ENHANCED ANTIBODY-MEDIATED PHAGOCYTOSIS AND ANTIBODY-MEDIATED CELL CYTOTOXICITY USING TETRAVALENT, BISPECIFIC INNATE CELL ENGAGERS (ICE®) IN 3D SPHEROIDS

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Background The redirected optimized cell platform (ROCK®) enables the generation of customizable innate cell engagers (ICE®) of varying valency, affinity, and pharmacokinetic profiles. Preclinical and clinical studies have demonstrated the advantage and unique features of this first-in-class ICE® antibodies across a multitude of cancers and its differentiation to monoclonal antibodies. ICE® are tetravalent, bispecific antibodies that bivalently bind to a unique epitope on CD16A, which is selectively expressed on natural killer (NK) cells and macrophages, while the other domains target a tumor antigen. In addition to promoting antibody-dependent cellular cytotoxicity (ADCC) of NK cells, ICE® can also promote tumor targeting of macrophages eventually inducing antibody-dependent cellular phagocytosis (ADCP).

Methods ADCP and ADCC assays were performed using monocyte-differentiated macrophages and NK cells derived from healthy donor PBMCs. Target tumor lines and patient-derived xenograft line-derived spheroids were labelled and co-cultured with macrophages or NK cells. Live-cell imaging (IncuCyte®) was used to measure ADCP and ADCC events.

Results We show that ICE® molecules can enhance ADCP of tumor cells mediated by various functional/phenotypic subsets of macrophages derived from in vitro differentiation of human monocytes. ICE®-induced ADCP of tumor target cells was seen across different macrophage subtypes (M1 and M2). We further investigated the expression of immune-suppressive checkpoint programmed death-ligand 1 (PD-L1) on macrophages upon ICE® treatment that could be a key anti-tumor molecule within the suppressive tumor microenvironment. Based on patient-derived xenograft line-derived spheroids (3D) generated from primary tumor samples of patients suffering from various malignancies, we could demonstrate robust ADCC and ADCP mediated by NK cells and macrophages, respectively.

Conclusions ICE® molecules are able to mount robust NK cell- and macrophage-mediated anti-tumoral innate immune responses. This combined immune activity has the potential to not only fight tumor cells directly but also to initiate a full immune response comprised of innate and adaptive components of the immune system.

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