EPSTEIN BARR VIRUS SPECIFIC T CELLS (EBVSTs) EXPRESSING B7-H3 TARGETING CHIMERIC ANTIGEN RECEPTORS (CAR) EXHIBIT GOOD PRE-CLINICAL ACTIVITY AND SAFETY AGAINST B7-H3 POSITIVE SOLID TUMORS

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Background The B7 homolog 3 protein (B7-H3, CD276) is an immune checkpoint member of the B7 and CD28 families that is minimally expressed in healthy tissues. In contrast, B7-H3 is found to be widely over-expressed in multiple types of human cancers, making it an excellent target for CAR T cell therapy.1 Allogeneic EBVSTs have demonstrated good safety and efficacy in clinical trials and hold the promise to enable broad application of CAR-based T cell therapy in the allogeneic setting.

Methods With the goal of creating off-the shelf allogeneic CAR T cell therapy for solid tumors, we developed Epstein-Barr Virus Specific T cells (EBVSTs) expressing a nanobody-based CAR (B7-H3 CAR EBVSTs) to target B7-H3 positive solid tumors.

Results Our optimised cell manufacturing protocol produced good cell expansion with more than 80% of EBVSTs expressing B7-H3 targeting CAR. B7-H3 CAR EBVSTs demonstrated excellent killing of several B7-H3 expressing colorectal, gastric, non-small cell lung and triple negative breast cancer cell lines while cytolysis of B7-H3 knockout counterparts of these cell lines were attenuated. In addition, EBVSTs expressing a truncated B7-H3 CAR that did not contain any intracellular signalling domains was devoid of activity against these cell lines. B7-H3 CAR EBVSTs retained good specificity and reactivity to EBV antigens, evident by abundant production of Tumor Necrosis Factor α and/or Interferon-γ in response to EBV but not to irrelevant HIV pepmixes stimulation.

To assess in vivo anti-tumor efficacy, immunodeficient mice were randomized to receive no treatment or treatment with un-transduced or B7-H3 CAR EBVSTs following xenografting of colorectal (HT-29 and SW480) or gastric cancer cell lines (NCI-N87) or triple negative breast cancer (MDA-MB-468) cells. Treatment with B7-H3 CAR EBVSTs induced significant tumor regression in all models compared to the unabated growth in mice that received un-transduced EBVSTs. Further evaluation revealed significantly greater numbers of B7-H3 CAR EBVSTs in blood, liver, lung, spleen and tumors of mice compared to un-transduced EBVST. Body weight of mice from all treatment groups was stable in the days post treatment in all studies, indicating the absence of major tolerability issues.

Conclusions Altogether, our data provides first proof that we are able to generate B7-H3 CAR EBVSTs with good in vitro and in vivo activity against B7-H3 expressing solid tumors. Given the excellent activity and tolerable safety profile observed, we believe that B7-H3 CAR EBVSTs is a promising candidate for allogeneic CAR T cell therapy against solid tumors.

REFERENCE


Ethics Approval This study was approved by Agency for Science, Technology and Research (A*STAR) Institutional Animal Care and Use Committee (IACUC) approval number: 211593.