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Ex vivo delivery of regulatory T-cells for control of alloimmune priming in the donor lung

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Shareable abstract (@ERSpublications)
A recipient-derived lung allograft-directed regulatory T-cell therapy administered prior to transplantation is feasible in rat and human lungs and demonstrates evidence of immune regulation post-transplant https://bit.ly/3D8MCBo

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Abstract

Background Survival after lung transplantation (LTx) is hampered by uncontrolled inflammation and alloimmunity. Regulatory T-cells (Tregs) are being studied as a cellular therapy in solid organ transplantation. Whether these systemically administered Tregs can function at the appropriate location and time is an important concern. We hypothesised that *in vitro*-expanded recipient-derived Tregs can be delivered to donor lungs prior to LTx *via ex vivo* lung perfusion (EVLP), maintaining their immunomodulatory ability.

Methods In a rat model, Wistar Kyoto (WKy) $CD4^+CD25^{high}$ Tregs were expanded *in vitro* prior to EVLP. Expanded Tregs were administered to Fisher 344 (F344) donor lungs during EVLP; left lungs were transplanted into WKy recipients. Treg localisation and function post-transplant were assessed. In a proof-of-concept experiment, cryopreserved expanded human $CD4^+CD25^+CD127^{low}$ Tregs were thawed and injected into discarded human lungs during EVLP.

Results Rat Tregs entered the lung parenchyma and retained suppressive function. Expanded Tregs had no adverse effect on donor lung physiology during EVLP; lung water as measured by wet-to-dry weight ratio was reduced by Treg therapy. The administered cells remained in the graft at 3 days post-transplant where they reduced activation of intra-graft effector $CD4^+$ T-cells; these effects were diminished by day 7. Human Tregs entered the lung parenchyma during EVLP where they expressed key immunoregulatory molecules ($CTLA4^+$, 4-$1BB^+$, $CD39^+$ and $CD15s^+$).

Conclusions Pre-transplant Treg administration can inhibit alloimmunity within the lung allograft at early time points post-transplant. Our organ-directed approach has potential for clinical translation.