IN VITRO EFFICACY STUDIES TO SUPPORT ENGINEERED T CELL THERAPIES

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Background Cell therapies such as Chimeric Antigen Receptor T cells (CAR-T) and T Cell Receptor (TCR) T cells are immune-therapeutic approaches showing great momentum in research and the clinic. To date, four anti-CD19 CAR-T products and one anti-BCMA CAR-T products have been approved by the FDA for the treatment of lymphoid malignancies. Many more CAR-T cell products are currently being explored, targeting a wide variety of tumor antigens directed towards both liquid and solid tumors as well other clinical indications. In early-stage pre-clinical development, the use of in vivo animal models has presented significant hurdles in translatability of cell therapies. As a result, the establishment of high-quality in vitro efficacy and safety studies to foster the development of such therapies has become critical. The purpose of this study was to develop several in vitro efficacy experiments aimed at determining cell therapy activity, specificity and potency.

Methods We have generated CAR-T cells targeting the Human Epidermal growth factor Receptor 2 (HER2) as a model system. In vitro cytotoxicity co-culture assays were developed using flow cytometry-, high content analysis- or impedance-based read-outs.

Results HER2 CAR-T cells efficiently reduced the viability of the HER2-positive cell line ZR-75-30 in an effector:target cell ratio-dependent manner but had a limited effect on the viability of the HER2-negative cell line MDA-MB-468, confirming the activity and selectivity of the T cell therapy. A more complex three-way co-culture system (HER2 CAR-T cells co-cultured with both HER2-positive and -negative target cells) confirmed HER2 CAR-T specificity under activating conditions. Finally, following several rounds of antigen stimulation, the HER2 CAR-T cells persistently killed HER2-positive tumor cells, indicative of ‘cellular fitness’.

Conclusions To conclude, we developed several in vitro proof of concept assays for the assessment of cell therapy activity, specificity, and potency during early-stage development. (Three-way) co-culture or repeated antigen stimulation assays can be used to aid cell therapy discovery research and lead optimization. These in vitro assays will provide the possibility to select the best therapies to further progress to clinic.

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