downstream of autoantibodies. A GILZ-based treatment could be a potential therapeutic strategy in SLE.

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FRI0270 IDENTIFICATION OF NOVEL DYSREGULATED INTERFERON-INDUCIBLE NON-CODING RNAs IN SJOÖGREN'S SYNDROME

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Background: Sjögren's syndrome (SS) is a chronic, heterogeneous disease with hallmark features of auto-inflammation and autoantibody production. Upregulation of type I and II interferon-stimulated genes (ISGs), known as the "Interferon (IFN) Signature" is correlated with anti-Ro titers and has been observed both in the salivary glands and peripheral blood of SS patients. Within the 2 p25.2 genomic interval, the long non-coding RNA (lncRNA) negative regulator of the interferon response (*NRIR*) has been identified as inducible by type I IFN and is responsible for the downregulation of the ISGs *CMK2* and *RSAD2*.

Objectives: We sought to identify additional unannotated ISGs lncRNAs that are differentially expressed (DE) in SS patients utilising correlated expression of *RSAD2*.

Methods: We evaluated and compared the transcriptome of anti-Ro(+) patients (n=27) and healthy controls (n=27) using RNA-seq with DE defined as $q < 0.05$ and a fold change (FC) ≥ 2 or ≤ 0.5 . qRT-PCR was used to validate DE with primers specific for each RNA of interest. To understand the biological relevance of these transcripts, we performed *in vitro* time-course experiments to compare the transcriptional changes of unstimulated cells and cells stimulated with either PMA/ionomycin (PMA/I) or universal type I IFN for 36 hours measuring 7 time points.

Results: One of the most overexpressed type I ISGs in the SS Ro(+) is *RSAD2* (FC=8.05, $p=3.29 \times 10^{-07}$). Because of its role in the type I IFN pathway, pairwise correlation coefficients between all DE transcripts and *RSAD2* for SS Ro(+) patients were calculated. In total, we found 223 transcripts exhibiting correlation with *RSAD2* expression (Pearson's $r > 0.70$ or < -0.60), including *NRIR* (FC=2.72, $p=5.87 \times 10^{-03}$) and *CMK2* (FC=2.53, $p=3.58 \times 10^{-03}$). Of the 223 transcripts, 14 DE expressed lncRNAs correlated with *RSAD2* expression. Several antisense ncRNAs situated nearby to other type I ISGs correlated with *RSAD2*, including: *AC099063.1* (FC=2.51), *AC004551.1* (FC=3.35), and *AP001610.1* (FC=4.12). We confirmed upregulation of these lncRNAs by qRT-PCR from the independent replication (14 Ro(+) and 36 controls) cohort ($p=2.49 \times 10^{-02}$, 8.63×10^{-06} , 1.17×10^{-04} , respectively). Based on the locations of the lncRNAs to type I ISGs, HSB-2 cells were stimulated with PMA/I or universal type I IFN. Using qRT-PCR to measure the protein coding genes *MX1*, *OAS1*, and *GBP5* along with the lncRNAs, *AC099063.1* (*GBP5-AS1*), *AP001610.1* (*MX1-AS1*), and *AC004551.1* (*OAS123-AS1*) showed coordinated regulation with their protein coding counterparts with both stimuli.

Conclusions: Given the importance of the IFN signature to disease pathogenesis in the autoantibody positive patients, it is critical that we better understand how this complex pathway is coordinately regulated. Since one critical function of lncRNAs is to regulate the genome, characterising the mechanisms by which these 14 identified by this study regulate the ISG coordinately could result in new diagnostic and/or therapeutic options.

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FRI0271 DIMETHYL FUMARATE INHIBITS UBE2L3 MEDIATED TLR7 SIGNALING AND AUTOREACTIVE B CELL DEVELOPMENT IN SLE

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Background: Genetic studies have identified a single *UBE2L3* risk haplotype which is associated with SLE and multiple autoimmune diseases, and leads to increased expression of *UBE2L3* in eQTL studies. The E2 ubiquitin-conjugating enzyme *UBE2L3* regulates NF- κ B activation through regulation of the Linear Ubiquitination Chain Assembly Complex (LUBAC). Thus *UBE2L3* regulates CD40-driven B cell activation. The *UBE2L3* risk allele correlates with circulating plasmablast and plasma cell expansion in SLE individuals.

Objectives: To determine the effect of *UBE2L3* and linear ubiquitination on TLR7 signalling, and test the effect of Dimethyl Fumarate (DMF), which has recently been shown to inhibit *UBE2L3*, on B cell and plasmablast differentiation in SLE.

Methods: Confocal microscopy, immunoprecipitation and western blot were used to assess linear ubiquitin chain accumulation in TLR7-HEK293 cells after TLR stimulation by Resiquimod. The effect of *UBE2L3* and LUBAC on TLR7 signalling was dissected by the use of *UBE2L3*/LUBAC overexpression, dominant negative mutants and shRNA silencing, measuring NF- κ B reporter activity, IkappaBalpha phosphorylation, gene expression by qPCR and IL-8 secretion. DMF was administered *in vitro* to human B cells isolated from SLE patients (n=15) and controls and cultured with Resiquimod and/or IFN α for 5–7 days. B cell viability/proliferation, plasmablast differentiation were analysed by 10-colour flow cytometry. Supernatants were assayed for immunoglobulin secretion and autoantibody production.

Results: TLR7 stimulation led to intracellular accumulation of linear ubiquitin chain comparable to TNF α . *UBE2L3* and LUBAC co-overexpression enhanced TLR7 driven NF- κ B activation and led to increased NF- κ B target mRNA expression and increased secretion of IL-8. The effect was specific to *UBE2L3* compared to other E2 enzymes. Dominant negative mutant *UBE2L3*(C86S) or HOIP (C885S) or *UBE2L3*/HOIP shRNA suppressed the response to TLR7 stimulation. DMF showed a dose-dependent inhibition of TLR7-mediated NF- κ B activation. In primary SLE and healthy B cells, DMF suppressed proliferation of switched and unswitched CD27+ memory B cells and blocked plasmablast differentiation. DMF profoundly inhibited immunoglobulin secretion and anti-nuclear autoantibodies production in response to TLR7 and IFN α stimulus.

Conclusions: Our data demonstrate that linear ubiquitination and *UBE2L3* regulate TLR7 activation of NF- κ B. *UBE2L3* silencing or pharmacological antagonism of *UBE2L3* by DMF suppressed the response to TLR7 activation. Excessive TLR7 signalling has been linked to SLE development and enhanced B cell autoreactivity. Thus our data identify a novel mechanism by which the *UBE2L3* risk haplotype contributes to SLE susceptibility. DMF suppressed plasmablast differentiation and inhibited TLR7 and IFN α induced autoantibody production. These results support a role for repositioning DMF (currently used to treat multiple sclerosis) in the treatment of SLE.

Disclosure of Interest: None declared

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FRI0272 PHARMACODYNAMIC EFFECTS OF ATACEPT TREATMENT IN A CYNOMOLGUS MONKEY KLH ANTIGEN CHALLENGE MODEL

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Background: Atacept is an antagonist of the B cell regulatory factors BlyS (B lymphocyte stimulator) and APRIL (a proliferation inducing ligand). It is capable of binding to all known conformations of BlyS and APRIL and is thus expected to modulate the maturation, differentiation, and effector function of B cells. We aimed to define the relationship between atacept drug exposure and pharmacodynamic (PD) effects *in vivo*. Here, we report results of our study examining the effects of atacept on the immune response in a keyhole limpet hemocyanin (KLH) challenge model in cynomolgus monkeys.

Methods: Cynomolgus monkeys (*Macaca fascicularis*) were injected with KLH on Day -33, and on Day 1 received the first dose of either atacept (0.3, 3, or 30 mg/kg) or vehicle followed by a KLH challenge. Animals were dosed weekly (Day 1, 8, 15) and were subsequently monitored for 2 weeks before the study ended on Day 29. Clinical signs, total and free drug levels, peripheral blood B and