Chimeric cytokine receptor provides IL-2 signaling for engineered regulatory T cell therapy

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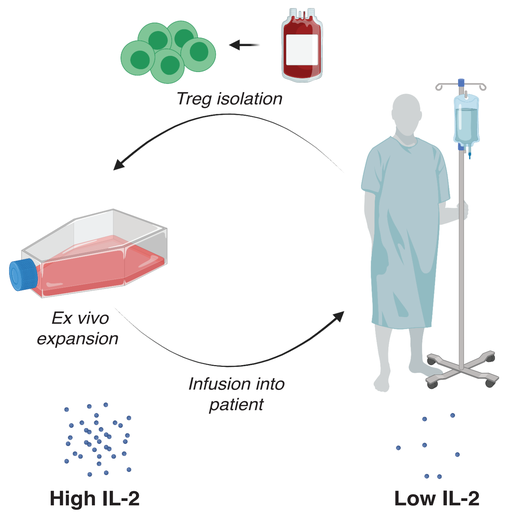
Abstract

Regulatory T cells (Tregs) are potent immune suppressors and critical to the maintenance of immunological tolerance. Interleukin 2 (IL-2) is essential for Treg survival, expansion, phenotypic stability, and suppressive function.[1] However, Tregs do not produce IL-2 and are dependent on exogenous sources of IL-2. This poses a significant challenge for Treg cell therapies in tissues with no or limited IL-2 availability in the microenvironment. Therefore, we have developed engineered Treg cells containing a chimeric cytokine receptor that provides an IL-2 signal. The chimeric cytokine receptor, termed IL-9 tethered switch receptor (IL-9TSR), consists of interleukin 9 (IL-9) tethered to the extracellular domain of IL9RA paired with the intracellular domain of IL2RB. We have shown that Tregs expressing IL-9TSR can survive and expand in the absence of exogenous IL-2 in vitro and in vivo but require TCR stimulation for prolonged persistency. IL-9TSR Tregs have stable FOXP3+HELIOS+ phenotype and superior suppressive function when compared to control Tregs. In conclusion, we have generated Treg cells engineered to survive and function in a low IL-2 environment. Treg cell therapies equipped with IL-2 signaling enable increased persistency and allows for potential use in more clinical indications than ever previously possible.

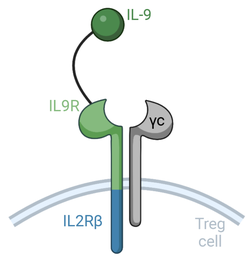
Tregs cannot persist in low IL-2 environments

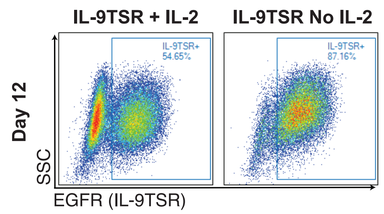


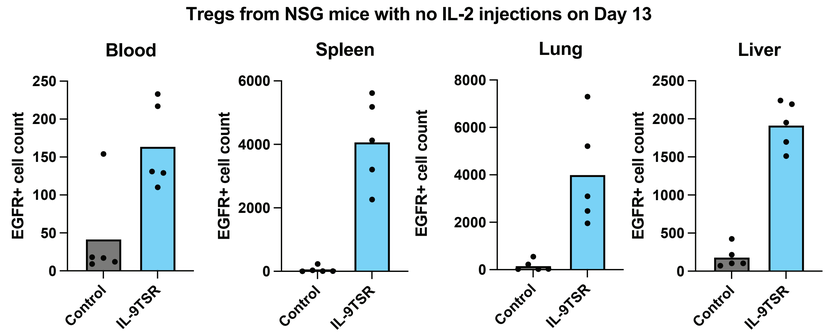
Project Goals

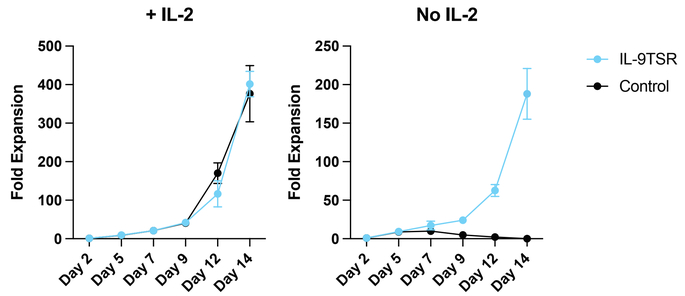
- Generate engineering solution that allows Treg persistence without IL-2
- Confirm intracellular IL-2 signaling is acheived with chimeric receptor
- Validate Treg stability and suppressive function in engineered Tregs

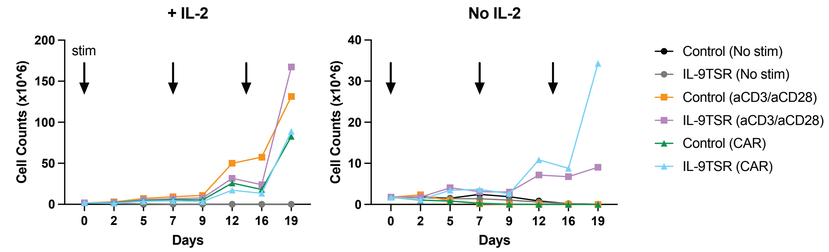
IL-9TSR Tregs persist in absence of IL-2



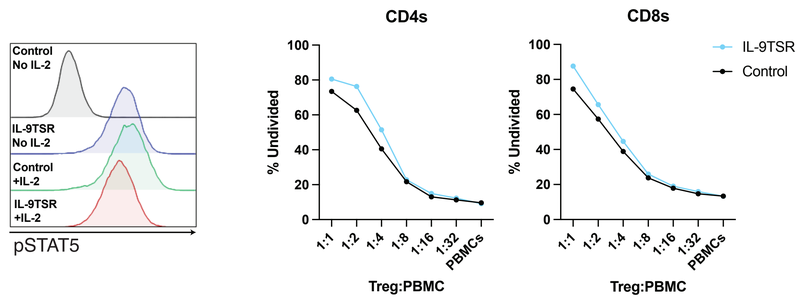




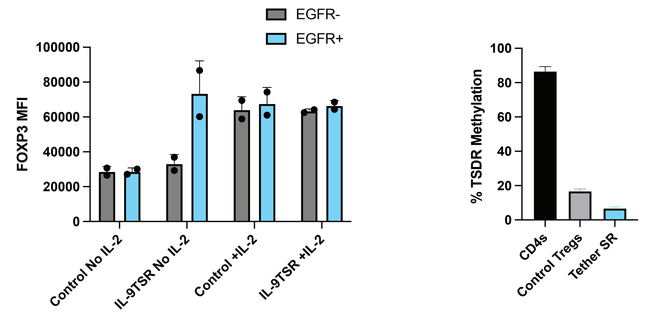




IL-9TSR Tregs signal and are suppressive



IL-9TSR Tregs are stable



Conclusions

- IL-9TSR Tregs can persist in absence of IL-2 *in vitro* and *in vivo*, but require TCR or CAR stimulation
- IL-9TSR Tregs signal through the IL-2 pathway, have a stable Treg phenotype and functional suppressive activity
- We have generated Tregs with self sufficient IL-2 signaling for clinical use in low IL-2 environments

References & Acknowledgements

References: 1.) Chinen T. *et al.* (2016). *Nat Immunol.* 17(11):1322-1333.

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