New perspectives on therapeutic immune tolerance.

**OP0002**

**IMMTOR NANOPARTICLES ENHANCE THE TOLEROGENIC ENVIRONMENT OF THE LIVER IN MICE**

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**Background:** Tolerogenic ImmTOR biodegradable nanoparticles encapsulating rapamycin have been shown to mitigate the formation of anti-drug antibodies against pegadricase, a pegylated uricase enzyme, which enabled monthly dosing of rapamycin have been shown to mitigate the formation of anti-drug antibodies (IV) administration in mice. In the spleen, ImmTOR has been demonstrated to induce tolerogenic dendritic cells and antigen-specific regulatory T cells and inhibit antigen-specific B cell activation. Splenectomized mice showed a partial but incomplete abrogation of the tolerogenic immune response mediated by ImmTOR.

**Objectives:** Here we evaluated the ability of ImmTOR to enhance the tolerogenic environment in the liver.

**Results:** All the major resident populations of liver cells, including liver sinusoidal endothelial cells (LSECs), Kupffer cells (KC), stellate cells (SC), and hepatocytes, actively took up fluorescent-labeled ImmTOR particles, which resulted in downregulation of MHC class II and co-stimulatory molecules and upregulation of the PD-L1 checkpoint molecule. The LSEC, known to play an important role in hepatic tolerance induction, emerged as a key target cell for ImmTOR. The tolerogenic environment led to a multi-pronged modulation of hepatic T cell populations, resulting in an increase in T cells with a regulatory phenotype, upregulation of PD-1 on CD4+ and CD8+ T cells, and the emergence of a large population of CD4+CD8+ (double negative) T cell population. Modulation of T cell phenotype was seen to a lesser extent after administration by empty nanoparticles, but not free rapamycin. The upregulation of PD-1, but not the appearance of double negative T cells, was inhibited by antibodies against PD-L1 or CTLA-4.

**Conclusion:** These results suggest that the liver may contribute to the tolerogenic properties of ImmTOR in mitigating anti-drug antibody responses to bio-logic therapies, such as pegadricase.


**REFERENCES:**


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**Autoimmune diseases by abnormal T cell function—**

**OP0003**

**AUTOACTIVE CD4+ T CELLS AND THEIR TCR REPertoire IN PR3-ANCA ASSOCIATED VASCULITIS**

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**Background:** ANCA-associated vasculitis (AAV) with proteinase 3 (PR3) ANCA is genetically associated with HLA-DP [1], is often relapsing in nature, and has a predisposition for kidneys, lungs and ear-nose-throat involvement [2]. Despite the presence of PR3-ANCA, indicating CD4+T-cell help in the disease, the knowledge about autoreactive CD4+T cells is scarce. Activated T cells have been shown at site of inflammation [3] and involvement of proinflammatory cytokines in circulation is also reported [4, 5].

**Objectives:** Identification of autoreactive T cells may help to identify the effector immune responses and chronically. We therefore aimed to investigate PR3-specific CD4+T-cell responses in peripheral blood of AAV patients with a focus on both phenotype and T-cell receptor (TCR) repertoires.

**Methods:** The study included sixty-six patients: 26 with active PR3 autoantibody+ AAV, 21 with inactive but PR3+ AAV and 19 with inactive PR3- AAV. In vitro cultures with PR3 protein were established to assess antigen-specific cytokine responses in a 3-color fluorescence assay. Deep immunophenotyping was performed by flow cytometry. Antigen-responsive CD4+ T cells were isolated and single cell TCRβ chain sequences were generated and analyzed from PR3+ AAV patients (n=5) using a previously published protocol [6].

**Results:** PBMCs from AAV patients demonstrated an HLA-DP associated cytokine response with PR3 stimulation including IFN-γ and IL-10, but not IL-17A. This T-cell autoreactivity was found to be confined to a highly differentiated CD4+ T cell population characterized by perforin and GPR56 expression, implicating a cytotoxic feature of the response. Active disease involved a reduction in expression of several markers associated with cytotoxicity amongst the CD4+GPR56+ T cells. Their frequency was also negatively associated with the doses of prednisolone. Similar phenotype was shared with T cells activated by human cyto-megalovirus (HCMV) peptides in the same patient cohort. Single cell sequencing of paired alpha beta T-cell receptors (TCRs) revealed different patterns of gene usage between PR3 and HCMV reactive T cells. Moreover, we could identify shared (public) PR3-reactive T-cell clones between different HLA-DPB1*04:01+ patients.

**Conclusion:** PR3 is an autoantigen which provokes ANCA responses in AAV patients. Our study identified PR3-reactive CD4+ T cells at the level of their phenotype and TCR repertoire. The autoreactive CD4+ T cells, present in both active and inactive disease, implicate chronic antigen exposure and the persistence of long-lived T-cell clones. The presence of public autoreactive clones between HLA-DPB1*04:01+ patients suggests an active role for these cells in pathogenesis of AAV and validates the link with predisposed genotype.

**REFERENCES:**


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**OP0004**

**AUTOIMMUNE AND INFLAMMATORY MANIFESTATIONS IN COMMON VARIABLE IMMUNODEFICIENCY DISORDERS**

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**Background:** Common variable immunodeficiency (CVID) disorders are the second most frequent immunodeficiency worldwide and autoimmune diseases (AD) are present in 20% of such patients, cytopenia being the most frequent manifestation [1]. Defects in central and peripheral tolerance, activation/proliferation of B cells, and hypogammaglobulinemia are key features of the disease, along with a reduction in CD4+T cells, abnormalities in Treg and defective secretion of regulatory cytokines, that could perpetuate autoimmune - autoinflammatory phenomena.

**Objectives:** To describe immune and inflammatory disorders in our CVID cohort.

**Methods:** Retrospective analysis of 33 patients who fulfill the European Society for Immunodeficiencies (ESID) Registry – Work criteria for CVID diagnosis [2] treated in the immunodeficiency unit of our tertiary university hospital. After getting an informed consent form, medical records were revised to obtain clinical, analytical and immunological data.

**Results:** Of the 33 CVID patients was shared that 11 had some autoimmune-inflammatory manifestation. Seven patients presented autoimmune thrombocytopenia (AIT), and one of them also had non-severe neutropenia. Two patients also had seronegative spondyloarthropathy, one patient had cutaneous psoriasis, and