New perspectives on therapeutic immune tolerance.

**OP0002** IMMOTOR NANOPARTICLES ENHANCE THE TOLEROGENIC ENVIRONMENT OF THE LIVER IN MICE

P. Iivinskas¹, C. Roy¹, J. Leprevost², K. Kishimoto¹.¹Selecta Biosciences, Biology, Watertown, United States of America

**Background:** Tolerogenic ImmTOR biodegradable nanoparticles encapsulating rapamycin have been shown to mitigate the formation of anti-drug antibodies against pegactridge, a pegylated uricase enzyme, which enabled monthly dosing and sustained reduction of serum uric acid levels in a Phase 2 clinical trial of SEL-212, a combination of pegadricase and rapamycin have been shown to mitigate the formation of anti-drug antibodies and 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 nanoparticles, 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+ cells (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 biologic therapies, such as pegactridge.


**DOI:** 10.1136/annrheumdis-2021-eular.1920

**Autoimmune diseases by abnormal T cell function**

**OP0003** AUTOREACTIVE CD4+ T CELLS AND THEIR TCR REPERTOIRE IN PR3-ANCA ASSOCIATED VASCULITIS

R. Kumar¹, N. Yosofu¹, A. Bartoletti², A. Avik³, B. Raposo¹, A. Jonasdottir⁴, B. Lövström¹, K. Chenin¹, A. Bruchfeld⁴, K. Gunnarsson¹, V. Malmström¹.¹Karolinska Institutet, Division of Rheumatology, Department of Medicine, Stockholm, Sweden; ²The University of Pavia, Medicine, Pavia, Italy; ³Karolinska University Hospital, CLINTEC, Stockholm, Sweden

**Background:** ANCA-associated vasculitis (AAV) with proteinase 3 (PR3) ANCA is genetically associated with HLA-DR [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 drivers of the immune responses and chronicity. 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 fluorospot assay. Deep immunophenotyping was performed by flow cytometry. Antigen-responsive CD4+ T cells were isolated and single cell TCRβ repertoire 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-DR associated cytokine response, PR3 stimulation including IFN-γ, 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. A 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 autotarget 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:**


**Disclosure of Interests:** None declared

**DOI:** 10.1136/annrheumdis-2021-eular.41

**Autoimmune and Inflammatory Manifestations in Common Variable Immunodeficiency Disorders**

**OP0004** AUTOIMMUNE AND INFLAMMATORY MANIFESTATIONS IN COMMON VARIABLE IMMUNODEFICIENCY DISORDERS

K. López-Aldae¹, R. Hidalgo¹, A. Antolí², G. Rocamora³, X. Corbella², X. Solanich³.²Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL, Internal Medicine, L'Hospitalet de Llobregat, Spain; ³Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL, Internal Medicine, Hospital de Llobregat, Spain

**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 studied, 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...