A regimen of nonmyeloablative conditioning and facilitated Allo-HSCT tips the balance towards immune down regulation and away from cytopathic activity in kidney allograft recipients

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- I hold patent W02018187521 “METHODS OF DETECTING CELL-FREE DNA IN BIOLOGICAL SAMPLES”

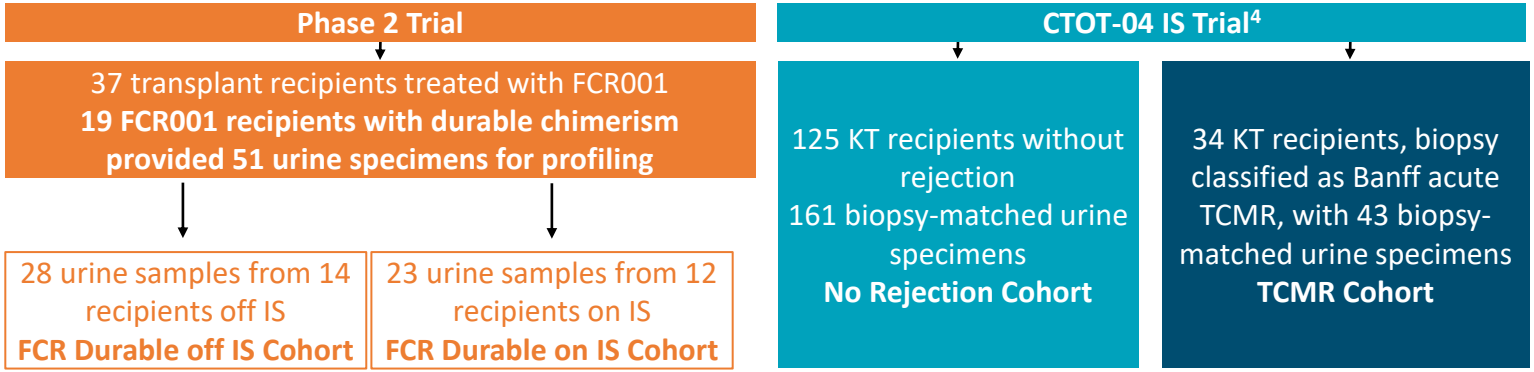
Kidney Transplant Tolerance with Facilitated Allo-HSCT

- Benefits of kidney transplantation (KT) are tempered by the adverse effects of chronic immunosuppressive therapy (IS)[1]
- Minimization or elimination of IS is a high-priority, unmet need
- FCR001 is an investigational allogeneic cell therapy for inducing hematopoietic chimerism and establishing kidney transplant tolerance in HLA-mismatched donor-recipient pairs[2]
- In an open-label, single-arm, phase 2 trial, 37 adult living donor kidney transplant (LDKT) patients were given a regimen of nonmyeloablative conditioning and facilitated Allo-HSCT. Durable chimerism was induced in 26 of 37 patients (70%) and complete discontinuation of immunosuppressive therapy without any organ rejection was observed during a median follow-up of 6 years[3]

1. Leventhal JR, et al. *Sci Transl Med*. 2012. 2. Leventhal et al. *Hum Immunol*. 2018. 3. Leventhal et al., 2021. American Transplant Congress. 21(suppl 3): Abstract 685.

Method and Objective

- Urinary cell mRNA profiling is a noninvasive means of interrogating kidney allograft status. We measured a hypothesis-based custom panel of urinary cell mRNAs in biopsy-matched urine specimens from a subgroup of patients in the Phase 2 FCR001 study and compared this panel to two standard-of-care cohorts from the Clinical Trials in Organ Transplantation-04 (CTOT-04)[4] study:

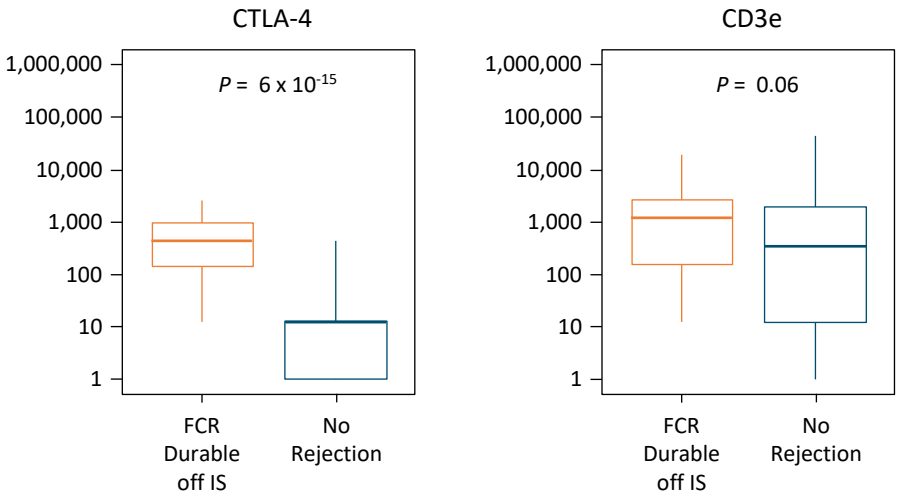


The objective was to identify a urinary cell mRNA signature in tolerant KT recipients conditioned with FCR001 facilitating cells and correlate it with donor chimerism.

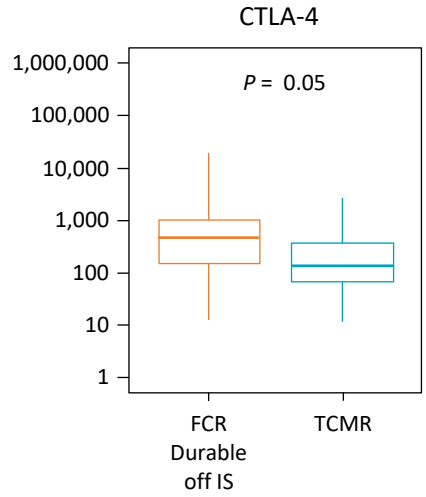
4. Suthanthiran M, et al. *N Engl J Med*. 2013.

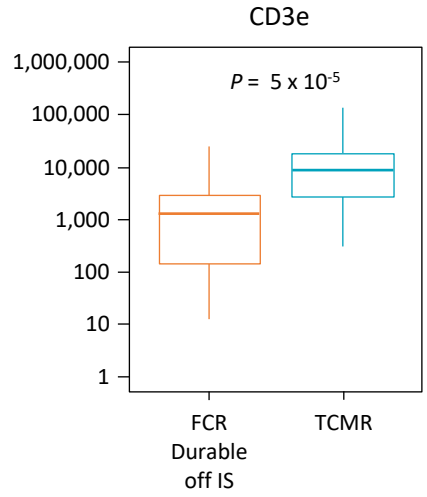
Urinary Cell mRNA Profiles from FCR001 Durable off IS Patients Have a Unique CTLA-4 mRNA Signature

FCR Durable off IS vs. No Rejection



FCR Durable off IS vs. TCMR



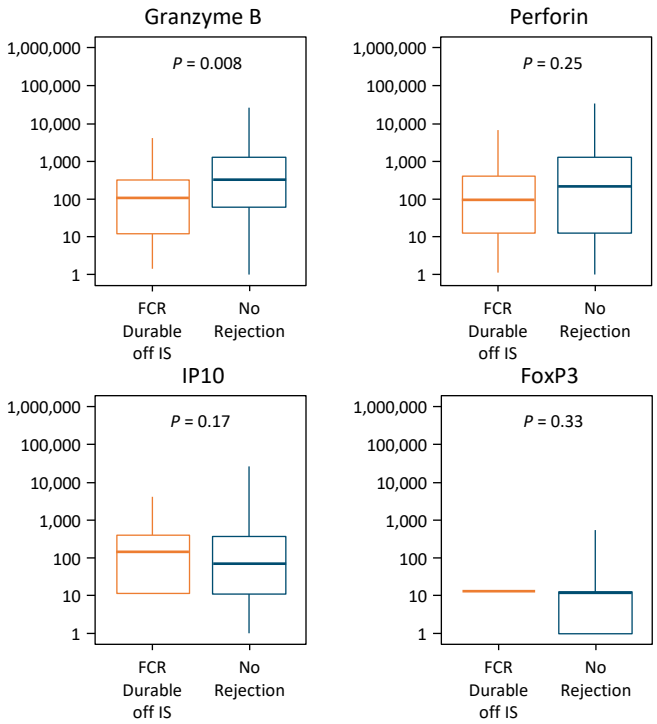


- CTLA-4 urinary cell mRNA level in the FCR Durable off IS Group was significantly higher than in the No Rejection Group and also higher than in the TCMR Group

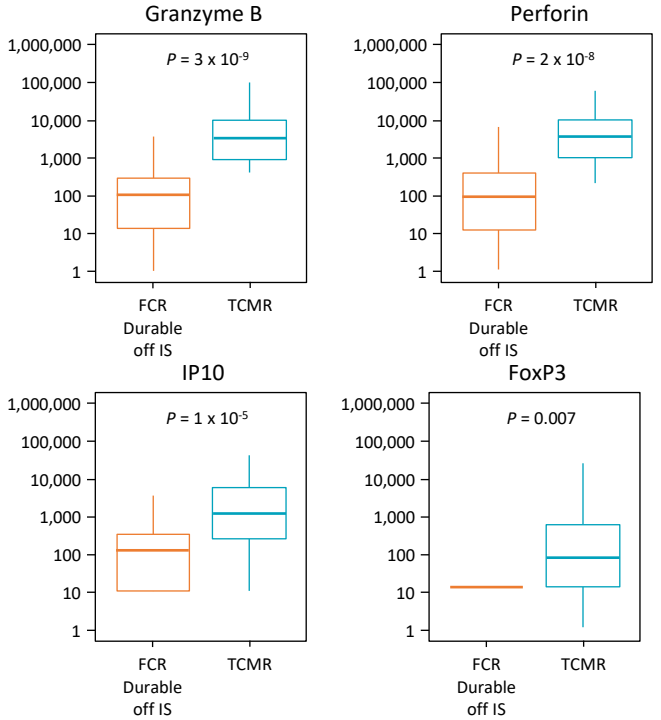
mRNA copy number per microgram of total RNA. *P*-values at the top of each box are based on Wilcoxon rank sum test comparing the two cohorts, using mRNA copy numbers as the dependent variable.

FCR001 Durable off IS Patients Have a Quiescent Profile Compared to KT with TCMR and Similar to the No Rejection Group

FCR Durable off IS vs. No Rejection

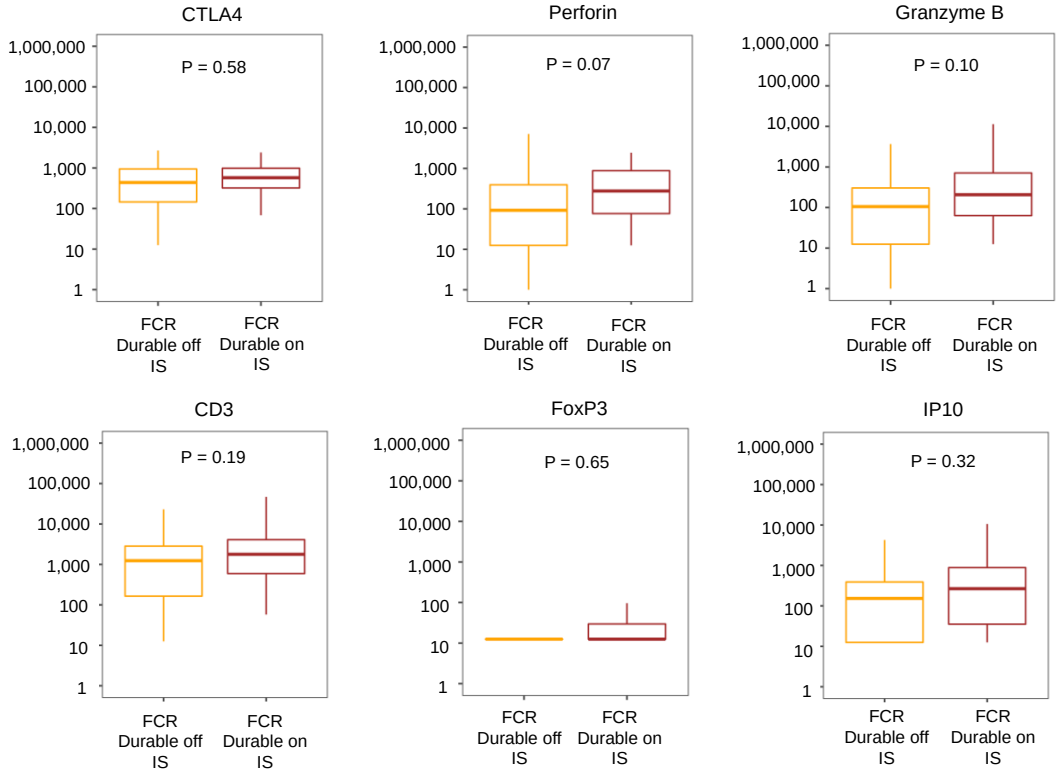


FCR Durable off IS vs. TCMR



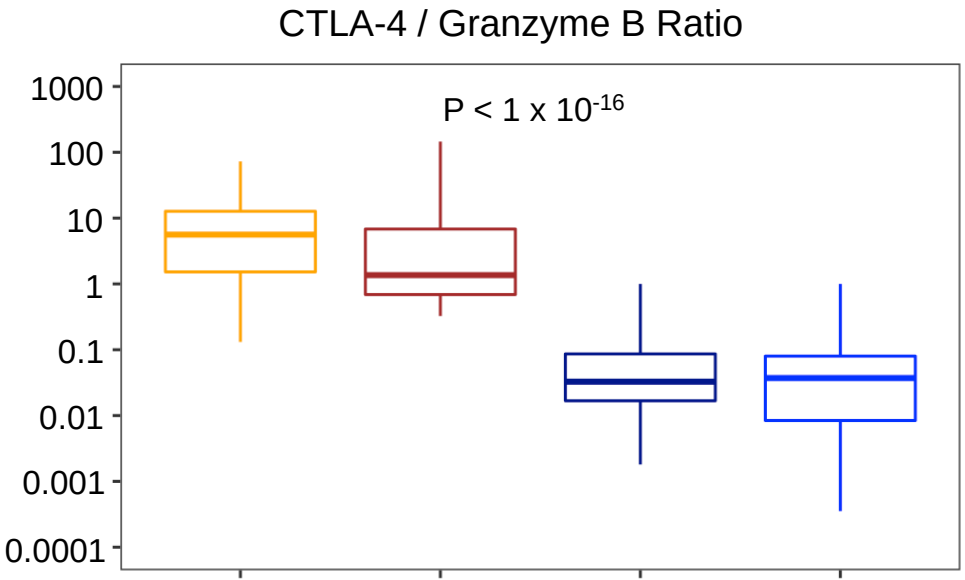
mRNA copy number per microgram of total RNA. *P*-values at the top of each box are based on Wilcoxon rank sum test comparing the two cohorts, using mRNA copy numbers as the dependent variable.

Similar Gene Expression Patterns in the FCR001 Durable off IS Cohort and the FCR001 Durable on IS Cohort



mRNA copy number per microgram of total RNA. *P*-values at the top of each box are based on Wilcoxon rank sum test comparing the two cohorts, using mRNA copy numbers as the dependent variable.

Significantly Higher Ratio of CTLA-4 mRNA to Granzyme B mRNA in the FCR001 Durable on IS and off IS Patients



- The ratio of CTLA-4 mRNA to granzyme B mRNA was significantly higher in the FCR Durable off IS Cohort and the FCR Durable on IS Cohort than the TCMR Cohort and the No Rejection Cohort (Kruskal Wallis $P < 1 \times 10^{-16}$).

Conclusions

- We have identified a unique and mechanistically informative urinary cell mRNA signature that is consistent with immune quiescence, defined by the ratio of CTLA-4 to granzyme B mRNA in tolerant kidney allograft recipients
- Urinary cell levels of several other mRNAs did not differ between FCR001 treatment and the No Rejection Cohort and were significantly lower than the levels in the TCMR Cohort
- This signature may help to identify FCR001 patients who could safely discontinue chronic immunosuppression