Conclusion: Results from CRISPRi and CRISPRa are concordant and support the idea that intronic enhancers within *ANKRD55*, containing SNPs associated with RA susceptibility, can regulate the expression of both *ANKRD55* and also modulate long range gene regulation with *IL6ST* to influence disease risk. These techniques are crucial to begin to dissect and translate GWAS findings.

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Disclosure of Interests: None declared

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OP0193 CAMP RESPONSE ELEMENT MODULATOR (CREM) α INDUCES DUAL SPECIFICITY PROTEIN PHOSPHATASE (DUSP)4 THROUGH EPIGENETIC REMODELING, PROMOTING IL-17A AND REDUCING IL-2 EXPRESSION IN T CELLS

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Background: Tissue inflammation and organ damage in systemic lupus erythematosus (SLE) have been linked to effector T cells that are characterized by increased IL-17A and reduced IL-2 production(1). T cells from patients with SLE express increased levels of the transcription factor cAMP response element modulator (CREM) α that contributes to altered cytokine expression(1-3). However, the exact molecular events contributing to dysregulated IL-17A and IL-2 expression are incompletely understood.

Objectives: To investigate molecular events that promote effector T cells in health and disease. The definition of molecular regulators of effector T cell generation and activity may deliver new biomarkers and potential therapeutic targets in disorders characterized by altered effector T cell function, including (but not limited to) SLE.

Methods: Using CRISPR/Cas9 genome editing and lentiviral transduction, we generated CREM α deficient or overexpressing Jurkat T cells. Gene expression profiles in Jurkat and primary human CD4⁺ T cells were assessed by qRT-PCR and mRNA probe-based hybridization techniques. Gene regulation events were investigated using luciferase reporter assays (*trans*-activation) and ChIP. Interactions between CREM α and the transcriptional co-activator p300 were assessed using proximity ligation assays and p300 knock-down with siRNAs.

Results: We link CREM α production in effector CD4⁺ T cells with increased expression of dual specificity protein phosphatase (DUSP)4. Using genetically modified Jurkat T cells, we demonstrate that CREM α induces DUSP4 through recruitment of the transcriptional co-activator p300 and histone H3K18 acetylation. Using DUSP4 transfection models and genetically modified Jurkat T cells, we support previous reports suggesting that DUSP4 induces IL-17A while limiting IL-2 expression. Furthermore, we demonstrate that CD4⁺ T cells from patients with juvenile-onset SLE share the phenotype with CREM α over-expressing CD4⁺ T cells with increased DUSP4 expression that contributes to imbalanced IL-17A and IL-2 production.

Conclusion: Collectively, our results deliver previously unknown CREM α -mediated molecular mechanisms promoting effector T cells and support the central involvement of CREM α in the pathophysiology of SLE. CREM α and DUSP4 may prove valuable as disease biomarkers and/or targets in the search for individualized and target-directed treatments.

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OP0194 HISTONE DEACETYLASE 1 (HDAC1): A KEY MEDIATOR OF T CELLS FOR THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

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Background: Despite enormous efforts to develop new therapeutic strategies for treatment of rheumatoid arthritis (RA), the large number of non responding patients to currently available drugs underlies the unmet need to identify new therapeutic targets. Certain CD4⁺ T cell subsets, especially those polarized toward the T helper (Th) subsets Th1 and Th17, have been shown to be major drivers of inflammation in patients with RA. The expression of their key transcription factors is controlled by histone modifications which includes acetylation of *lysine residues* mediated by histone deacetylases (HDAC). Indeed, pan HDAC inhibitors have been shown to be a potential therapeutic strategy. However, major side effects limited the clinical use and underline the need of more specific HDAC inhibitors.

Objectives: We addressed the individual role of HDAC1 on the development of collagen-induced arthritis model (CIA), which partially reflects human RA.

Methods: Mice with a T cell specific deletion of HDAC1 (HDAC1 cKO) were generated by using the CD4Cre/LoxP system. At week 8 of age arthritis was induced in wild type (WT) and HDAC1 cKO mice by immunizing with chicken collagen II (CII), emulsified in complete Freund's adjuvant. After 21 days mice received a booster injection of CII. The animals were 3 times per week scored for paw swelling and grip strength. Anti-CII antibody levels were determined by ELISA. Various cell subsets, including Th cells, were detected in the blood, the spleen and the draining lymph node by FACS analysis. To test antigen-specific T cell activation we performed in vitro restimulation of spleen and lymph node cells with collagen II followed by assessment of cytokine production and quantification of the proliferation rate using 3Hthymidine incorporation.

After 4 and after 10 weeks mice were sacrificed and paraffin sections of the affected joints were analyzed for histomorphologic signs of inflammation, cartilage and bone destruction.

Results: Eighty percent of the animals developed serum anti-CII antibodies (IgM and IgG) whereby the antibody levels were a day 21 of disease similar between the HDAC1 cKO and the WT mice. Furthermore, no differences in the production of antibody subclasses, especially of pathogenic IgG2c antibodies, were observed. Enhanced percentages of Th1 and Th17 cells among HDAC1-null CD4⁺ T cells were detected after immunization in the HDAC1 cKO mice. Nonetheless and unexpectedly, these mice did not develop any signs of disease at the clinical level while WT mice developed pronounced paw swelling and loss of grip strength. In accordance with the clinical data, histological analysis revealed no signs of inflammation, no bone erosion and no appearance of osteoclasts in the joints of HDAC1 cKO mice. This appeared to be mainly caused by an impaired migratory capacity of HDAC1 cKO CD4⁺ T cells, so that they were unable to invade the joints.

Conclusion: Our data show the importance of HDAC1 as a key immune regulator in the pathogenesis of T cell driven collagen induced arthritis. Therefore it might be considered as an interesting novel therapeutic target in RA.

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OP0195 SELECTIVE EXPANSION OF REGULATORY T-CELLS IN HUMANS BY A NOVEL IL-2 CONJUGATE T-REG STIMULATOR, NKTR-358, BEING DEVELOPED FOR THE TREATMENT OF AUTOIMMUNE DISEASES

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Background: Impaired IL-2 production and dysfunction of regulatory T cells (Tregs) have been identified as key immunological defects leading to the