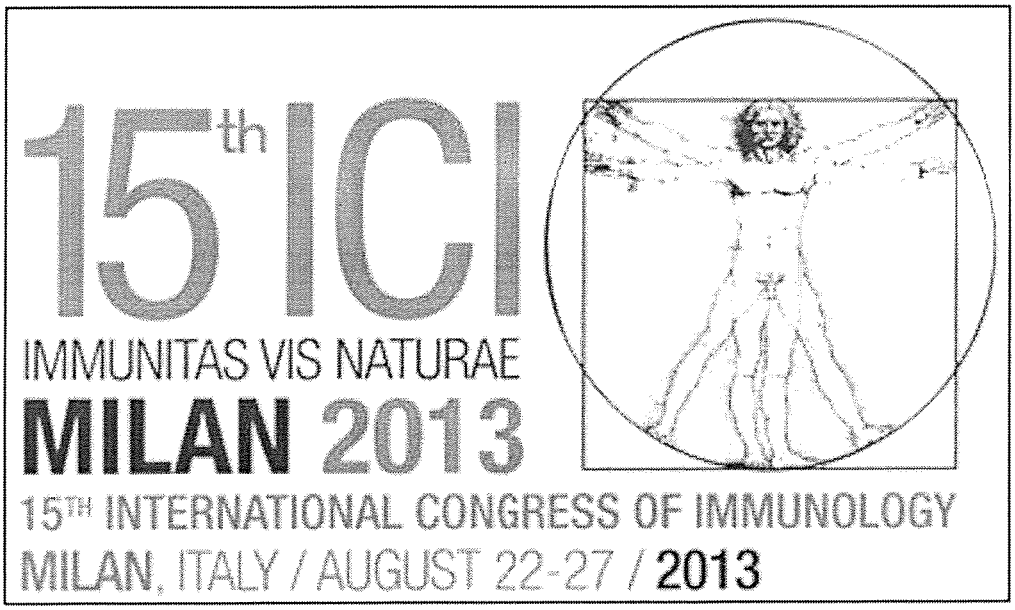
# BOOK OF ABSTRACTS

**Co-Editors: Luciano Adorini, Massimo Locati**



# ANNOTATIONS

In the following we are publishing the abstracts as submitted by the authors.

Missing session numbers represent sessions with no abstracts associated.
Missing presentation numbers represent talks with no abstracts received as per date of production. Bold presentation numbers indicate the presenting author.

The sessions are in numerical order.

Keys and Abbreviations:

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| IL1.01.01 | Invited Lecture |
| LB.1 | Late Breaking Session 01 |
| LL.1 | Lunchtime Lecture |
| P1.01 | Poster Presentation |
| PL.1 | Plenary Lecture |
| PS.1 | Lecture: Perspectives in Immunology |
| S.1 | Symposium |
| SS.1 | Sponsored Session |
| W1.01 | Workshop |

The Editors

recent onset T1D in NOD mice, partially by boosting pancreatic regulatory T cells (Treg cells). These approaches are currently being evaluated in humans. Here, we studied the mechanism of action of higher IL-2 doses and low-dose IL-2 and RAPA (RAPA/IL-2) combination. We assessed the effect of high doses of IL-2 or the combined treatment in NOD T1D evolution, including flow cytometric analysis of immune-competent cells and glucose metabolism assessment by glucose tolerance tests and microarray analysis of liver response to glucose. We show that high doses of IL-2, despite further boosting Treg cells, rapidly precipitated T1D in pre-diabetic female and also male mice and induced a striking increase in pancreatic myeloid cells. RAPA counteracted IL-2 effects on Treg cells, failed to control IL-2-boosted NK cells and broke IL-2-induced tolerance in a reversible way. Notably, RAPA/IL-2 combination failure to cure T1D was associated to an unexpected deleterious effect on glucose homeostasis at multiple levels. Our data help understand the therapeutic limitations of IL-2 alone or RAPA/IL-2 combination and could lead to the design of improved therapies for T1D.

**P6.03.17**
**Treg CD39+ and Th17 cells in Type 2 Diabetes Mellitus Patients**

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Type 2 diabetes mellitus (T2D) represents a chronic and progressive syndrome characterized by hyperglycemia which results from insulin resistance and pancreatic β-cell dysfunction. It is clear that inflammation and cytokine production by the immune system and adipose tissue plays an important role in the pathogenesis of T2D. On the other hand, naturally occurring regulatory T (Treg) cells maintain the tolerance to self-antigens. A dysregulation in the number or function in Treg cells contributes to autoimmune diseases, chronic inflammatory diseases, and cancer. CD39, an ectonucleotidase which hydrolyzes ATP is expressed on a subset of human natural Treg cells. IL-17-producing $CD4^+$ T cells (Th17 cells) could be pathogenic in many diseases and are resistant to suppression by human $Foxp3^+$ Treg cells. The aim of this work was to evaluate the expression of Treg CD39+ and Th17 cells in peripheral blood mononuclear cells from T2D patients. We found similar levels of CD4+Foxp3+CD39+ and CD4+Foxp3+CD39- Treg, in healthy subjects (n=24) and T2D patients (n=24). In contrast, Th17 cells were found significantly diminished in T2D patients compared to healthy subjects. T2D patients were classified according to the WHO body mass index categories and patients with overweight and obesity showed the lowest levels of CD4+IL-17+ T cells, compared to T2D patients with normal weight. These data are in agreement with the levels of mRNA IL-17. In conclusion, our results indicate that decreased expression of Th17 cells could be important in understanding the defective regulation of inflammation in diabetes.

**P6.03.18**
**Immunohistochemical study of the pancreas of patients with long termed diabetes mellitus type 1**

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Pathological findings in the pancreases of diabetes mellitus type1 (DM1) patients include peri-and intra-insular inflammatory infiltrates, namely insulitis. Although considered to be pathognomonic for recent onset disease, insulitis has only been described in approximately 150 cases over the past century.
We have studied the autopsy samples of the pancreas of 5 adult patients with long termed DM1 and of 9 adults not suffering from disorders of carbohydrate metabolism as a control. Antibodies to insulin and glucagon were used for the detection of hormones of the endocrine cells. Antibodies to CD8, CD16, CD20, CD25 and CD71 were used as immunological markers.
In the control samples of the pancreas as well as in the pancreas of two patients with DM1 CD16-, CD25-, CD8-, CD20- and CD71-positive cells were observed only in a small number among the blood cells.
We have identified the inflammation in the acinar part of three patients with DM1. CD16+ and CD25+ cells have made the largest contribution to this reaction. The number of cells positive for antibodies to the transferrin receptor (CD71) was increased compared to the control. The amount of cells positive for antibodies to CD8 and CD20 in these samples was small.
It is believed that insulitis is characteristic for the islets, which have retained a significant part of the b-cells. We have detected the inflammation in exocrine part of the pancreas in 2 patients with DM1 with absolutely absence of b-cells. Therefore, this reaction can hardly be regarded as directed only against insulin-containing cells.

**P6.03.19**
**ST2 deficiency enhances diet-induced inflammation in visceral adipose tissue and obesity in mice**

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Obesity associated low-grade chronic inflammation in adipose tissue and may contribute to type 2 diabetes. Although interleukin (IL)-33 may have protective role in obesity and atherosclerosis, the contribution of IL-33/ST2 axis in metabolic disorders needs to be elucidated. We investigated the role of ST2 in high-fat diet (HFD)-induced obesity using ST2-deficient ($ST2^{-/-}$) and wild type mice on BALB/c background relatively resistant to HFD-induced obesity. The deletion of ST2 enhanced systemic and visceral adipose tissue (VAT) inflammation and was associated with significantly higher weight gain and amount of total VAT in $ST2^{-/-}$ mice fed HFD for 18 weeks. More numerous M1 macrophages and markedly decreased M2 macrophages were observed in VAT of HFD-fed $ST2^{-/-}$ mice. Additionally, VAT of $ST2^{-/-}$ mice fed HFD had increased percentage of $CD3^+$ T cells with lower incidence of $CD4^+CD25^+FoxP3^+$ T regulatory cells and $CD4^+PD\text{-}1^+$ T cells in comparison with low-fat diet fed controls and a pronounced increase of the percentage of $CD19^+$ B cells. The incidence of IL-5 and IL-17 expressing stromal vascular fraction cells were significantly lower in HFD-fed $ST2^{-/-}$ mice. Serum levels of pro-inflammatory cytokines IL-1β and IFN-γ were also increased in HFD-fed $ST2^{-/-}$ mice, while the levels of IL-6 and CRP did not differ among groups. Importantly, the levels of anti-inflammatory IL-10 and IL-13 were significantly lower in the sera of $ST2^{-/-}$ mice compared with wild type controls. Our findings suggest that protective role of IL33/ST2 signaling in diet-induced adipose tissue inflammation is mediated by downregulating M1 macrophages and Th1 cell induction.

**P6.03.20**
**Oral administration of L. Lactis secreting $hGAD65_{370\text{-}575}$ and hIL-10 can revert diabetes in recent-onset NOD mice when combined with low-dose anti-CD3**

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In type 1 diabetic patients insulin-producing pancreatic beta-cells are destroyed by self-reactive autoantigen-specific T cells. As a therapy, reinstalling antigen (Ag)-specific tolerance is considered the favorable approach. Previous studies show that orally-administered genetically-modified *lactococcus lactis* (*L. lactis*) secreting human pro-insulin and human IL10 (hIL10) induce diabetes remission in NOD mice when combined with low-doses of anti-CD3. Using *L. lactis* as an innovative protein carrier this study aimed to determine whether another islet autoAg, GAD65, could establish or increase this diabetes reversal rate in new-onset NOD mice. Based on epitope spreading, bacterial secretion and growth profile, a bacterial strain secreting hIL10 and $hGAD65_{370\text{-}575}$ was evaluated *in vivo*. New-onset diabetic NOD mice were given a subtherapeutic dose of anti-CD3 for 5 consecutive days (clone 145-2C11, 2.5 µg/d, iv.) and *L. lactis* 5 times weekly for 6 weeks ($10^9$ CFU/d, by gavage). Treatment with low-dose anti-CD3 and $hGAD65_{370\text{-}575}$ plus hIL10 (n=36) significantly induced 67% diabetes reversal in new-onset diabetic NOD mice compared to 31% and 37% using anti-CD3 alone (n=42) or with empty vector (n=32),