Title	**HSPG2/Perlecan as a Therapeutic Target in Metastatic Cancers**
Keywords (up to 5)	Cancer, HSPG2/Perlecan, Antibody, Metastasis, Target
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Abstract	Significant advancements in chemotherapy have improved survival rates of patients presenting with local or regional breast cancer to as high as 99% and 85% respectively. On the contrary, patients with metastatic breast cancer have a dismal 5 - year survival rate of 26%. Thus, there is an urgent need for research strategies directed towards treatment of metastasis. Our lab used a phage display based cell panning procedure to develop two fully humanized antibodies (Tw1S4_6 and Tw1S4_AM6) that bind specifically to breast cancer metastatic cells. Target deconvolution revealed HSPG2/Perlecan Domain 1 as the cell surface antigen bound by the antibodies. Immunohistochemistry studies revealed high HSPG2 expression across various tumor sub-types including melanoma, bladder cancer, glioblastoma and ovarian cancer. There was significant correlation between high HSPG2 expression and poor survival in triple negative breast cancer, bladder and ovarian cancers. Considering the expression and significance of HSPG2, we tested it as a therapeutic target. We observed significant tumor growth inhibition with Tw1S4_AM6 in the triple negative MDA-MB-231 breast cancer xenograft model. This efficacy was reduced when the studies were repeated in NSG mice, suggesting NK cell-mediated antibody dependent cellular cytotoxicity (ADCC) as a potential mechanism of action. *In vitro* studies using human PBMCs were carried out to confirm ADCC as a mechanism for anti-HSPG2 antibodies. Further studies are required to understand if other immune or receptor based mechanisms are involved. In addition, conjugation of Tw1S4_AM6 on the surface of polymeric nanoparticles enabled increased tumor cell uptake of nanoparticles, suggesting Tw1S4_AM6 could be valuable as a targeting ligand for drug delivery systems. The data presented here points towards the relevance of HSPG2 as a novel target for not only breast cancer but other malignancies as well. Further studies are required to understand the significance of HSPG2 overexpression and its correlation with tumor progression.
References	