

## **“Cellular therapy with regulatory type 1 T cells”**

Maria Grazia Roncarolo, Manuela Battaglia, Silvia Gregori, Rosa Bacchetta  
San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Milano, Italy  
Università Vita-Salute San Raffaele, Milan, Italy

Regulatory T cells (Tregs) represent specific T-cell subsets that plays a key role in inducing and maintaining immunological tolerance. The CD4<sup>+</sup> Tregs have been categorized into two major subgroups based on their ontogeny. The natural occurring Tregs, which develop in the thymus and are present in normal naive mice and healthy individuals since birth, and the adaptive Tregs that are induced in the periphery under various tolerogenic conditions. Among the adaptive Tregs, the T regulatory type 1 (Tr1) cells represent one of the most extensively characterized subset (Roncarolo, 2006). They are induced in the periphery by chronic exposure to antigen in the presence of IL-10 and they are defined by their unique cytokine production profile (*i.e.* IL-10<sup>+</sup>, IL-5<sup>+</sup>, TGF- $\beta$ <sup>+</sup>, IL4<sup>-</sup>, IL-2<sup>low</sup>, IFN- $\gamma$ <sup>low</sup>). Tr1 cells can suppress undesired immune responses mainly through production of IL-10 and TGF- $\beta$ .

Tr1 cells were originally described *in vivo* in severe combined immunodeficient (SCID) patients after allogeneic HLA-mismatched hematopoietic stem cell transplantation (HSCT). The presence of host-reactive Tr1 cell clones correlated with the absence of graft versus host disease (GvHD) and with long-term graft tolerance without the need for immunosuppression (Bacchetta, 1994). These data strongly supported the use of Tr1 cells generated *ex vivo* as immunomodulatory cell therapy in T-cell mediated diseases.

We are currently performing at our institute a clinical trial in which donor T cells anergized *ex vivo* against the host cells in the presence of IL-10 are infused post-transplant in hematological cancer patients undergoing HLA-haploidentical HSCT. The goal of this cellular therapy with anergized donor T cells is to induce immune-reconstitution without GvHD. The administered cells are indeed anergic towards host-antigens, contain precursors of host-specific Tr1 cells able to differentiate in fully competent suppressor cells, but also include T cells able to respond to infectious agents and possibly to provide a graft versus leukemia effect (Battaglia, 2006). An alternative protocol to generate Tr1 cells *ex vivo* more efficiently is currently under development. Host dendritic cells differentiated in the presence of IL-10 can indeed generate anergic donor CD4<sup>+</sup> T cells highly enriched in allo-Ag specific Tr1 cells.

Cellular therapy with alloantigen-specific Tr1 cell can be envisaged in the context of HLA-aploidentical bone marrow transplantation but also in allogeneic unrelated bone marrow transplants and in cell/organ transplantations in which there is high risk of graft rejection.

### **References**

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