# IDO1-targeting intervention by proteasome inhibition in autoimmune diabetes

E. Albini[†], G. Mondanelli[†], C. Volpi[†], M.T. Pallotta[†], P. Puccetti[†] , U. Grohmann[†] and C. Orabona[†]

[†] University of Perugia, Dept. Experimental Medicine, ITALY

Indoleamine 2,3-dioxygenase 1 (IDO1) is a metabolic enzyme involved in the catabolism of tryptophan. Its metabolic activity has become pivotal in the regulation of the immune responses. The functional expression of IDO1 enzyme confers a tolerogenic phenotype to different subsets of dendritic cells (DCs). Our previous data suggested a defective IDO1 expression in a prediabetic phase of nonobese diabetic (NOD) mice, a prototypic model of human type 1 diabetes. Based on the recent finding that IDO1 may be subjected to regulatory proteolysis, which is triggered by IL-6 and mediated by the immunoproteasome, this pathway was explored in splenic plasmacytoid dendritic cells (pDCs) of NOD mice. The in vitro conditioning of murine NOD pDCs with the proteasome inhibitor Bortezomib, increased the functional expression of IDO1 enzyme, conferring those cells an immunoregulatory phenotype that is strongly inhibited for presenting in vivo the diabetogenic antigen IGRP, an effect accompanied by increased IGRP-specific regulatory T cells in pancreatic lymph nodes. The inhibition of IDO1 by 1-methyl tryptophan (MT) completely abolished the immunoregulatory effect of Bortezomib in NOD pDCs, indicating the involvement of the enzyme. Moreover, the pharmacologic treatment of NOD female mice with Bortezomib during prediabetic phase (8-10 weeks old) prevented the onset of hyperglycemia, reducing the diabetes incidence. Overall, our data suggest that the control of proteasomal degradation in pDCs may represent an innovative strategy for inducing/potentiating IDO1-mediated immunoregulation in autoimmune diabetes.