Plenary Scientific Session 2

Wednesday, May 22 | 7:00 a.m. – 8:15 a.m.
Salons A-F

S60

EXTENDING THE 'WINDOW OF TOLERANCE': REGULATORY T CELLS PERMIT LATE GESTATION IN UTERO HEMATOPOIETIC CELL TRANSPLANTATION

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Purpose
In utero hematopoietic cell transplantation (IUHCT) has the potential to cure congenital hematologic diseases. IUHCT must be performed early in gestation prior to immunologic maturity; this is technically challenging, however, and mandates that the target disease be diagnosed during the first trimester. Regulatory T cells (Tregs) are a population of T cells that can promote a tolerogenic immune state. The purpose of this study is to define the threshold of immunocompetence in murine gestation and determine if enrichment of the allograft with Tregs can promote tolerance thereafter.

Methods
9.7x10^6 T cell-depleted bone marrow cells (TCDBMCs) from B6GFP (H2kb) donors were injected into cohorts of Balb/c (H2kd) fetuses shortly after birth (gestational day 19-21). The frequency of macrochimeric engraftment (donor cell chimerism >1% at 4 weeks of age) was correlated with gestational age and the prevalence of T cell subtypes in the blood of uninjected littermates. The ability of Tregs to promote tolerance late in gestation (E20±0.5) was assessed by enriching the allograft with 0.5x10^6 CD4+CD25+ donor-derived Tregs. Fetuses injected with 9.7x10^6 TCDBMCs early in gestation (E14) served as positive controls.

Results
CD4+CD8- T cells, absent at E19, increase steadily through E21 (Figure 1A). The frequency of engraftment, by contrast, decreases (Figure 1B). CD4+CD8- / CD3+ >10% was found to be an excellent predictor of immunocompetence with respect to donor rejection. Enrichment of the allograft with Tregs successfully restored engraftment beyond the threshold of immunocompetence (Figure 1C), achieving an overall frequency of engraftment (84%) equivalent to IUHCT performed at E14 (90%) (P=0.68) (Figure 1D). There was no evidence of graft-versus-host-disease, and all animals demonstrated multilineage engraftment.

Conclusion
Enrichment of the allograft with CD4+CD25+ Tregs allows engraftment to occur in immunocompetent murine fetuses. A similar strategy may be useful to overcome technical and practical challenges to the clinical application of IUHCT.

Plenary Scientific Session 2 (cont.)