Conclusions Autoantibody profiling using 86 antigens provides an opportunity for identifying subgroups of patients with distinct marker profiles for designing clinical trials and evaluating clinical response in defined patient subgroups.

38 DISCOVERY AND EVALUATION OF A MULTIPLEXED MASS SPECTROMETRY PANEL FOR MEASURING CANDIDATE PEPTIDE BIOMARKERS IN URINE FROM PATIENTS WITH LUPUS NEPHRITIS

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Background and aims Lupus nephritis (LN) is a clinical manifestation of systemic lupus erythematosus (SLE) associated with significant morbidity and mortality. Although proteinuria is highly correlated with disease progression in LN, the composition of the LN urinary proteome remains poorly characterised. To address this issue, complementary mass spectrometry (MS)-based approaches were used to identify candidate urinary biomarkers and a targeted proteomics panel was developed to further assess levels in LN samples.
Methods LN urine samples were profiled using three MS-based methods: 2D SDS-PAGE, chemical labelling using isobaric mass tags, and data-independent acquisition (DIA). A quantitative, multiple reaction monitoring method was developed to further evaluate levels of these candidate peptide biomarkers in a larger cohort.
Results Using these discovery proteomic approaches>2600 proteins were identified, 290 of which are up-regulated in LN samples. While chemical labelling enabled identification of more total proteins, DIA outperformed chemical labelling in identification of proteins significantly up-regulated in LN samples. Further evaluation of a selected panel revealed increases in the majority of candidate peptide biomarkers in LN samples compared to healthy controls, including peptides from proteins involved in inflammation and adaptive immunity.
Conclusions These results indicate that peptides from proteins involved in inflammation and adaptive immunity can be quantified in urine of LN patients using a multiplexed MS-based method. Results from this study will be used to inform longitudinal and interventional studies focused on understanding the biological implications of these candidate biomarkers and to direct development of novel tools to evaluate disease progression and treatment efficacy of current and future LN therapeutics.

39 PERIPHERAL IMMUNOPHENOTYPING IDENTIFIES THREE SUBGROUPS BASED ON T CELL HETEROGENEITY IN LUPUS PATIENTS

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Background and aims To elucidate the diversity of systemic lupus erythematosus (SLE), we stratified SLE patients based on immunophenotyping.
Methods Peripheral blood mononuclear cells were obtained from 80 active SLE patients (with one or more BILAG category A, or two or more BILAG category B). Circulating B, T and dendritic cells were defined based on flow cytometric analysis for human immune system termed "the Human Immunology Project". Based on these results, the immunophenotype was visualised by principal component analysis and SLE patients classified into subgroups by cluster analysis.
Results Principal component analysis indicated that the immunophenotype of active SLE patients was consistent with T and B cell axes. Among these correlations, Th17 and Treg cells were statistically close, and showed positive correlation ($p<0.001$). Furthermore, Tfh and Th1 cells were also statistically close, and showed positive correlation ($p=0.04$). The same pattern was also noted between Tfh and plasmablasts ($p=0.02$). Cluster analysis showed that SLE patients were divided into three subgroups (with high proportions of plasmablasts in all groups): patients did not show any characteristic features other than increased plasmablasts (T cell-independent group), patients with high percentage of Tfh cells (Tfh-dominant group), and patients with high proportions of activated Treg and memory Treg and low proportion of naïve Treg (Treg-dominant group).
Conclusions Our study indicates that SLE patients can be divided into three subgroups based on T cell heterogeneity. This heterogeneity should be taken into consideration not only in basic research but also in patient selection in clinical trials for development of new drugs.

40 ELUCIDATING GENETIC PATHWAYS IN SLE AND STRATIFYING PATIENTS VIA WHOLE GENOME SEQUENCING

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Background and aims Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease. Twin studies indicate a strong genetic contribution to lupus, yet often the pathogenic variant remains unknown. A better understanding of the individual genetic causes of SLE will enable personalised therapies. Using next generation sequencing technologies (WES/WGS) it is now possible to identify rare/novel gene variants that cause disease.
Methods We have used WES/WGS to identify rare genetic variants with strong effects that contribute to SLE and complex autoimmunity. The effect of variants on protein function were evaluated using *in vitro* biochemical and over-expression assays. Immunophenotyping of patient PBMCs and the use of bespoke mouse models engineered by CRISPR/Cas9 to harbour patient-specific variants were used to dissect disease mechanisms.
Results We identified a genetic variant in TREX1 as a cause of cerebral SLE, providing proof of principle that rare genetic variants do contribute to complex autoimmunity. The patient was revealed to be a prime candidate for tailored therapies

targeting type-I interferons. Using our validated bioinformatics pipeline and methodology, we have now identified two other cohorts of patients with genetic variants that impair thymic tolerance and T1-IFN signalling, respectively. Biochemical assays confirmed the variants impair protein function. Furthermore, flow cytometry identified immunophenotypes in the patients' PBMCs that may explain disease pathogenesis. The mechanisms by which they drive SLE pathogenesis are being evaluated in patient-specific mice mouse models.

Conclusions By understanding the precise genetic mechanisms that contribute to SLE pathogenesis, our data is able to stratify patients and, through a personalised approach, identify tailored therapeutic options.

41 RELEVANCE OF MOUSE LUPUS MODELS OF LUPUS NEPHRITIS TO PROGRESSION OF CKD

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Background and aims Risk for progression of CKD in humans is associated with an interstitial molecular signature containing 68 genes. Of these, a decrease in renal expression of EGF with a concomitant increase in urinary EGF improves the ability to predict CKD expression.

Methods To determine whether these 68 genes can be used in pre-clinical studies to model disease and therapeutic responses, we analysed microarray data of kidneys from three mouse lupus strains at various disease stages and after remission induction. Renal macrophage gene expression was assessed using RNASeq.

Results 61/64 genes have mouse gene IDs and are represented on the mouse microarray chip. Of these 49 were regulated in the same direction as in humans in at least one mouse strain with 28 common to all three strains. 9/61 genes, including EGF and TIMP1 only became abnormally regulated during established disease or during complete proteinuric relapse, confirming their association with CKD progression. Renal C1qa is a CKD marker produced mainly by renal macrophages but has a similarly high expression level in isolated pre-nephritis and nephritic renal macrophages. It can therefore be used as a biomarker of increased macrophage infiltration, a known poor prognostic feature in human lupus nephritis.

Conclusions Mice with lupus nephritis have a similar pattern of CKD-related gene expression to humans and these genes can be used to track therapeutic responses. Downregulation of EGF and upregulation of TIMP1 indicate progressive disease and C1qa can be used as a marker of macrophage infiltration. The fibrosis signature is best modelled in NZW/BXSB mice.

42 GENE EXPRESSION PROFILE FROM 1,760 SLE PATIENTS REVEALS NOVEL COMPLEX INTERFERON RESPONSIVE GENE NETWORKS

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Background and aims RNA profiling was performed on 1760 SLE patients from two, large Phase III clinical trials, ILLUMINATE-1 and −2. SLE was compared to both healthy controls and other autoimmune diseases, including rheumatoid arthritis, psoriasis and psoriatic arthritis. The goals of this study were to characterise gene expression networks in SLE using these large cohorts, and to compare gene expression phenotypes in SLE to healthy controls and other autoimmune diseases.

Methods Blood was collected at baseline and RNA was interrogated on all samples using Affymetrix HTA 2.0 microarrays and on select SLE samples using NanoString nCounter™. Complete demographics, serum IgG anti-dsDNA antibodies, and complement were measured in SLE. Analyses of gene expression and gene pathways were performed.

Results Baseline elevation of interferon responsive genes (IRG) was detected in SLE and associated with younger age, elevated anti-dsDNA antibodies, elevated SLEDAI and decreased levels of C3. Significant differences in SLEDAI organ domain involvement between IRG-positive and IRG-negative groups were observed. Elevated expression of IRG, genes involved with B cell and plasma cell biology, and with cell cycling and signalling were detected in SLE. A bimodal expression pattern of IRG was unique to SLE. Substantial heterogeneity of expression of IRG and complex relationships in interferon (IFN) gene networks were observed.

Conclusions There was substantial heterogeneity of gene expression in IFN gene networks when examining individual IFN genes and complex relationships were observed among IFN gene networks. Low *IFI27* was identified as a novel subtype of IFN signature in SLE.

Poster Session

Adaptive immunity and lymphocytes

43 ENHANCED IMMUNE CELL ACTIVITY BY KOREAN RED GINSENG IN PORCINE

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Background and aims In search of immunomodulatory agents, natural products play a vital role since they have relatively low toxicity in clinical applications. Korean red ginseng (KRG) has been used in Korea, Japan, and china as a traditional medicine. KRG has proven for its efficacy against various human diseases such as cancer, diabetes, and atherosclerosis.

Methods In this study, KRG was assessed for its ability to act as an adjuvant for the immune response of porcine splenocytes.

The porcines were administered with different concentrations (200 and 400 mg/kg/day) of KRG, orally for 28 days.

Results The splenocytes isolated from KRG treated group showed enhanced immune response in a concentration dependent manner when compared to untreated porcine splenocytes. Further, the intracellular levels of perforin, Granzyme B and NKG2D were found to be significantly increased in transcriptional and translational level as revealed by RT-PCR and western blot analysis respectively. In addition, we compared the cytotoxic ability of splenocytes treated with KRG against K-562 cell for 28 days. The KRG activated porcine