## Improving CAR T cell therapy to treat CD19$^{+}$ malignancies

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T-cells armed with antibody-based chimeric antigen receptors (CAR) are showing early exciting proof of clinical efficacy against B-cell lymphoma/leukaemia. In recent years CAR T cell therapy for CD19+ malignancies has shown much success in clinical trials with most recent reports showing 90% complete response rates (CRR) in acute lymphoblastic leukaemia (ALL) patients. Response rates in other CD19+ malignancies have been considerably lower. These may be improved by increasing the persistence of circulating CAR T cell as well as their anti-cancer potency. Standard CAR T cells perform poorly without lymphodepleting pre-conditioning. This is not an obstacle in the clinic as CAR T cell administration can be co-ordinated with existing chemotherapy regimens. In this study we looked for improvements in CAR T cell engraftment, persistence, and potency in the suboptimal scenario of mice receiving no lymphodepleting preconditioning. CAR T cells were further engineered to constitutively express IL-12 to increase their engraftment and also to increase their potency and encourage epitope spreading. IL-12 expressing CAR T cells have shown increased potency both in vitro and in vivo. Interestingly, 41BB, rather than CD28 co-stimulation was required for eradication of established systemic tumour load without lymphodepleting pre-conditioning. Results so far suggest that these methods are successful, however, it remains to be seen whether these successes will translate to a significant increase in potency in conjunction with pre-conditioning. In addition, these approaches could raise additional safety concerns related to transgene expression of an increased persisting numbers of CAR T cells.

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