

## CONFIRMATION OF ABSTRACT SUBMISSION

The following abstract has been successfully submitted to the Combined EPC & IAP Meeting.

<b>Abstract No:</b>	662
<b>Date of submission:</b>	03.03.2014
<b>Section:</b>	Basic science - Chronic pancreatitis
<b>Preferences:</b>	Oral or Poster
<b>EPC Travel scholarship request for the first author:</b>	Yes

### Comparative effectiveness of immune-cell depletion and a targeted therapy against LT $\beta$ R-signaling in the treatment of autoimmune pancreatitis

Gitta Maria Seleznik<sup>1</sup>, Theresia Reding<sup>1</sup>, Sabrina Sonda<sup>1</sup>, Jeffrey Browning<sup>2</sup>, Stephan Segerer<sup>3</sup>, Mathias Heikenwalder\*<sup>4</sup>, Rolf Graf\*<sup>1</sup>

<sup>1</sup>Swiss HPB Center, Visceral & Transplantation Surgery, University Hospital Zurich, Switzerland

<sup>2</sup>Department of Microbiology, Boston University School of Medicine, Boston, United States

<sup>3</sup>Division of Nephrology, University Hospital Zurich, Switzerland

<sup>4</sup>Institute of Virology, Technische Universität München-Helmholtz Zentrum München, Munich, Germany

**Background:** Long-term management of autoimmune pancreatitis (AIP) - a relapsing steroid-responsive disorder - is still elusive. To study AIP pathogenesis and develop novel, steroid sparing therapies, we used our recently published mouse model, Tg(Ela1-Lta,b), that develops autoimmunity reminiscent to human AIP including tertiary lymphoid organ (TLO) formation. In this model we have previously shown that in contrast to corticosteroids, which only diminished inflammation, inhibition of Lymphotoxin beta receptor signaling (LT $\beta$ R-Ig) also abrogated autoimmunity.

**Aim:** To investigate the effectiveness of LT $\beta$ R inhibition compared to depletion of specific immune cell subsets (B-cells, CD4+ T-cells), which are suggested to be involved in AIP development.

**Materials & methods:** Transgenic mice with established AIP were treated with anti-CD20, anti-CD4 mAb or LT $\beta$ R-Ig fusion protein. Histology, autoantibodies, cytokine and chemokine expression, TLO integrity and extrapancreatic manifestations were tested. Macrophage and T helper cell polarization was evaluated upon different treatments.

**Results:** LT $\beta$ R-Ig and anti-CD20 treatment led to significant improvement of AIP. The molecular mechanism of this beneficial effect possibly involves downregulation of Stat3 and non-canonical NF- $\kappa$ B activation. Additionally, in contrast to anti-CD20 and anti-CD4, blocking LT $\beta$ R-signaling reverted acinar-to-ductal metaplasia formation and disrupted TLOs. Anti-CD4 treatment resulted in reduced Th1 and Th2 polarization; however did not ameliorate AIP.

**Conclusion:** In this unique genetic mouse model of AIP, we demonstrate that therapy with LT $\beta$ R-Ig and anti-CD20 antibody is superior to CD4+ T-cell depletion. With these targeted therapies we reveal novel anti-inflammatory and anti-autoimmune mechanisms. Assessing parameters associated with AIP pathogenesis, LT $\beta$ R-Ig achieved the greatest improvements. Therefore, inhibition of LT $\beta$ R-signaling could become an alternative or supplementary approach for AIP treatment.