Selective Regulatory T Cell Expansion by Novel IL-2 Mutein Prolongs Skin Transplant Survival

T.J. Borges[1], O. Efe[1], R.B. Gassen[1], A. Al Jurdi[1], I.T. Lape[1], G.J. Babcock[2], S.M. Carlson[2], J.C. Madsen[1], L. V. Riella[1]
[1]Center for Transplantation Sciences, Massachusetts General Hospital, Charlestown, MA.
[2]Visterra, Inc., Waltham, MA

Introduction:

- Long-term immunosuppression predisposes transplant patients to a greater risk of infection, malignancy and kidney toxicity. Low-dose IL-2 therapy has been reported as an alternative method to expand Tregs *in vivo* but can promote the proliferation of unwanted effector cells.

- This led us to develop and test a novel human IL-2 mutein (mIL-2) fused with a human antibody Fc domain (IL-2-Fc), designed to selectively induce Tregs with minimal effects on effector cells. Herein, we investigate the immune regulatory effects of mIL-2 in transplantation.

Methods:

- *In vitro* experiments: mouse splenocytes stimulated with the wild-type IL-2-Fc, the mIL-2 or a negative control and evaluated for levels of pSTAT5 by flow cytometry.
- *In vivo* experiments: minor-mismatch murine skin transplant model treated twice weekly with either PBS or mIL-2 (Fig 1A). Prospective immune phenotyping of immune cells and *ex vivo* Treg function assay. Cynomolgus monkeys were treated with either control or mIL2 to assess effect on Tregs.

Results

- *In vitro*, we found that the mIL-2 increased the levels of pSTAT5 selectively in Tregs, with minimal effects on NK cells, and $CD8^+$ T cells (not shown).
- *In vivo*, we found that mIL-2 alone significantly prolonged the allograft survival when compared to PBS group (MST 20.5 vs 47.5, *p= 0.0067*; Fig. 1B).
- The mIL-2 treatment led to significant increase in circulating Tregs (Fig 1C), with no effects on other immune cells such as NK cells (Fig. 1D)

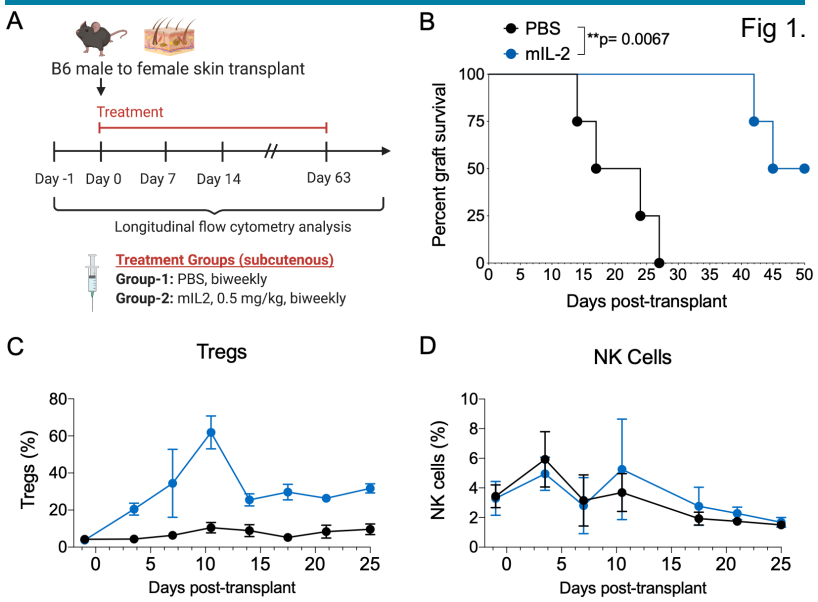

Fig 1.

Results (continued):

- Moreover, Tregs from mIL-2 treated animals demonstrated increased suppressive function as observed by an *ex vivo* suppression assay when compared to controls (Fig. 2).

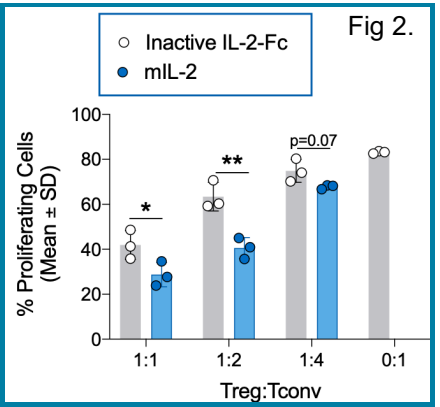

Fig 2.

- Lastly, mIL-2 significantly expanded circulating Tregs (blue/red vs. green controls) with no detectable effects on Teff or NK cells in cynomolgus monkeys (Fig 3).

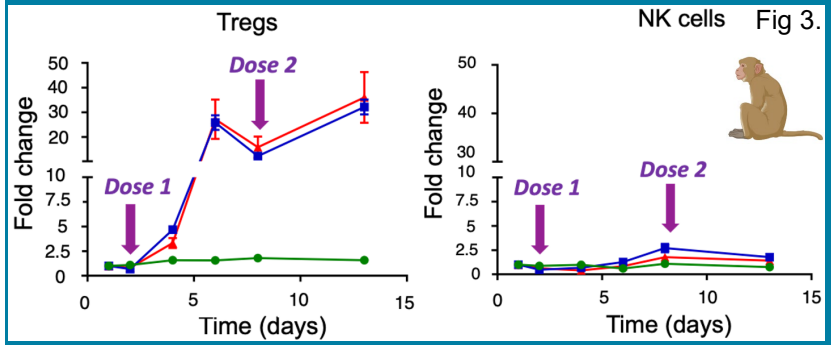

Fig 3.

Conclusion:

Overall, mIL-2 prolongs graft survival by the selective and sustained expansion Tregs while also enhancing Treg function with minimal effect on other immune cells.

MASSACHUSETTS GENERAL HOSPITAL
CENTER FOR TRANSPLANTATION SCIENCES

RIELLA LAB

HARVARD MEDICAL SCHOOL

American Transplant Congress. June 4-9, 2021
tdejesusborges@mgh.harvard.edu; lriella@mgh.harvard.edu