1453 IN-VIVO TUMOR IMPLANTATION SITE EXHIBITS DIFFERENTIAL IMMUNE RESPONSE IN SOLID TUMORS

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Background Emerging evidence highlights the importance of the local tumor microenvironment (TME) in evaluating the efficacy of new therapeutics, especially for immunotherapies. Historically, patient-derived xenograft (PDX) modeling involves subcutaneous implantation which minimally represents the actual human tumor site, as opposed to orthotopic implantation (O-PDX) which more accurately reflects the local TME. In this study, we sought to determine the immunological and functional differences between subcutaneous and orthotopic modeling.

Methods We implanted PDX models subcutaneously and orthotopically and performed gene set enrichment analysis (GSEA) on tumors to determine the differences in gene expression influenced by the TME. Furthermore, we developed peripheral blood mononuclear cell (PBMC) humanized PDX models to demonstrate differences in overall immune response and pharmacological outcome between the two implant settings.

Results GSEA revealed several significant pathways altered between subcutaneous and orthotopic tumors, including immunoregulatory interactions. PBMC humanized mice also showed differences in tumor infiltrating lymphocytes (TILs) as well as differential in vivo efficacy and immunophenotypes when challenged with checkpoint inhibition.

Conclusions We observed biological, immunological, and pharmacological differences between subcutaneous and orthotopic implantation of the same PDX model, highlighting the importance of study design when testing new therapies for greater translation into clinical success.

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