activity was potent across a broad concentration spectrum and corresponded directly with B7H3 target expression. These studies represent the proof-of-concept of a novel pairing of off-the-shelf, engineered iNK cells with B7H3-directed pancreatic cancer engager molecules (TriKeEs and CARs) to enhance specificity, persistence and anti-tumor function.

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### 471 PANCREATIC CANCER THERAPY BASED ON COMBINATION OF DNA VACCINATION AND PI3KGAMMA INHIBITION

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**Background** Pancreatic ductal adenocarcinoma (PDA) is the 4th leading cause of cancer mortality in developed countries, with one of the poorest prognoses among all cancers. Although 10–15% of patients are candidates for gross total surgical resection, recurrence is frequent, and the overall 5-year survival rate is around 8%. Using a proteomic approach, we have identified alpha-Enolase 1 (ENO1) as PDA-associated antigens. We have shown that ENO1 DNA vaccination efficiently prolongs survival of engineered mice that spontaneously develop PDA (both KC and KPC mice). Recently, we have demonstrated that PI3K gamma play a critical role in PDA by driving the recruitment of myeloid derived suppressor cells into tumor tissues and it’s genetic or pharmacologic inhibition effectively inhibits PDA progression and metastasis. In this study we assessed the hypothesis that targeting myeloid derived suppressor cells, via pharmacological PI3Kgamma inhibition, synergizes with ENO1 DNA vaccination by inducing a strong and sustained immune response.

**Methods** KPC mice were vaccinated 4 times with ENO1 starting at 4 weeks of age; 2 weeks after the last immunization mice were treated with the PI3Kgamma inhibitor TG100-115 (2.5 mg/kg), for further two weeks. At sacrifice necroplastic lesions, immune infiltrate, T and B cell response were analyzed.

**Results** Mice that received ENO1 and TG100-115 therapy showed a significant decrease in tumor size compared to both ENO1 and PBS treated mice. Moreover, the analysis of pancreas tissues indicated that combined therapy induced an increased number of CD8 and F4/80 cells and a decrease of cancer tissues indicated that combined therapy induced an increase of Granzyme B in both ENO1 and ENO1+TG100-115 and a down modulation of genes involved in fibroblast activation, suggesting a modulation of microenvironment in the combined therapy group.

**Conclusions** Treatment with ENO1 plus TG100-115 is able to reduce tumor size in pancreas, increase immune cell infiltration and modulate stroma cell compartment, making the therapy a suitable approach for PDA treatment.

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**Ethics Approval** All animal experiments were approved by the University of Torino, Italian Ministry of Health and performed in accordance with EU laws in the animal facility of the Molecular Biotechnology Center (MBC). Reference no: 378/2015-PR and 597/2019-PR.

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### 472 IMMUNOPET-INFORMED SEQUENCE FOR FOCUSED ULTRASOUND-TARGETED MCD47 BLOCKADE CONTROLS GLIOMA


**Background** The natural disease course for glioblastoma (GB) entails invariably grim outcomes for patients. Phagocytic immunotherapies, such as CD47 blockade (e.g. mCD47), have recently demonstrated promise for GB therapy. However, their efficacy is challenged by presence of the blood brain and tumor barriers (BBB/BBT). Transient disruption of the BBB/BBT via focused ultrasound (FUS) and circulating microbubbles (MB) holds promise for improving therapeutic outcomes in the context of mCD47. However, critical questions regarding the optimal protocol for therapeutic antibody delivery with FUS remain. We herein leverage immuno-PET imaging to spatiotemporally map [89Zr]-mCD47 delivery across the BBB/BBT with FUS in an orthotopic GB model. We then use these insights to design a combinatorial paradigm for mCD47 delivery with repeat FUS BBB/BBT-D.

**Methods** MRI-guided FUS BBB/BBT-D was performed in the presence of systemically circulating MBs in mice with orthotopically implanted GL261 tumors. Mice received i.v. [89Zr]-mCD47 either without FUS, immediately prior to FUS [FUSPRE] or following FUS [FUSPOST]. Subsequently, mice underwent serial PET/CT imaging followed by terminal ex vivo assessment of antibody biodistribution. A therapeutic paradigm was then executed, wherein GL261-bearing mice received i.v. mCD47 (8 mg/kg) either as monotherapy or in combination with FUS BBB/BBT-D over three sessions spaced three days apart. Overall survival was monitored and tumor outgrowth was tracked via serial contrast-enhanced MRI.

**Results** Contrast-enhanced MRI confirmed BBB/BBT-D in GL261 tumors (figure 1A). However, PET/CT imaging revealed a lack of tumor-preferential [89Zr]-mCD47 uptake with or without FUSPRE, suggesting that neither condition improved antibody penetration over that in naïve brain (figure 1B-C). Remarkably, FUSPOST conferred superlative [89Zr]-mCD47 uptake at the site of BBB/BBT-D, boasting between 4.3- to 6.7-fold more uptake relative to other groups (figure 1C). This elevation in uptake was sustained over the time points assessed (0–72 hours post-FUS) (figure 1C-D). Using these insights, we evaluated a rational paradigm (figure 2A) combining mCD47 with repeat FUSPOST BBB/BBT-D (figure 2B-C) for glioma therapy. FUS-mediated delivery of mCD47 across the BBB/BBT significantly constrained tumor outgrowth (figure 2D-E) and enhanced survival (figure 2F) in GL261-bearing mice.


Conclusions

Taken together, our findings suggest that mCD47 delivery with FUS BBB/BTB-D is a promising therapeutic strategy for GB. For myriad ongoing pre-clinical and clinical evaluations of FUS-mediated immunotherapy delivery, these findings generate timely and compelling insights regarding impact of injection timing on antibody penetrance in brain tumors. This study underscores the outstanding potential role of immuno-PET imaging for rational design and monitoring of response to FUS immunotherapy approaches.

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Ethics Approval

This study was prospectively reviewed and approved by the University of Virginia Animal Care and Use Committee.

Consent

N/A

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MAVRILIMUMAB, A HUMAN MONOCLONAL ANTIBODY TARGETING GM-CSFRα, INHIBITS POLARIZATION TO MYELOID-DERIVED SUPPRESSOR CELLS (MDSCS) THAT EXPRESS PD-L1 AND RESTORES T-CELL PROLIFERATION IN VITRO

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Background

Myeloid-derived suppressor cells (MDSCs) accumulate in the blood and tumor microenvironment (TME) and suppress anti-tumor immune responses.1 Cancer cells express the granulocyte-macrophage colony-stimulating factor (GM-CSF), which drives MDSC differentiation and function.2 3 4 It is upregulated in several cancers, including mesothelioma, pancreatic and colorectal, and it is linked to higher levels of intra-tumoral MDSCs and poorer overall survival.2 4 5 In