149 IN VITRO EFFICACY STUDIES TO SUPPORT ENGINEERED T CELL THERAPIES

Sabrina de Munnik*, Monique Hazenoot, Sophie Vermond, Rene McLaughlin, Marco Guadagnoli, Gemma Moiset, Sann Holt, Marijn Vlaming. *Charles River, Leiden, Netherlands*

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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