Immunotherapy of autoimmune diseases using autologous IL-10 producing Tr1 regulatory cells- A first injection trial in humans.

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IL-10 producing regulatory type 1 (Tr1) cells represents a subpopulation of CD4+ regulatory cells able to prevent in vitro bystander T-cell proliferation and to cure ongoing chronic colitis in mice.
In order to assess the efficacy and tolerance of Tr1 cell therapy in patients displaying severe Crohn's disease, we set-up a reproducible manufacturing process for the GMP production of human ovalbumin specific Tr1 cells. Procedures used for Tr1-cell production includes the use of Drosophila derived artificial Antigen Presenting Cells transfected with specific stimulatory molecules. This process allows the efficient cloning of ovalbumin specific Tr1 cells and their clonal expansion in serum-free medium up to three billions.
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 product (tumorogenicity, karyotyping, telomerase activity) show a safety profile compatible with the use of these regulatory Tr1 lymphocytes for cell therapy.
Based on these elements, a phase I/IIa clinical trial was initiated in March 2008 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. The endpoints of this study are 1) the evaluation of the safety of use of this cell therapy and 2) the determination of efficient doses that could show a real benefit for patients who are refractory to current treatments.