ENHANCEMENT OF THE ANTI-TUMOR EFFECTS OF CD47 BLOCKADE IN SOLID TUMORS BY COMBINATION WITH TARGETED RADIOIMMUNOTHERAPY

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Background
One mechanism that tumors use to escape immunosurveillance is the overexpression of CD47, which inhibits the macrophage mediated phagocytosis pathway. Although blockade of the CD47-SIRPα axis is a promising approach to enhance tumor targeted phagocytosis, anti-CD47 monotherapies have not shown meaningful responses in clinical studies of solid tumors. Combination cancer therapies aim to increase the probability of response in settings of resistance by combining drugs with different mechanisms of action. Antibody radioconjugates (ARCs) specifically target and deliver therapeutic radiation directly to cancer cells. We rationalized that the immunogenic and cytotoxic properties of ARCs will upregulate calreticulin (CRT), a pro-phagocytic signal, thereby synergizing with CD47 blocking therapies to enhance phagocytosis and antitumor activity. Here for the first time, we demonstrate the combination benefit of a HER2 specific targeting ARC and a CD47 blocking antibody to enhance therapeutic efficacy in preclinical solid tumor models.

Methods
The anti-HER2 antibody trastuzumab was conjugated with p-SCN-DOTA and radiolabeled with Ac-225 or Lu-177. The biological activity of both radioconjugates was evaluated using human recombinant HER2 and receptor positive tumor cell lines. The cytotoxic effect of radioconjugates and the ability to upregulate CRT was evaluated using XTT assay and flow cytometry, respectively, in a panel of HER2 expressing cells. To evaluate the synergy of anti-HER2 ARC and CD47 antibody combination in vitro, a flow cytometry macrophage phagocytosis assay was developed. We further evaluated the antitumor synergy in vivo between anti-HER2 ARC and CD47 antibody in human HER2 positive tumor xenograft mouse model.

Results
The anti-HER2 ARCs have similar binding properties to native antibody and demonstrate specific cytotoxicity. Importantly, we observe ARC-mediated CRT upregulation in HER2 expressing cells. Furthermore, the combination of HER2 targeting ARC and CD47 blocking antibody enhances in vitro macrophage mediated tumor cell phagocytosis compared to each agent alone. Remarkably, the in vivo anti-HER2 ARC and CD47 antibody combination shows enhanced therapeutic effect with reduced toxicity and improved survival benefit in a human preclinical solid tumor model.

Conclusions
Here for the first time, we demonstrate enhanced therapeutic efficacy between an anti-HER2 ARC and CD47 blocking antibody combination in a preclinical solid tumor model. The finding suggests that ARC mediated upregulation of CRT potentiates the pro-phagocytic signal and synergizes with the anti-CD47 mode of action thereby enhancing antitumor immune response. This combination mechanism provides a very promising strategy to improve therapeutic responses in patients harboring solid tumors and warrants further preclinical evaluation.

Ethics Approval
All animal experiments were approved by IACUC.

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