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Development and non-clinical evaluation of an 111In/225Ac theranostic for triple negative breast cancer

Purpose: The purpose of this study was to develop an Indium-111/Actinium-225 based theragnostic utilizing the tMUC1 targeting humanized antibody, TAB004, and its evaluation in a tumor bearing rodent model.

Triple negative breast cancer (TNBC) is an aggressive phenotype that comprises only 15-20% of all new breast cancer cases but is responsible for a majority of related deaths. Chemotherapy is the current mainstay treatment for TNBC but side effects and drug-resistance remain an issue, so development of targeted therapies for TNBC is critical. Tumor associated Mucin 1 (tMUC1), an aberrantly glycosylated transmembrane glycoprotein, is overexpressed in >90% of TNBCs and as such is an attractive target. The humanized antibody hTAB004 shows high affinity and selectivity to tMUC1 and was thus used to develop a theranostic strategy for TNBC.

Method: hTAB004 was conjugated to DOTA-NHS, purified, formulated in a metal free buffer and radiolabeled with Indium-111 or Actinium-225 to produce 111In-DOTA-hTAB004 and 225Ac-DOTA-hTAB004, respectively. The radiolabeled molecule was evaluated for stability. Retention of affinity of cold-labeled molecules was validated.

In vivo and ex vivo biodistribution studies of 111In-DOTA-hTAB004 were performed in HCC70 orthotopic xenograft tumor-bearing female NSG mice (n=3) using SPECT/CT imaging over 120h. Dosimetry analysis was performed utilizing the in vivo data. Therapeutic efficacy of 225Ac-DOTA-hTAB004 was determined in HCC70 orthotopic xenograft tumor-bearing female nude mice (n=5/group) by monitoring bodyweights and tumor sizes over time.

Results: DOTA-hTAB004 was labeled successfully with both Indium-111 and Actinium-225. The radiolabeled molecules were found stable in both formulation and mouse serum and the non-radioactively labeled surrogates 115In-DOTA-hTAB004 and 139La-DOTA-hTAB004 retained their affinity to tMUC1.

In vivo biodistribution data revealed increased tumor accumulation of 111In-DOTA-hTAB004 over 120 h, reaching 65±15 percent of injected dose per gram (%ID/g). The next organs of significant uptake (Spleen 8.9±0.6 %ID/g and Liver 8.3±1 %ID/g) had a 7-fold lower uptake at 120 h. All mice treated with a single injection of 225Ac-DOTA-hTAB004 (500 nCi, 18 kBq) showed a complete response with tumor volumes shrinking by > 89% within 48 days. No therapy associated toxicities were seen in any of the mice outside of tail necrosis in one animal which may have been due to dose extravasation. All the control mice, which received the DOTA-hTAB004, showed continued tumor growth and had to be sacrificed by day 35.

Conclusions
111In-DOTA-hTAB004 biodistribution data indicates the excellent tumor targeting capabilities of hTAB004. 225Ac-DOTA-hTAB004 therapy data shows exceptional clinical benefit in mice bearing human tumors. Given this data, radiolabeled hTAB004 is a promising targeted treatment and imaging option for TNBC.

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