# IMMUNOLOGY AT THE CONFLUENCE OF MULTIDISCIPLINARY APPROACHES

# ABSTRACT BOOK

**Institute for Biological Research "Siniša Stanković" National Institute of Republic of Serbia**
**University of Belgrade**

**Immunological Society of Serbia**

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Poster presentation

## ETHYL PYRUVATE STIMULATES DIFFERENTIATION OF REGULATORY T CELLS *IN VITRO* AND *IN VIVO*

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Ethyl pyruvate (EP) is a stable form of pyruvate that has shown potent anti-oxidant and anti-inflammatory properties both *in vitro* and *in vivo* and was able to ameliorate systemic inflammation and multiple organ dysfunctions in multiple animal models. Our recent study suggests that the application of EP in the mouse model of type 1 diabetes successfully prevents the clinical manifestation of the disease by augmenting the number of tolerogenic dendritic cells and regulatory T cells (Treg). Our present study indicates that during *in vitro* differentiation of $CD4^+$ naïve cells into Treg, the addition of EP stimulated Treg generation. This was in line with the observed increased proliferation of newly differentiated Treg ($Ki67^+FoxP3^+$). Surprisingly, EP did not scavenge reactive oxygen species (ROS), but rather stimulated ROS production by Treg. In Treg, ROS is mainly generated during oxidative phosphorylation (OXPHOS) during which the majority of energy for the cell is produced. EP probably acted as a substrate in Krebs cycle because the cells produced more pyruvate dehydrogenase, which converts pyruvate to acetyl CoA. EP treatment also resulted in less kinase of pyruvate dehydrogenase, which acts as an inhibitor of Krebs cycle. As a result, there was an evident stimulation of OXPHOS, confirmed by increased ATP production in differentiated Treg. Additionally, EP exerted its stimulatory function on Treg in healthy C57BL/6 mice. When given either intraperitoneally or *per os*, EP increased Treg numbers within the peritoneal cavity or gut-associated lymphoid tissue, respectively. Seemingly, EP promoted differentiation of Treg *in vivo* and did not affect their suppressive properties (proportion of CTLA-$4^+$, $CD39^+$, PD-$1^+$, IL-$10^+$ Treg) or their affinity towards specific effector T helper cells ($ROR\gamma T^+$, $Tbet^+$ or GATA-$3^+$ Treg). In conclusion, EP acts as specific metabolic fuel for Treg generation, likely because these cells mainly rely on OXPHOS-derived energy