Abstract 8 Figure 2

Methods Patients with active (SLEDAI-2K$\geq$6), autoantibody-positive SLE receiving standard therapy were randomised to weekly subcutaneous injections of atacicept (75 or 150 mg) or placebo for 24 weeks. **Results** In the ITT population (n=306), there was a trend towards improved SRI-4 response rates with both atacicept doses vs placebo at Week 24 (primary analysis, Screening as baseline). In a sensitivity analysis using Day 1 as baseline, both atacicept doses significantly increased SRI-4 responses (Table 1). In patients with high disease activity (HDA, n=158), serologically active (SA) disease (n=84), or both (HDA SA, n=69), enhanced improvements in SRI-4 and SRI-6 response rates were seen with atacicept (Tables 1 and 2; Figure 1). Atacicept significantly reduced severe flares in the ITT (75 mg: BILAG A p=0.019; 150 mg: SLEDAI flare index [SFI] p=0.002) and HDA populations (75 mg: BILAG A HR=0.1, SFI HR=0.3; 150 mg: BILAG A HR=0.3, SFI HR=0.2; all p<0.05). At Week 24, serum IgG was reduced from baseline by ~25% and ~30% with atacicept 75 and 150 mg, respectively (Figure 2); serum complement C3 and C4 increased while IgM, IgA, and anti-dsDNA antibodies decreased with atacicept. Risk of SAEs and serious/severe infections did not increase with atacicept (Table 3). **Conclusions** Atacicept demonstrated evidence of efficacy in SLE, particularly in HDA and SA patients, with reduction in disease activity and severe flares, and showed a favourable safety profile.

Plenary Session 4: Cutting edge science in SLE

9   BIM SUPPRESSES THE DEVELOPMENT OF SLE BY LIMITING MACROPHAGE INFLAMMATORY RESPONSES

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Background and aims There are numerous endogenous Bcl-2 antagonists that share similar homology, structure, topology and expression pattern, yet only the loss of Bim in mice is sufficient to lead to the development of a systemic autoimmunity. **Methods** We investigated the contribution of Bim in monocytes/macrophages and its effect on systemic autoimmunity by establishing conditionally Bim-deleted mice in the monocyte/ macrophage compartment (Cre^{LysM}Bim$^{fl/fl}$ mice) and examined the development of lupus-like disease over time. **Results** Patients with lupus display decreased expression of Bim in circulating monocytes and reduced Bim expression in kidney macrophages. Cre^{LysM}Bim$^{flox/flox}$ mice develop a lupus-like disease that mirrors aged Bim$^{-/-}$ mice including loss of the marginal zone macrophages, splenomegaly, lymphadenopathy, autoantibodies including anti-DNA IgG, and a type I interferon signature as compared to control mice. Cre^{LysM}Bim$^{flox/flox}$ mice also exhibit increased mortality attributed to immune complex deposition and increased numbers of kidney macrophages all of which contribute to glomerulonephritis. The loss of Bim in macrophages is sufficient to break tolerance as adoptive transfer of wild-type lymphocytes into Cre^{LysM}Bim$^{flox/flox}$-Rag$^{-/-}$ mice leads to systemic autoimmunity. We also identified that the loss of TLR signalling adaptor protein TRIF but not MyD88 is essential for progression to GN phase but is dispensable for systemic autoimmunity. RNA seq analysis of sorted kidney macrophages revealed a novel Bim and lupus specific signatures. **Conclusions** These data add another facet to the conventional dogma that Bim's central role in autoimmune disease is to prevent the escape of autoreactive lymphocytes from apoptosis. Thus, Bim may be a novel therapeutic target for treating SLE.

10   SINGLE CELL EXPRESSION QUANTITATIVE TRAIT LOCI (EQTL) ANALSIS OF ESTABLISHED LUPUS-RISK LOCI IN PATIENT MONOCYTES

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Background and aims While most of the confirmed SLE-risk loci are in or near genes with immune system function, a major unanswered question is how these loci influence diverse immune cell subsets. **Methods** CD14++CD16- classical monocytes (CL) and CD14dimCD16+ non classical (NCL) monocytes from SLE patients were purified by magnetic separation. The Fluidigm C1 System was used for single cell capture and target gene pre-amplification and equal numbers of classical and non-

classical monocytes were studied. 90 monocyte-related genes and 7 SLE-risk SNPs were included in eQTL analyses.

Results The SLE-associated SNPs demonstrated more eQTLs in NCLs as compared to CLs ($p=2.5\times10^{-8}$). For a given SNP, the associated transcripts differed between cell types ($p<0.001$ for all 7 SNPs for discordance), suggesting that the same SNP resulted in different cellular events between the two monocyte subsets. Loci which shared a significant proportion of eQTL associations with each other in NCLs included TNFAIP3, IRF5, IRF7, PTPN22, and SPP1. In CLs, TNFAIP3 shared a large number of eQTLs with SPP1 and ITGAM, although SPP1 and ITGAM showed more limited overlap with each other. Thus, SLE-associated risk loci exert coordinated effects on gene expression within individual human monocytes, and the risk loci interact in different ways in different cell types.

Conclusions Our study revealed striking differences in the occurrence and interaction between of SLE risk associated eQTLs within different but closely related cell types. This suggests pleiotropic effects from each locus across various immune cell types, and a high degree of complexity when considering how these loci impact the immune system.

Plenary Session 5: Outcome measures and treatment targets in SLE

| 11 | **DEVELOPMENT AND INITIAL VALIDATION OF A NOVEL LUPUS DISEASE ACTIVITY INDEX TO ACCOUNT FOR GLUCOCORTICOIDS: SLEDAI-2K GLUCOCORTICOIDS INDEX (SGI)** |

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Background and aims To develop and validate a new index, SLEDAI-2K Glucocorticoids Index (SGI), to accurately describe disease activity while accounting for GC doses.

Methods Phase 1: Identification of patient scenarios followed in a longitudinal cohort. Phase 2: Equation's derivation explaining the association between SLEDAI-2K and GC dose while using physician global assessment (PGA) as Gold Standard. Phase 3: Validation of SGI against SLEDAI-2K in active patients.

Abstract 11 Table 1

	Visit Yield	Patient Yield	Final Scenarios
Approach 1	29577	1400	51
Approach 2	18178	1086	80

Abstract 11 Table 2

GC weight score corresponding to different GC doses		Example on the application of SGI to a patient with SLEDAI-2K of 6	
GC Dose (mg/day)	GC weight score	SLEDAI-2K	SGI= SLEDAI-2K + GC weight score
5	1	6	SGI= 6+1=7
7.5	2	6	SGI= 6 +2=8
10	3	6	SGI= 6 +3=9
12.5	3	6	SGI= 6 +3=9
15	4	6	SGI= 6 +4=10
17.5	4	6	SGI= 6 +4=10
20	5	6	SGI= 6 +5=11
22.5	5	6	SGI= 6 +5=11
25	6	6	SGI= 6 +6=12
27.5	6	6	SGI= 6 +6=12
30	6	6	SGI= 6 +6=12
32.5	7	6	SGI= 6 +7=13
35	7	6	SGI= 6 +7=13
37.5	7	6	SGI= 6 +7=13
40	7	6	SGI= 6 +7=13
42.5	7	6	SGI= 6 +7=13
45	8	6	SGI= 6 +8=14
47.5	8	6	SGI= 6 +8=14
50	8	6	SGI= 6 +8=14
52.5	8	6	SGI= 6 +8=14
55	8	6	SGI= 6 +8=14
57.5	8	6	SGI= 6 +8=14
60	8	6	SGI= 6 +8=14