
TSS
2017
15th TRANSPLANTATION SCIENCE SYMPOSIUM
May 24–26 • Victoria, BC, Canada • www.tss2017.org
FINAL
PROGRAM

205.3 THYMUS-DERIVED TREG INFUSION TO PREVENT GRAFT REJECTION IN HEART-TRANSPLANTED CHILDREN: INITIAL EXPLORATION OF A NEW THERAPEUTIC ARSENAL TO BOOST IMMUNE TOLERANCE.

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Introduction: Immune graft rejection is the main obstacle to successful transplants. Immunosuppressive drugs fail to prevent chronic rejection and also impair the immune system, resulting in reduced lifetime survival rates. Transfer of regulatory T cells (Treg) has acquired growing interest in attempts to achieve indefinite graft survival [1]. The limited Treg numbers that can be purified from peripheral blood, along with low survival and limited suppressive capacity of expanded Treg obtained from adults, constitute important drawbacks for the effectiveness of this strategy.
Methods: We established a collaboration amongst several teams working in the field to overcome current barriers and make Treg therapy a reality equipped to achieve indefinite graft survival. The major innovation is the employment of thymus, the site of Treg generation, as a new source of Treg [2]. Our goal is to perform a first-in-human trial treating heart-transplanted children with autologous thymus-derived Treg (thy-Treg) to prevent graft rejection.
Results: We purified Treg from thymuses discarded routinely during cardiac surgeries in children with congenital diseases, obtaining massive quantities of thy-Treg with >98% purity. The final thy-Treg product shows high suppressive capacity, decreasing the proliferation of CD4+ and CD8+ T cells in co-cultures by more than 70%. Next, we propose to conduct a clinical trial transferring thy-Treg to heart-transplanted children. In the first instance, thymuses removed during transplant surgery will be processed in GMP-conditions, and autologous thy-Treg will be infused back to the patient at day +10, when immunosuppressant doses are routinely reduced. Due to the high quality and quantity of these thy-Treg and the favorable features of the pediatric immune system, we are confident that this strategy will boost Treg-mediated tolerance and reduce the incidence of graft rejection.

Conclusion: Thymic tissue constitutes an alternative source of Treg that could be employed as cellular immunotherapy to prevent rejection. The massive quantity of Treg obtained from thymus, their high suppressive capacity, stability and survival, could overcome the drawbacks of employing Treg from peripheral blood. We propose that thy-Treg will constitute a therapeutic arsenal with infinite possibilities for the treatment of immune-related diseases, including graft rejection or autoimmune disorders.

This work was supported by grants from Instituto de Salud Carlos III (ISCIII) co-financed by FEDER funds (PI15/00011; ICI14/00282).

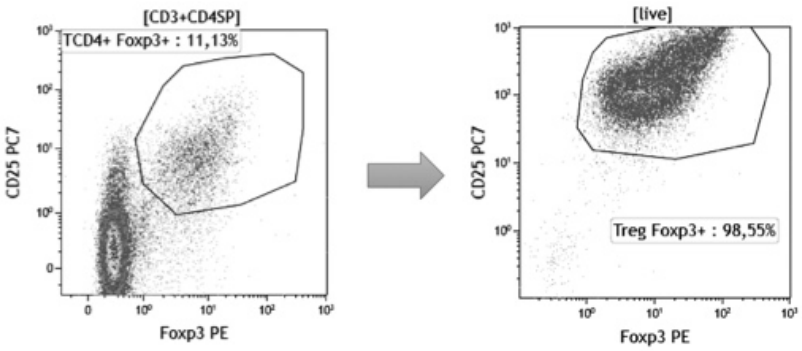

Figure 1. Purification and enrichment of thymus-derived Treg. Thymus tissue from one 5-months old children was processed. Left: frequency of Treg cells in the total of thymocytes before purification. Right: Highly pure thymus-derived Treg obtained after purification and 10-day culture.

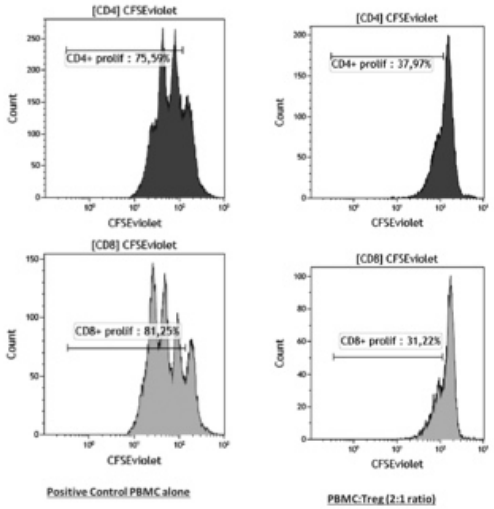

Figure 2. Suppressive capacity of thymus-derived Treg. Allogenic PBMCs were stained with CFSE and then co-cultured alone or with thymus derived Treg (ratio PBMC:Treg 2:1). Proliferation of CD4+ and CD8 T cells was analysed after 3 days of culture.

References:

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