*Font: Arial 11 pt - alpha/numeric characters only*

Abstract title (max. 25 words):

*The title should be as brief as possible and clearly indicate the nature of the abstract. If you wish to include a subtitle, it must be included in this field and included in the 25-word limit.*

Abstract content (max. 300 words):

*The abstract structure should include: Aim/s, Methods, Results, Conclusion.*

*A single table or single figure is allowed (up to 6 lines –word limit is reduced to 240 words; 7 to 10 lines - 10 lines maximum size – word limit is reduced to 200 words).*

Title:

Designing a Novel C-Peptide Specific T-Regulatory Cell Therapy for Type 1 Diabetes.

Aim:

This study aims to identify novel C-peptide specific TCRs for the development of antigen-specific T-regulatory (Treg) cell therapy for Type 1 Diabetes (T1D), generate C-peptide specific Tregs, and develop a novel humanised T1D mouse model to assess their functionality.

Method:

CD4⁺ T cells from healthy HLA DQ2 donor were co-cultured with autologous dendritic cells pulsed with C-peptide, a T1D-associated autoantigen. Proliferative responses were tracked over two rounds of stimulation using CellTrace dye labeling. Highly proliferative T cells were isolated by FACS and profiled using 10x single-cell sequencing. Antigen-specific T cells were identified based on activation markers. Selected TCRs were cloned into 3rd generation lentiviral vectors and transduced into T cells.

NSG-MHC I/II DKO mice were injected with human PBMCs from a HLA DQ2 donor. A week later, mice were given low dose streptozotocin (STZ) over a period of 5 days. Blood was collected pre STZ treatment and on days 18 and day 25 to collect plasma, determine immune engraftment and human immune cell activation. Pancreas tissue was also harvested for histological analysis.

Results:

We have successfully identified C-peptide specific TCRs associated with high expression of activation induced markers. 3rd generation lentiviral constructs with C-peptide specific TCR sequences have been generated and transduced on T cells. We successfully generated a humanized diabetes model in mice, as evidenced by clinical levels of hyperglycaemia and destruction of pancreatic islets. Analysis of immune cells showed increased CD69 expression on T lymphocytes.

Conclusion:

We identified and expressed C-peptide specific TCR on T cells, with functionality currently being assessed in vitro to explore antigen-specific efficacy. We have also generated a humanized model of T1D showing symptoms similar to those observed in patients, including hyperglycemia, islet destruction, and T cell activation. This model will be highly relevant for evaluating the potential of our TCR-Treg therapy in vivo.