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Nicolas Poirier[1,2], Nahzli Dilek[1,2], Caroline Mary[1,2], Jeremy Hervouet[1], David Minault[1], Julien Branchereau[1], Xavier Tillou[1], Stephanie Le Bas-Bernardet[1], Bernard Vanhove[1,2*], Gilles Blancho[1]

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Background

Targeting CD28 costimulation with antagonist anti-CD28 antibodies has the potential to block effector T cells without perturbation of the CTLA-4 and PDL-1-mediated inhibitory signals important for the function of Treg cells, which might favour tolerance induction.

Methods and results

Here we evaluated in a non-human primates this "Treg sparing strategy" with FR104, a novel monovalent humanized and pegylated Fab' anti-CD28 antibody fragment. PK/PD studies in monkeys revealed that FR104 presented an elimination half-life of 8 days and 100% target saturation over at least a month after a single iv injection of 5 mg/kg. FR104 was next evaluated in a baboon kidney allograft model at the dose of 5 mg/kg at day 0, 4, 14 and then every two-week until 3 months. Monotherapy modestly but significantly prolonged allograft survival (MST: 18.5 days for monotherapy vs 6 days for untreated recipients). FR104 synergized with low doses tacrolimus (lowTac, trough: 5-10 ng/ml; MST >100 days for FR104/lowTac vs. 15 days for lowTac alone) as well as with calcineurin-free regimens: therapeutic doses of MMF or rapamycin (day 0-90) with 1 mg/kg of corticosteroids from day 0-14 (MST >100 days for FR104 + MMF/Rapa vs. 18/15 days for MMF/Rapa alone). Flow cytometry analyses indicated that blood Treg cells of the natural and inducible types were preserved in FR104/MMF or FR104/lowTAC bitherapies and accumulated in FR104 monotherapy and in FR104/Rapa bitherapy, whereas Treg cells were lowered by MMF and lowTac monotherapies. Histology also revealed that CTLA4+ and Foxp3+ T lymphocytes were accumulated into the graft of FR104 treated recipients.

Conclusion

FR104 presented Treg sparing properties in kidney transplantation and this was associated with prevention of graft rejection in synergy with tacrolimus, MMF or rapamycin.

Author details
[1]Institute of Transplantation Urology Nephrology, University of Nantes, INSERM UMR 1064, Nantes, France. [2]Effimune, Nantes, France CHU Nantes, Nantes, France.

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[1]Institute of Transplantation Urology Nephrology, University of Nantes, INSERM UMR 1064, Nantes, France
Full list of author information is available at the end of the article