NIHR | Blood and Transplant Research Unit in Stem Cells and Immunotherapies at University College London

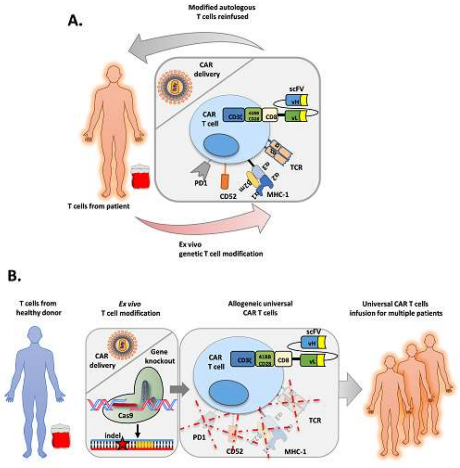
Research summary: Editing DNA to produce universal T cell therapies

by Roland Preece, former PhD student in Research Theme 4

Background: T cells are a group of white blood cells that make up an essential component of the immune system, protecting the body from bacterial and viral infections, and preventing the formation of cancers. An emerging branch of therapies referred to as *T cell immunotherapies* aim to harness the power of these important immune responses and redirect them towards cancer cells while avoiding the damage of healthy tissue often associated with chemotherapy. Such therapies have proven particularly successful against cancers like *B cell acute lymphoblastic leukaemia (B-ALL)* which uses the patient's own T cells engineered in a laboratory to recognise a marker only found on B cells (CD19). These triumphs have led to a global initiation of clinical trials as well as FDA (United States Food and Drug Administration, a government agency responsible for protecting the public health, equivalent to the Medicines and Healthcare products Regulatory Agency in the UK) approved therapies (e.g. Kymriah™ for use in paediatric and young adult patients), providing a potential cure for otherwise untreatable patients who have relapsed or have become resistant to other treatment options.

The problem: T cell immunotherapies have to be made with the patient's own white blood cells to prevent the treatment from turning on the body of the patient and causing graft vs host disease (donated cells attacking the recipient's body). The need to produce these therapies for each individual patient limits the wide-spread availability of this therapy as 1) it requires a centre with the expertise to make them and 2) the relatively long time to produce the therapy (~2 weeks) is not be suitable for all patients.

Current project: To overcome this issue, my project applied new gene editing techniques that change the DNA code called CRISPR/Cas9 to engineer universal T cells from a healthy blood donor that can be provided as an "off-the-shelf" treatment for any patient. These universal T cells are able to recognise B-ALL and have had the ability to recognise anything else removed, preventing graft vs host disease. This cutting-edge technology also enhanced these T cells' survival by making them compatible with chemotherapy and by protecting them from the patient's own immune system.



Graphic showing T cell immunotherapies made with the patient's own white blood cells versus the approach to use universal T cell from health donors

Techniques developed throughout this project are in preparation for early phase 1 clinical trial (NCT04557436, https://www.clinicaltrials.gov/ct2/show/NCT04557436?term=TT52&draw=2&rank=1) for the treatment of B-ALL in paediatric and young adult patients (6 months to 18 years) who have relapsed or become resistant to traditional chemotherapy. Results produced throughout this research project have contributed to a number of publications, listed below. Ultimately, this approach could create banks of healthy donor T cells to be used in various patients against different types of viruses and cancers.

Publications:

1. Georgiadis, C., R. Preece, L. Nickolay, A. Etuk, A. Petrova, D. Ladon, A. Danyi, N. Humphryes-Kirilov, A. Ajetunmobi, D. Kim, J. S. Kim and W. Qasim (2018). "Long Terminal Repeat CRISPR-CAR-Coupled "Universal" T Cells Mediate Potent Anti-leukemic Effects." Mol Ther **26**(5): 1215-1227.
2. Rasaiyaah, J., C. Georgiadis, R. Preece, U. Mock and W. Qasim (2018). "TCRalphabeta/CD3 disruption enables CD3-specific antileukemic T cell immunotherapy." JCI Insight **3**(13).
3. Preece, R., C. Georgiadis, S. A. Gkazi, A. Etuk, A. Christi and W. Qasim (2020). "'Mini' U6 Pol III promoter exhibits nucleosome redundancy and supports multiplexed coupling of CRISPR/Cas9 effects." Gene Ther.
4. Preece, R., A. Pavesi, S. A. Gkazi, K. A. Stegmann, C. Georgiadis, Z. M. Tan, J. Y. Joey Aw, M. K. Maini, A. Bertoletti and W. Qasim (2020). “CRISPR mediated base conversion allows discriminatory depletion of endogenous T cell receptors for enhanced synthetic immunity” (Mol Ther Methods Clin Dev).