Immunotherapy approaches for pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL)

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B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is the most common form of cancer in children. Intensive multiagent chemotherapy and hemopoietic precursor cell transplantation (HPCT) lead to cure in nearly 80% of patients. Patients that bear tumors resistant to the high toxicity standard therapies need new therapeutic strategies in order to improve overall survival and decrease treatment-associated morbidity.

Immunotherapy could represent one of these approaches. Laboratorial alternatives for new protocols based on genetic manipulation of leukemia cells, as well as the generation of tumor antigen loaded Dendritic Cells (DC) to be used with HPCT on BCP-ALL, have been proposed. We have evaluated the effectiveness of BCP-ALL as Antigen Presenting Cells (APC) to T cells, as well as the effects of the stimulation by the ligand of CD40 (CD40L) on these cells. BCP-ALL cells were shown to be deficient as APC. For this reason we used DC to stimulate T cells. An *in vitro* protocol for the generation of cytotoxic T lymphocytes (CTL) specific against leukemia cells was developed. To achieve the expression of CD40L on the surface of BCP-ALL cells we exploited both lentiviral vectors and the recently described CD40L protein transfer phenomenon. The CD40L+ BCP-ALL cells generated were induced to apoptosis and phagocyted by immature DC, inducing DC maturation through CD40L stimulus. The mature DC were used for the generation of CTL against leukemia. Since graft versus host disease (GVHD) is one of the major causes of treatment failure in HPCT, we aimed to develop an approach to eliminate T cells causing GVHD. We developed improvements for the suicide gene system based on CD3+/CD20+/Rituximab through the utilization of lentiviral vectors and changes in the T cell culture conditions. This protocol could

be applied in combination with allogeneic CTL in immunotherapy protocols, reducing the risk of developing GVHD and increasing the applicability and safety of this approach.