1149 SENSITIZING AGGRESSIVE MURINE PANCREATIC CANCER TO IMMUNE CHECKPOINT BLOCKADE USING A TUMOR-TARGETED, STING AGONIST 'PAYLOADED' ANTIBODY

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Background Previously we have shown that intratumoral injection of IACS8803, a potent synthetic agonist of the Stimulator of Interferon Genes (STING) innate immune sensor, can act as an '*in-situ* vaccine' that orchestrates a proinflammatory rewiring of the immunosuppressive myeloid stroma thereby driving robust T cell activation and infiltration into otherwise 'cold' tumors. While this approach promotes cure of numerous murine models, clinical application of STING agonists has been limited by IR-guided direct injection into single tumor lesions, an invasive practice with limited potential for re-administration which has failed to significantly benefit metastatic cancer patients. Immune-Stimulating Antibody Conjugates (ISACs) leverage the specificity and safety of traditional antibody-drug conjugates but carry immuno-stimulatory payloads rather than cytotoxic warheads.

Methods With ImmunoGenesis and Silverback, Inc. we developed an ISAC using our highly potent STING agonist IACS8803 conjugated to the Her2/neu antibody trastuzumab. We characterized the specificity and uptake of this ISAC by Her2-expressing tumor cells, and the capacity of associated PBMC for downstream STING activation using ELISA or a THP1-dual reporter assay. Next, in the MT4-LA orthotopic $Kras^{+/LSL\text{-}G12D}$; $Trp53^{+/LSL\text{-}R172H}$; *Pdx-Cre* ('KPC') derived model of pancreatic ductal adenocarcinoma (PDAC), we compared the ability of intratumorally-administered IACS-8803 to intraperitoneally administered Her2-IACS8803 to sensitise PDAC to checkpoint blockade using bioluminescent in vivo imaging and multi-parameter flow cytometry of tumor stroma post-therapy. We also assessed their toxicity and tolerability with multiple low-dose treatments.

Results In mT4-LA cells expressing Her2 protein, fluorophore-conjugated Her2-IACS8803 ISAC was taken up readily using receptor-mediated endocytosis across a concentration gradient. In tumor and human PBMC coculture assays we observed an elevated expression of downstream STING pathway targets such as type I IFNs and cytokines such as CXCL10, TNFα etc. Next, in the multi-focal mT4-LA PDAC tumor model (orthotopic and flank tumors), we found that systemic administration of a low concentration of the Her2-IACS8803 ISAC could provide equivalent tumor control and survival extension to multiple intra-tumoral injections of the STING agonist in combination with immune checkpoint blockade. Finally, TIL analyses of multiparameter flow cytometry data show a proinflammatory remodeling of the myeloid stroma and enhanced T cell function as salient features of synthetic agonists in orchestrating the in vivo therapeutic benefit, an effect that mirrors intratumoral IACS-8803 delivery.

Conclusions These preclinical studies demonstrate the potential of STING agonist 'payloaded', tumor-targeted antibodies non-invasively administered to provide better control of aggressive and multifocal PDAC in combination with immune checkpoint blockade.

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