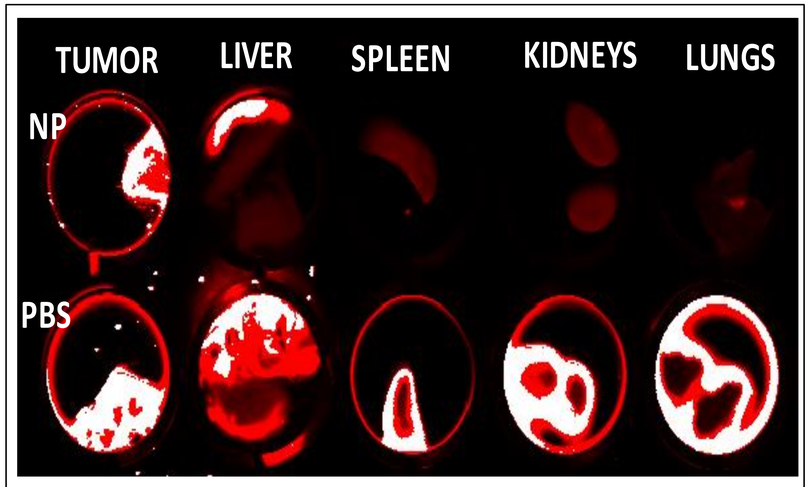

Figure 3. Dextran accumulation in tumor-bearing mice after endothelial tightening. Mice were injected with either PEGylated lipoplexes (NP) or PBS, followed by DIR-labelled dextran (100kD; 3-day interval).

Results:

A viral-like nanoparticle (DAPC 20:0, Sphingosine 18:1, Cholesterol, C16 PEG750-Ceramide liposomes complexed with plasmid DNA) pretreatment leads to a dramatic increase in tumor accumulation of a subsequently administered particle (i.e. 150kD FITC-Dextran ~75nm diameter). Additionally, our data shows a significant decrease in liver accumulation. These results clearly demonstrate that a "tightening" pretreatment can be used to reduce off-target deposition and increase tumor accumulation of a subsequent nanoparticle injection.

Future Directions:

Quantify the accumulation and efficacy of a chemotherapeutic nanomedicine in organ and tumor tissues with or without "tightening" in a murine cancer model.

a) Quantify the accumulation of Doxil in organs/tissues.
b) Compare the efficacy of a "tightening" pretreatment + Doxil to a standard Doxil treatment.
c) Determine changes in toxicity between treatments.

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