MODULAR P329G-BINDING CAR T CELLS ENGINEERED TO RECOGNIZE HUMAN EFFECTOR-SILENCED ANTIBODIES CARRYING A P329G FC-MUTATION FOR TARGETING OF SOLID TUMOR ANTIGENS

Background Chimeric antigen receptor (CAR) T cell therapy revolutionized the treatment of patients with B cell and plasma cell malignancies. However, treatment success is still limited by treatment-associated toxicities and antigen-negative relapse after an initial complete remission. Moreover, efficacy of CAR T cell therapy is insufficient in solid tumors. Modular CAR T cells in combination with CAR-adaptor molecules have the potential to mitigate severe adverse events and overcome antigen escape, so that various modular platforms are currently under investigation. To enable an optimized modular CAR T cell platform, we developed a P329G-targeting CAR. This novel and modular platform for CAR T cell therapy. P329G-targeting CAR T cells mediated effector functions in a modular and reversible fashion.

Conclusions Taken together, we showed the introduction of a novel and modular platform for CAR T cell therapy. P329G-targeting CAR T cells combined with effector-silenced tumor antigen-binding antibodies of the IgG1 subtype carrying the clinically validated P329G LALA mutations in the Fc part can mediate profound in vitro and in vivo effector functions in various solid tumor models, warranting further clinical translation of the concept.

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ACTIVATION OF IL-22 SIGNALING CORRELATES WITH HIGHER CD155 EXPRESSION AND STRATIFIES POOR OUTCOMES OF EARLY-STAGE LUNG AND BREAST CANCER PATIENTS

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Background CD155 (poliovirus receptor, PVR) is an immunosuppressive molecule overexpressed in lung adenocarcinoma (LUAD) and breast cancers (BCRA). However, no mutation has been identified that could be linked to such overexpression, and therefore it is likely regulated on the transcriptional level. Previously we identified interleukin-22 (IL-22) signaling as one of the pathways that upregulate CD155 expression in mouse models of lung and breast cancer. However, it is difficult to assess the activity of the IL-22 axis in the publicly available datasets since IL-22 signaling involves several components that must be considered: IL22, IL22RA1 and IL10RB, which encode heterodimeric IL-22 receptors found on tumor cells, and IL22RA2, which encodes soluble IL-22 binding protein (IL-22BP), an antagonist of IL-22 secreted by myeloid cells. The expression of IL22 itself is often missing in the dataset to assess the activity of the IL-22 axis in the publicly available datasets. Here we identified that early-stage lung and HER2+ breast cancer patients could be stratified according to their IL22RA1, IL22RA2, IL10RB, and PVR expression with cluster 0 predicting lower OS and shorter RMST. Mechanistically, the activity of such a pathway defines the immunosuppressive axis we identified previously.

Conclusions Here we identified that early-stage lung and HER2+ breast cancer patients could be stratified according to their IL22RA1, IL22RA2, IL10RB, and PVR expression with cluster 0 predicting lower OS and shorter RMST.

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