Strategies for Development of Interleukin-2 Therapy in Transplant Recipients: What Works and What Doesn't

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Purpose

Using an IL-2 mutein optimized for preferential binding to the human IL-2R-alpha chain (CD25), we explored how IL-2 might be employed to promote Treg dependent allograft survival in murine cardiac allograft models (BALB/c->C57BL/6).

Results

Two injections/week for 2 weeks of IL-2 mutein (10 µg) expanded the Treg population to ~50% of CD4 T cells but prolonged allograft survival by only 3-4 weeks.

Combination of IL-2 with rapamycin (RPM), using 2 injections/week of IL-2 and rapamycin (0.5 mg/kg/d) delivered by Alzet pump, both for 14 days, led to >100 d of survival and led to donor-specific allograft tolerance, while IL-2 or RPM alone prolonged allograft survival only transiently).

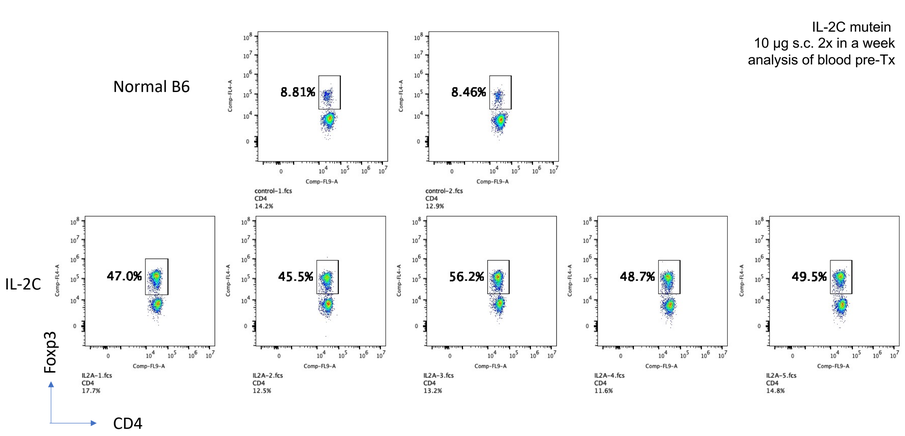
IL-2 mutein or CTLA4Ig each prolonged allograft survival but their combination (e.g., CTLA4Ig 250 µg at days 0, 4, 14 and 28, among other regimens) gave worse results than CTLA4Ig alone.

CNI therapy is a mainstay of clinical immunosuppression and primarily inhibits IL-2 production, such that we tested if its use in conjunction with an IL-2 mutein might inhibit conventional T cells but allow Treg function. We found FK506 (Tacrolimus) prolonged cardiac allograft survival in a dose-dependent manner but as dosing was reduced, consistent with how clinical CNI use is often weaned, rejection occurred. At such doses, the addition of IL-2 mutein therapy prevented rejection and induced long-term allograft survival.

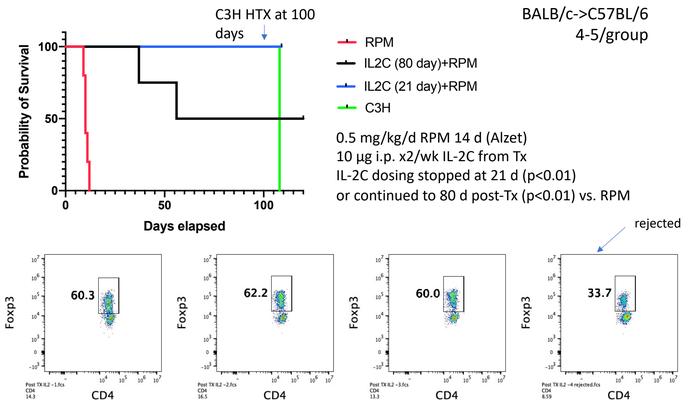
Conclusions

We conclude that an IL-2 mutein can promote Treg expansion and function to the extent that it can usefully be employed in conjunction with a "Treg-friendly" agent such as rapamycin, is ineffective when essential Treg survival signals involving CD28 are inhibited, and, surprisingly, can be used in a clinically relevant manner in conjunction with FK506.

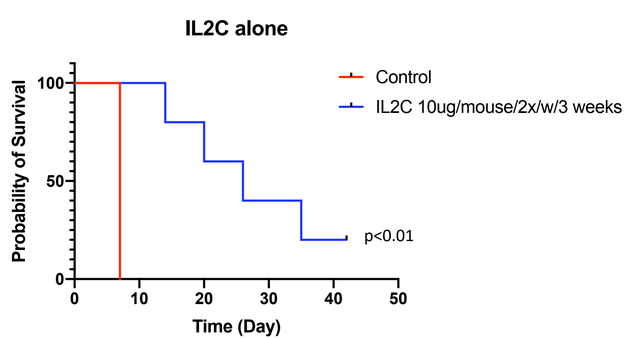
IL-2C mutein induces a >5-fold expansion of circulating Tregs in vivo



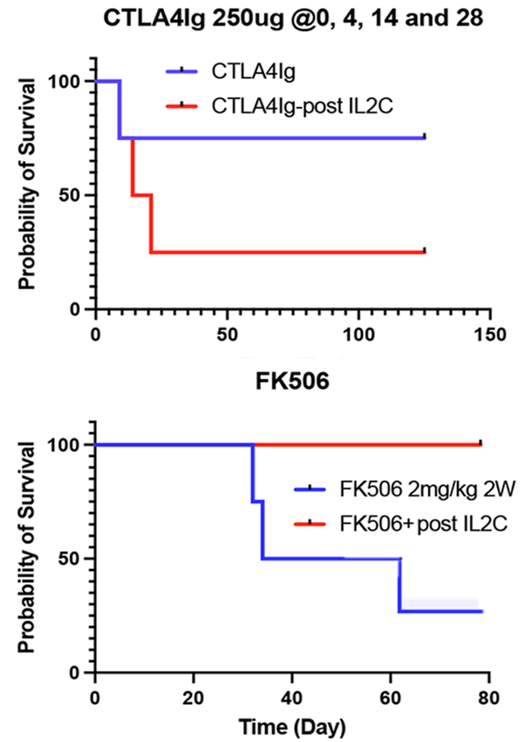
Limited post-transplant IL-2C mutein can prolong murine cardiac allograft survival indefinitely and induce donor-specific tolerance



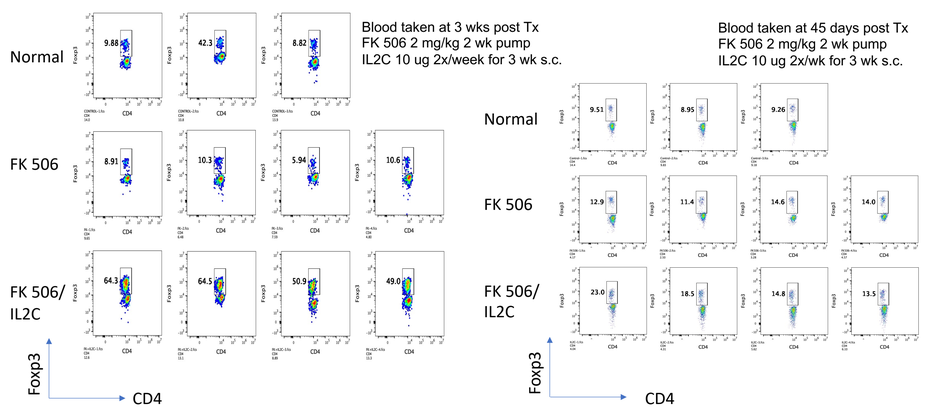
Efficacy of post-Tx IL-2C mutein therapy alone in murine cardiac allograft recipients (BALB/c->C57BL/6, n=5)



In contrast to the synergy observed between IL-2 and RPM, use of CTLA4Ig plus IL-2 markedly reduced allograft survival compared to CTLA4Ig alone (p<0.01), whereas IL-2 increased the efficacy of FK506 (Tacrolimus, p<0.01)



While the CD4+Foxp3+ Treg population is expanded by IL-2 mutein despite concomitant FK506 therapy, and declines after cessation of IL-2, its beneficial effects on graft survival are sustained



Disclosures: L. Wang and W. Hancock: None. G.J. Babcock: Employee of Visterra, Inc.