



TOXIC OR HELPFUL? EXPLORING THE BODY'S RESPONSE TO VIRUS-LIKE NANOPARTICLES

Scott Tilden

Background:

- A poorly understood “refractory” response to intravenously injected lipid nanoparticles conjugated to gene therapy vectors (lipoplexes) leads to reduced organ accumulation of subsequently administered lipoplexes.
- This response may be an anti-viral reaction to lipoplexes, due to their virus-like characteristics, that specifically “tightens” the endothelium in healthy tissues to restrict paracellular transport and limit potential viral spread.
- From a drug delivery standpoint, limiting organ accumulation of potentially toxic chemotherapeutic nanoparticles could be beneficial.
- By initiating this “refractory” response it may be possible to systemically limit nanoparticle accumulation while simultaneously leaving tumor accumulation unaltered due to the heavily immunosuppressed microenvironment of the tumor.
- To quantify the effects of this response I compared organ and tumor accumulation of I.V. administered FITC-dextran, commonly used to quantify paracellular permeability, between lipoplex or PBS treated mice.

Hypothesis:

- Intravenous injection of a virus-like nanoparticle will induce an anti-viral response that will limit major organ deposition of a subsequently administered particle while simultaneously increasing tumor accumulation.

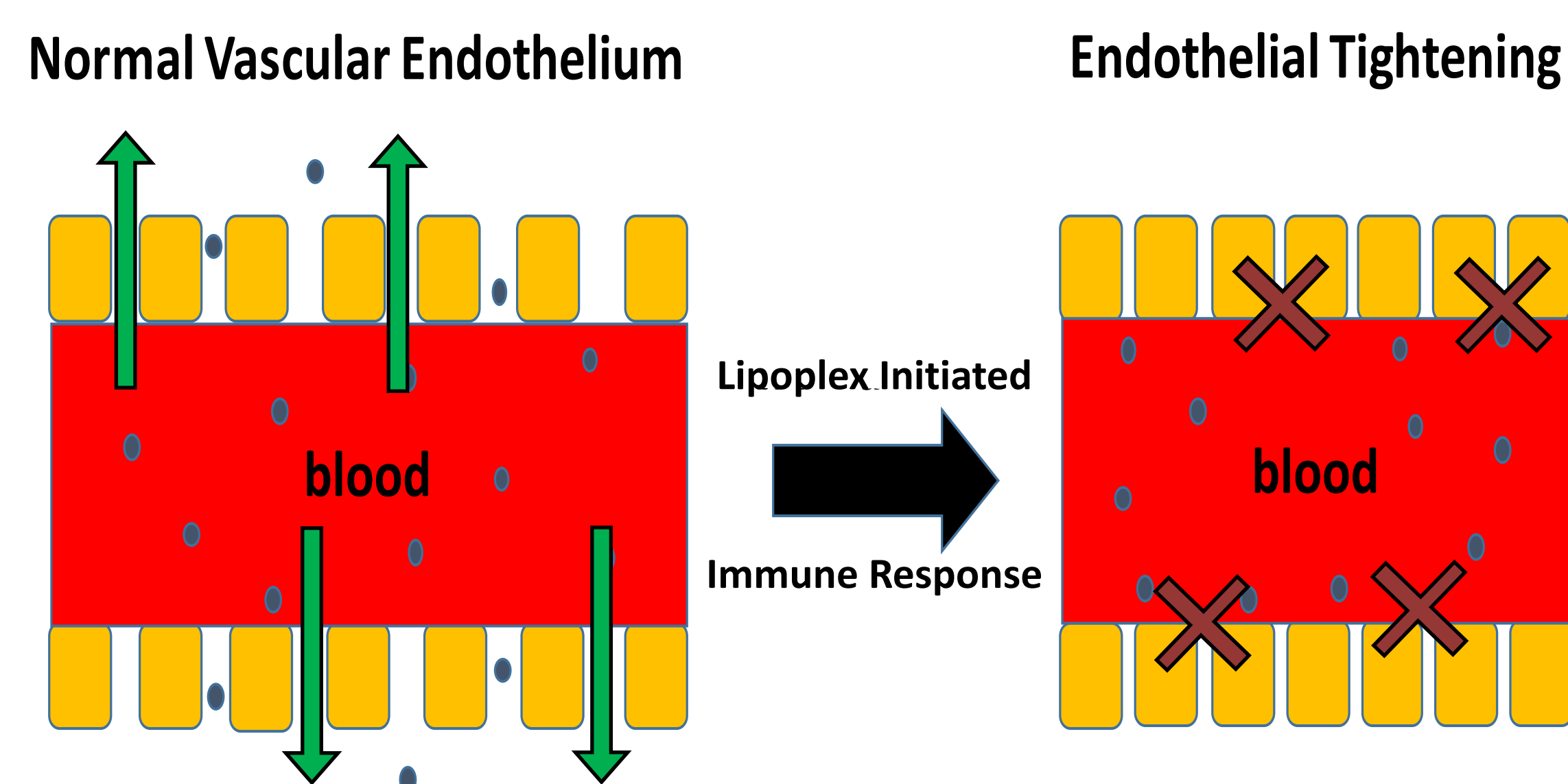


Figure 1. Diagram of immune reaction to lipoplexes “tightening” the endothelium and shutting down paracellular transport of viruses and nanoparticles.

Methods:

- PBS or liposome (DAPC 20:0, Sphingosine 18:1, Cholesterol, C16 PEG750-Ceramide) or lipoplexes (liposomes complexed with plasmid DNA) were injected in immunocompetent Balb/c mice bearing CT26 subcutaneous tumors.
- 24h after treatment, FITC-Dextran (~100nm hydrodynamic diameter) was injected.
- 24h after the dextran injection, organs were extracted and FITC fluorescence quantified.

Lipoplex Pretreatment Significantly Reduces Dextran Accumulation In Major Organs, While...

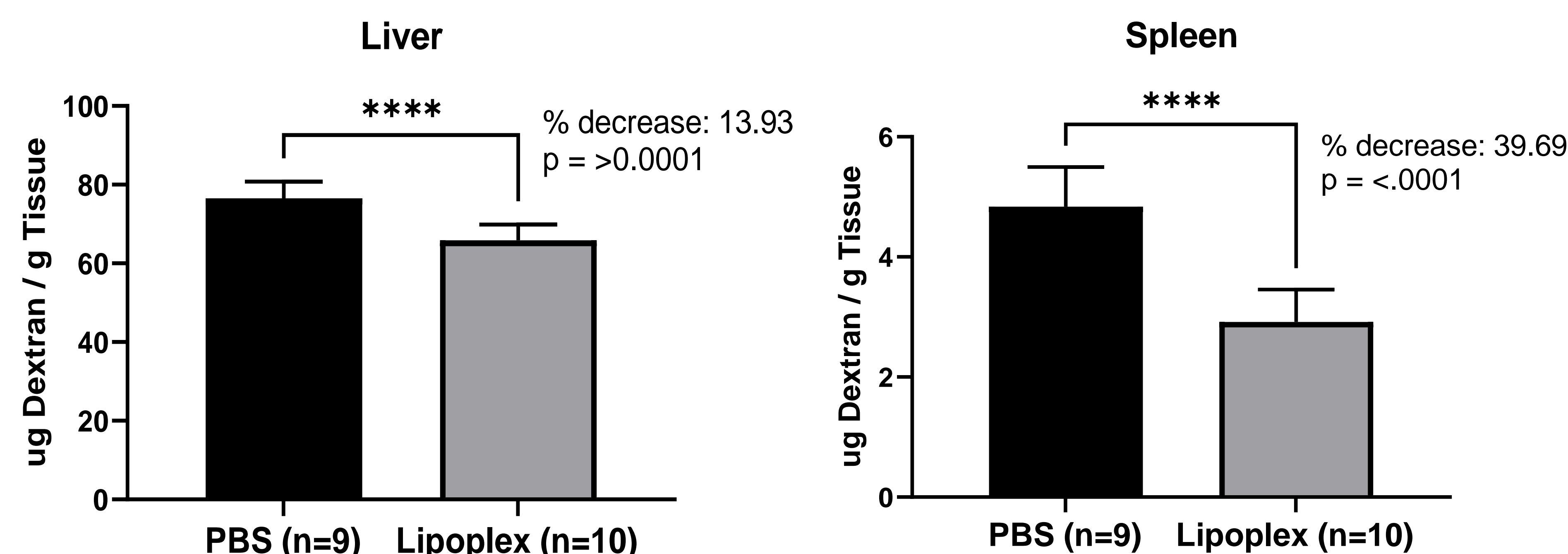


Figure 2. Accumulation of dextran per gram of liver and/or spleen tissue, 24 hours after PBS or Lipoplex pretreatment.

Simultaneously Increasing Tumor Accumulation

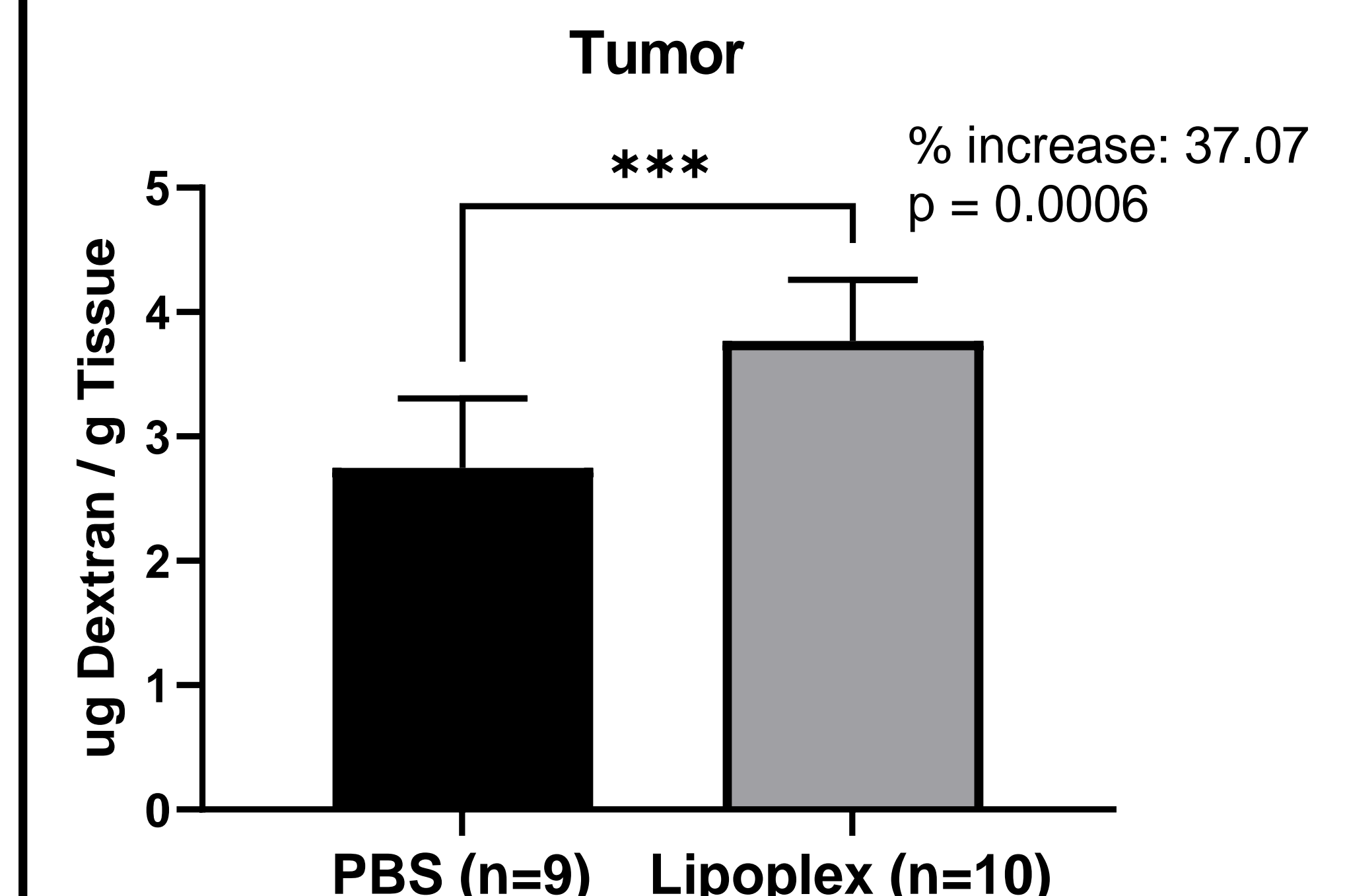


Figure 3. Dextran per gram of tumor tissue, 24 hours after treatment.

Organ Accumulation Decrease with Simultaneous Tumor Accumulation Increase Is Dependent On Pretreatment DNA Content

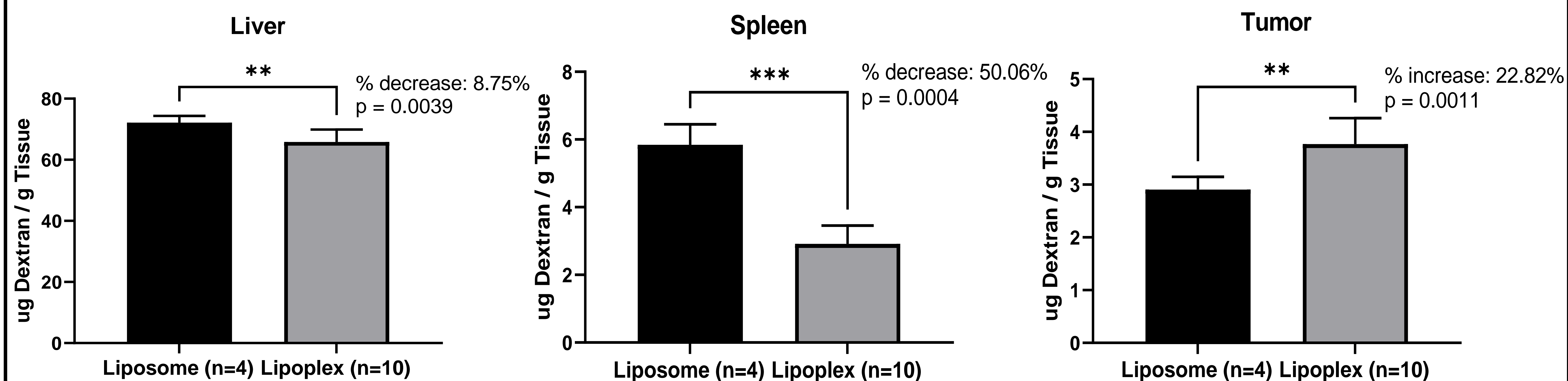


Figure 4. Accumulation of dextran per gram of liver/spleen/tumor tissue, 24 hours after Liposome (- DNA) or Lipoplex (+ DNA) pretreatment.

Lipoplex Pretreatment Increases Tumor to Major Organ Dextran Accumulation Ratio

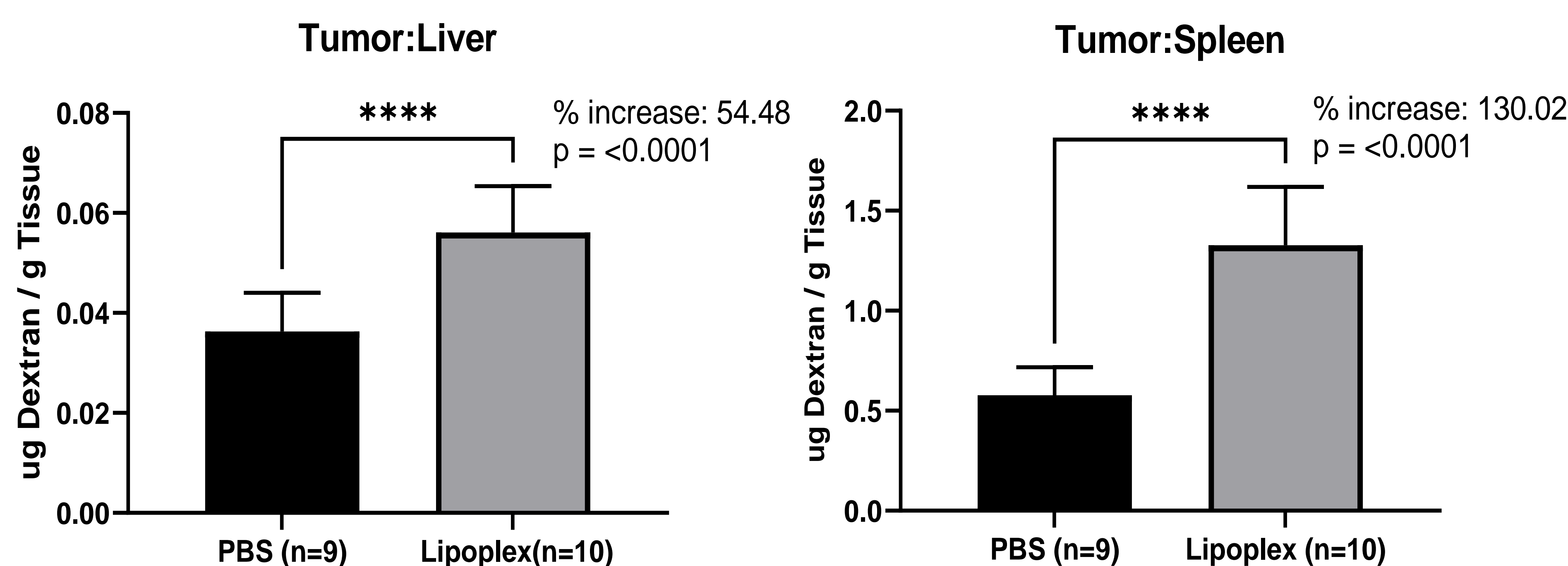


Figure 5. Ratio of dextran accumulation when comparing tumor to liver/spleen, 24 hours after PBS or Lipoplex pretreatment.

Future Directions:

- Characterize the cytokine and interferon response to lipoplexes.
- Elucidate the molecular mechanism of endothelial “tightening” with specific regard to paracellular pathways.
- Determine if a lipoplex pretreatment can improve toxicity and efficacy of a chemotherapeutic nanomedicine (i.e., Doxil/Myocet) in a mouse tumor model.

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