Bladder tumor metabolic alterations in response to IFNα gene therapy predict clinical disease response and identify clinically targetable tumor escape pathways

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Introduction

•Intravesical interferon-alpha (IFNα) gene therapy with Nadofaragene firadenovec has shown clinical efficacy in patients with non-muscle invasive bladder cancer (NMIBC) in a phase 3 clinical trial

•Improving IFNα gene therapy against bladder cancer requires an understanding of oncogenic pathways capable of creating tumor resistance

Objective

•To evaluate the impact of IFNα gene therapy on bladder tumor glucose and lipid metabolism *in vitro, in vivo,* and in patients to elucidate mechanisms of tumor resistance and identify predictive biomarkers

Methods

•*In vitro* models utilized murine bladder cancer cell lines treated with recombinant IFNα (rIFNα) and lentiviral IFNα (LV-IFNα) and analyzed by whole-transcriptome sequencing, glucose uptake, and lactate production

•*In vivo* models utilized MB49 flank tumors treated with Poly(I:C) (potent IFNα inducer) and analyzed by whole-transcriptome sequencing to assess effects of IFNα therapy on tumor metabolism and lipidomics. Differential expression of candidate lipid classes was analyzed from the lipidomics data

•Lipidomic profiling was performed on NMIBC patient urine samples after intravesical Nadofaragene firadenovec (7 clinical responders and 6 non-responders) to assess for clinically-relevant differences in lipid metabolism

A) *In vitro* Results

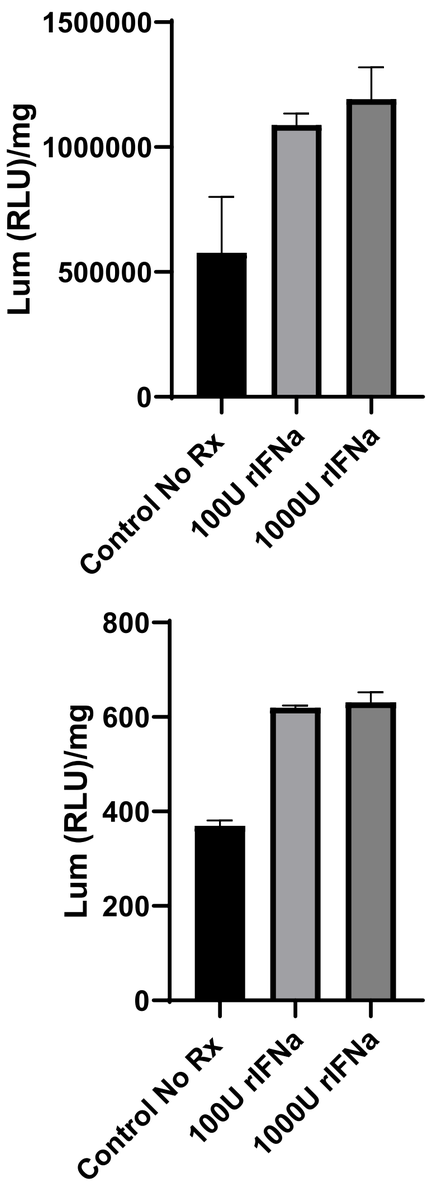

Figure 1: Increased glucose uptake (upper) and supernatant lactate levels (lower) for MB49 cells treated with IFNα in vitro.

B) *In vivo* Results

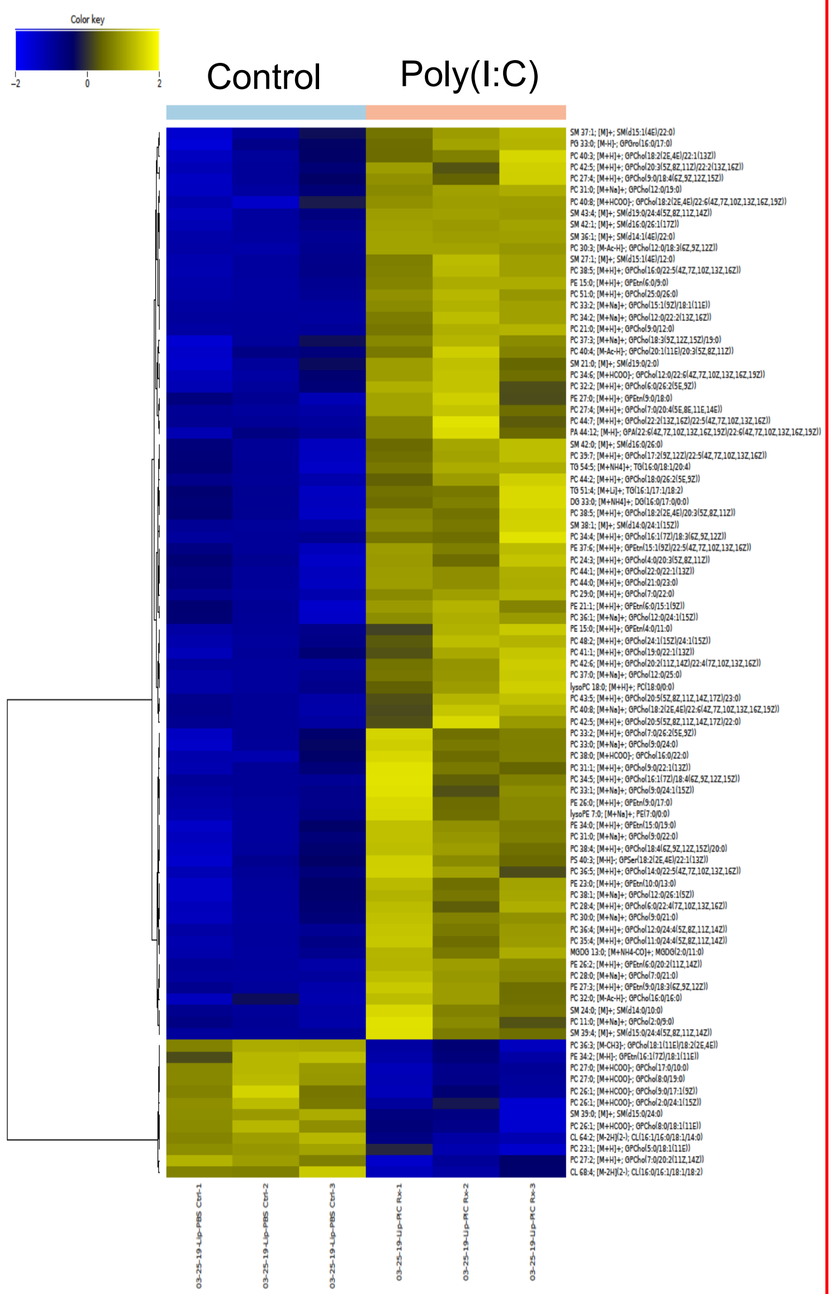

Figure 2: Lipidomic gene expression heatmap from murine MB49 tumors treated with poly(I:C) showing significant upregulation of 79 lipids (including phosphatidyl choline, sphingomyelin, and phosphatidyl ethanolamine), and downregulation of 12 lipids including cardiolipin.

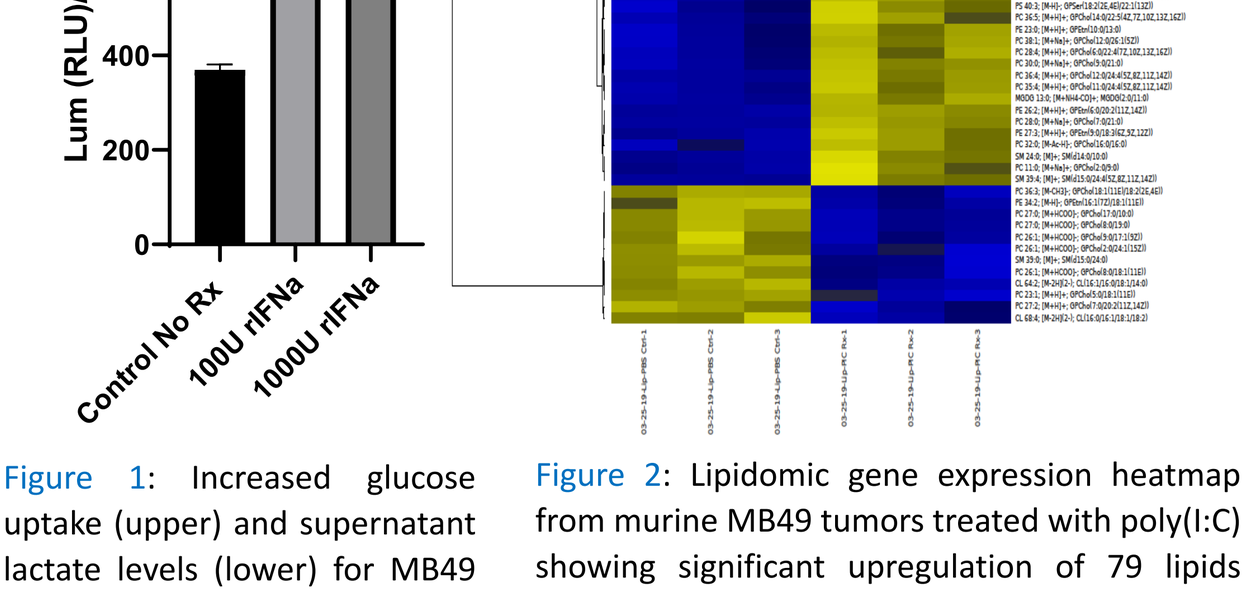

Figure 3: Quantitative representation of multiple lipid classes from MB49 murine tumors after treatment with poly(I:C) or control. SM- Sphingomyelin, TG- Triglycerides, PE- Phosphatidyl ethanolamine, PC- Phosphatidyl choline, CL- Cardiolipin.

C) Clinical Results

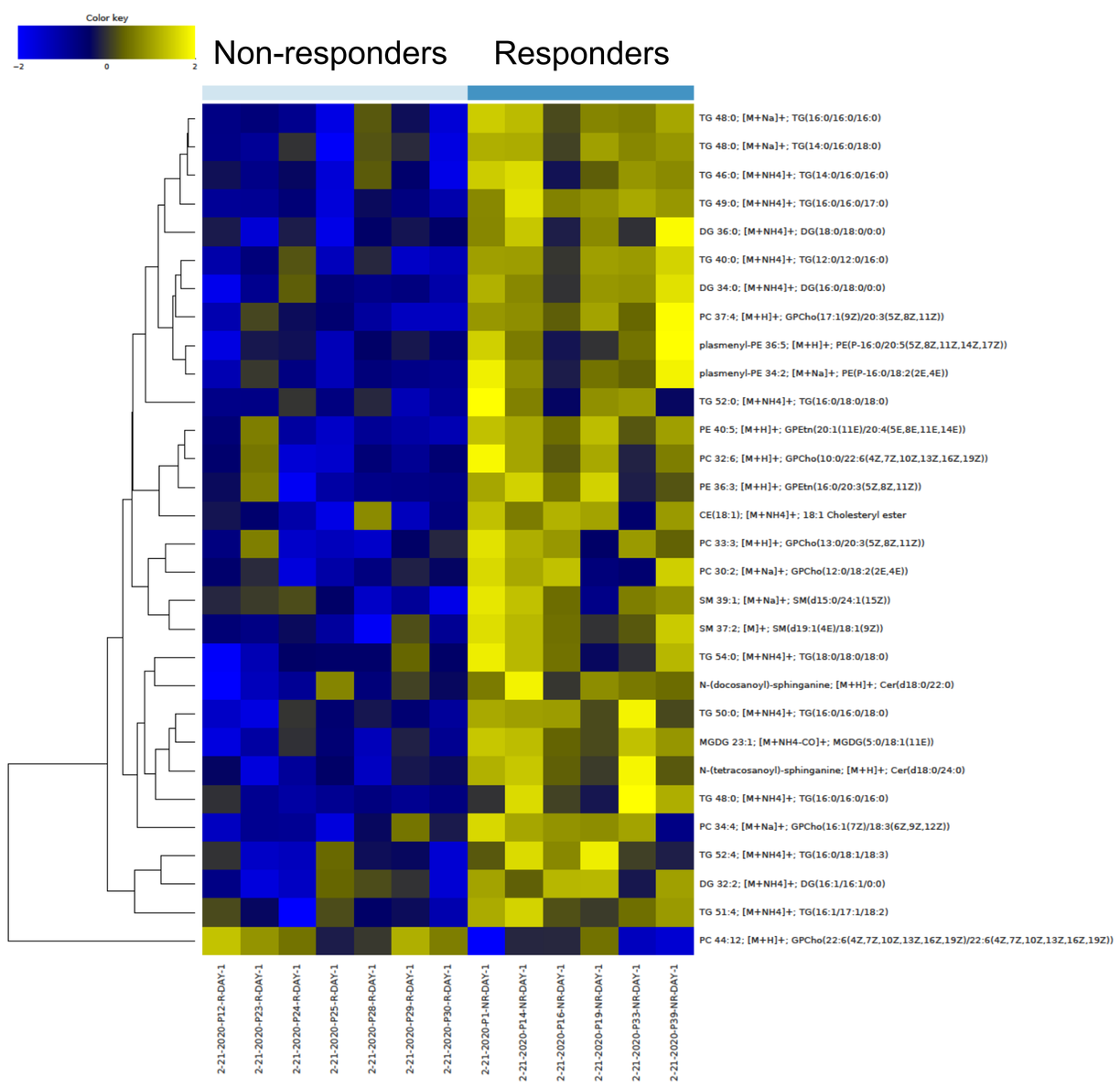

Figure 4: Lipidomics performed on patient urine samples collected pre-treatment and day one post-treatment with intravesical Nadofaragene firadenovec detected >592 lipids with distinct expression profiles differentiating those who ultimately became clinical responders versus non-responders. Clinical responders achieved 12-month recurrence-free survival from high-grade disease.

Conclusions

•*In vitro* IFNα gene therapy against bladder cancer cell lines induces increases uptake of glucose and lactate production, as well as upregulation of genes involved in glycolysis and downregulation of genes involved in fatty acid synthesis

•Lipidomic gene expression profiling of MB49 tumors treated with the IFNα inducer Poly(I:C) shows significant upregulation of multiple lipid families including phosphatidyl choline, sphingomyelin, and phosphatidyl ethanolamine, and downregulation of multiple lipid families including cardiolipin

•Urine lipiodomic profiles from NMIBC patients treated with Nadofaragene firadenovec show differential expression profiles for hundreds of lipids capable of differentiating clinical responders from non-responders as early as one day after therapy

References

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2) Shore *et al*. Intravesical rAd-IFNα/Syn3 for Patients With High-Grade, Bacillus Calmette-Guerin-Refractory or Relapsed Non-Muscle-Invasive Bladder Cancer: A Phase II Randomized Study. *Journal of Clinical Oncology* 2017.