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Transcriptional engineering of TR1 cell therapies

Type 1 regulatory T cells (Tr1s) are an inducible subtype of regulatory T cells that can play a beneficial (autoimmune diseases, allergy, hematological malignancies) or detrimental role (some solid tumors and infectious diseases) in human diseases. Tr1 cells. Currently, we do not have means for in vivo therapeutic targeting of Tr1 cells, but Tr1 cells differentiated in vitro have a potent therapeutic potential. However, in vitro differentiated Tr1 cell therapy products, called T-allo10 cells, contain ~10% of Tr1 cells. Thus, strategies to target Tr1 cell differentiation in vivo and generate purified Tr1 cell products in vitro can provide therapeutic benefit in wide variety of human diseases.

Inventors at Stanford developed a method targeting master regulator transcription factors of Tr1 cells to increase the efficacy of their differentiation and manipulate their functions. Master regulators are key transcription factors that regulate cell lineage identity, differentiation and functions. They showed that the transcription factors IRF4 and BATF are necessary for Tr1 differentiation, and that the activation of transcription factor MAF potentiates Tr1 cell differentiation. Using CRISPRa, the inventors than developed a method that allows the manipulation of Tr1 cell induction, which will enable the manipulation of endogenous or adoptively transferred Tr1 cells in vivo. The ability to genetically engineer Tr1 cells can lead to better treatments for graft-versus-host disease, rejection of solid organ transplants, severe autoimmunity and allergy.

Applications

- Treatments for immune mediated diseases and diseases driven by Tr1 dysregulation such as certain cancers and infections.
- Discovery and drug development to increase IRF4, BATF, and MAF expression in vivo, potentiating the function of Tr1 cells in vivo.

- In vitro differentiation of Tr1 cells by genetic engineering of CD4+ cells leading to expression of IRF4, BATF, and MAF.
- In vivo prevention of Tr1 cell differentiation by targeted degradation of IRF4, BATF, and MAF in CD4+ T cells.

Advantages

- Our method of transcription factor engineering by activation of IRF4, BATF, or MAF has the potential to generate new, improved antigen-specific Tr1 cells with high enrichment
- Differentiation and expansion of Tr1 cells specific for target antigens of immune mediated diseases.
- Transcription factor engineering can be applied to induce polyclonal Tr1 cells, or to impart desirable features to polyclonal Tr1 or Tr1-like cells, and more broadly to other T cell therapies.

Publications

- Cepika, A. M., Amaya, L., Waichler, C., Narula, M., Mantilla, M. M., Thomas, B. C., ... & Roncarolo, M. G. (2024). " Epigenetic signature and key transcriptional regulators of human antigen-specific type 1 regulatory T cells". bioRxiv, 2024-03.
- Bertaina, A., Bacchetta, R., Shyr, DC., Saini, G., Lee, J., Kristovich, K., Agarwal-Hashmi, R., Klein, OR., Melsop, K., Tate, K., Barbarito, G., Oppizzi, L., Chen, P., Porteus, M.H., Cepika, A-M., Roncarolo, M-G (2024). Enhanced Immune Reconstitution and Reduced GvHD Risk with T-allo10 Infusion Post A?depleted-HSCT in Pediatric and Young Adult Patients with Hematologic Malignancies. *Transplantation and Cellular Therapy*. Vol. 30 Issue 2, Supplement Pages S13.

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