Non-clinical development of IL-10-producing regulatory type 1 (Tr1) cell therapy of inflammatory bowel disease.

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Objectives
IL-10 producing regulatory type 1 (Tr1) cells were discovered in 1997 based on their properties to prevent in vitro bystander T-cell proliferation and to inhibit in vivo chronic colitis in mice. Non-clinical studies were performed to assess the feasibility of a cell therapy treatment with Tr1 cells in patients displaying Inflammatory Bowel Disease.
Aims and Methods
Non-clinical development of Tr1 cell therapy was performed focused on three sides: 1) Tr1 cell mechanism of action using mice models of chronic and acute colitis, 2) the development of a GMP manufacturing process for a human Tr1 cell product and 3) the identification Tr1 expression of key surface or soluble molecules ensuring the potency and safety of cell infusion to patients.
Results
Tr1 cell transfer in colitis prone mice showed a curative action on ongoing colitis in mice dependent on IL-10 induction after antigen specific activation of the transferred cells. This therapeutic action was observed after a specific migration within inflamed sites followed by the local activation of the Tr1 cells. A reproducible manufacturing process for ovalbumin specific human Tr1 cell was set-up in GMP conditions. Characterization of the human cell therapy product shows an in vitro suppressive activity on T-cell proliferation dependent on the production of both IL-10 and TGF-beta. Manufactured Tr1 cells display a regulatory phenotype including Foxp3, GITR and CTLA4 surface expression and express a set of homing molecules crucial for the homing to inflammatory tissues. In vitro toxicity studies of human Tr1 cell products (tumorogenicity, telomerase activity) showed a safety profile compatible with the use of these lymphocytes for cell therapy.
Conclusion
Based on these elements, a phase I/IIa clinical trial was initiated in severe Crohn's disease patients. In this trial, concomitant administration of the control antigen (ovalbumin) and of the autologous ovalbumin specific Tr1 cells is performed in order to induce a massive release of suppressive cytokines in the inflamed gut tissues upon encounter of the cells with the antigen.

Keywords: Cell therapy, Tr1 lymphocytes, Inflammatory Bowel Disease.