Pancreatic Cancer Therapy Based on Immunopet-Informed Sequence for Focused Ultrasound-Targeted MCD47 Blockade Controls Glioma

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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/BTB). Transient disruption of the BBB/BTB 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/BTB with FUS in an orthotopic GB model. We then use these insights to design a combinatorial paradigm for mCD47 delivery with repeat FUS BBB/BTB-D.

Methods MRI-guided FUS BBB/BTB-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/BTB-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/BTB-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/BTB-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/BTB-D (figure 2B-C) for glioma therapy. FUS-mediated delivery of mCD47 across the BBB/BTB significantly constrained tumor outgrowth (figure 2D-E) and enhanced survival (figure 2F) in GL261-bearing mice.