Conclusions As has been seen in previous cohorts, a quarter of healthy individuals in this study made antinuclear antibodies, often at high titers. ANA testing, however, underestimates the repertoire of autoantibodies in these individuals. Healthy individuals who react in ANA testing produce antibodies against both non-nuclear and cytoplasmic antigens while SLE patients react to the classical RNA and DNA associated proteins. There is genetic risk for the development of ANA that includes many of the previously documented SLE risk haplotypes. However, other genetic associations are specific for SLE, suggesting distinct risk factors for ANA and for lupus.

GG-09 COMPARATIVE ANALYSIS OF GENE EXPRESSION IN LUPUS-AFFECTED TISSUES REVEALS COMMON AND DISPARATE PATHWAYS OF INFLAMMATION

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Background Immunologic mechanisms causing tissue damage in autoimmune diseases such as SLE are not fully understood. The hypothesis to be tested is that gene expression analysis of lupus-affected tissues will generate novel insights into targets of immunological intervention.

Materials and methods To gain additional insight, gene expression profiles obtained from lupus affected skin, synovium and kidney were obtained, compared to meta-analysed data obtained from active lupus B, T and myeloid cells, and cross-referenced to various pathway analytic tools including Molecular Signature (MS)-Scoring, Ingenuity Pathway Analysis© Upstream Regulator (IPA©-UR) analysis, and Library of Integrated Network of Cellular Signatures (LINCS).

Results More than 300 arrays from lupus patients and appropriate controls were analysed to determine differentially expressed (DE) genes [8279 discoid lupus skin, 5465 synovial lupus arthriti, 6381 glomerulos (G) lupus nephritis, 5587 tubulointerstitial (TI) lupus nephritis]. Notably, the majority of lupus affected tissue DE genes were detected in more than one tissue and 439 were differentially expressed in all tissues. Tissue lymphocyte infiltration was documented by cell markers as well as by published unique gene expression signatures (BIG-C©). Common up-regulated transcripts in affected tissues displayed a variety of functions including pattern recognition receptors, p38/MAPK14 activation, endothelial endocytosis, and TLR activation. Unique targets of intervention were discovered when up-regulated transcripts in all lupus tissues were cross-referenced to molecular pathway and drug interaction databases. Canonical signalling pathways, published to be important for lupus pathogenesis, such as CD40L-CD40, IL-6, and IL-12/23 were visualised in IPA. Both MS©-scoring and IPA©-UR analysis predicted that signalling mediated by CD40 and IL12R occur in lupus skin, synovium and kidney glomeruli. LINCS connectivity analysis the effect of in vitro knockdown of ligand-receptor pairs and compared the genes affected with lupus tissue DE lists. Lupus nephritis (LN) kidney glomeruli received a LINCS connectivity score of −77 for CD40, implying that DE genes in this tissue have a high likelihood of being regulated by CD40-induced signalling. Skin and lupus nephritis kidney glomeruli received LINCS connectivity scores of −73 and −97, respectively, for the key signalling molecule required for IL6 signalling, IL6ST/gp130. All lupus-affected tissues had negative connectivity scores (skin, −98; synovium, −89; LN glomeruli, −91 and LN TI, −87) for IL12α. Examination of curated functional groups from the STRING output of
common up-regulated transcripts in lupus tissue using IPA's BioProfiler® function predicted therapeutic targets and drugs for all three ligand-receptor pairs examined by MS®-scoring, IPA®-UR and LINCS.

Conclusions This approach demonstrated that there are pathways common to all lupus tissue, and there are pathways involved in inflammatory response of some but not all tissues. Further analysis should generate a model of lupus immunopathogenesis and could identify therapies that may be useful in all lupus patients versus those with involvement of specific tissues.

GG-10 IMAGINE SLE: I INTERNATIONAL MULTI-SITE ASSESSMENT OF GENETICS AND INFLAMMATION IN EARLY ONSET AND FAMILIAL SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Systemic Lupus Erythematosus (SLE) is a severe, multisystem autoimmune disease. Twin and sibling studies indicate a strong genetic contribution (44–69%) to SLE. Although numerous recent GWAS studies have identified gene variants, few have been linked to causal polymorphisms in SLE. It may be that few, rare variants could have large impact on SLE risk. Paediatric SLE patients have earlier onset of disease, suffer aggressive course of illness, and may have a stronger genetic risk than adults. Studying aggressive disease in paediatrics has led to myriad breakthroughs in disease pathogenesis, as demonstrated by familial hypercholesterolemia and atherosclerosis, and fever syndromes and autoinflammation. Whole exome sequencing (WES) is a powerful tool to identify rare coding variants for complex phenotypes such as that of SLE. We have established a multisite international paediatric SLE collaboration at four sites: USA, Canada, South Africa, and Mexico. We will use WES to investigate the genetic variants which may give insight into molecular pathways contributing to SLE.

Materials and methods Paediatric SLE patients at sites in the USA, Canada, South Africa and Mexico will be consented. Whole exome capture/sequencing will be performed on patients with paediatric-onset SLE age ≤10 years and/or SLE with strong familial aggregation, defined as ≥ one first degree relative or two second degree relatives with SLE. Patient and parent samples will be processed and analysed as trios.

We will collect standard information on all cohorts, including demographic information, clinical history, family history, medications, exam findings, laboratory values, SLEDAs and SLICC-DI. Organ damage will be defined as end stage renal disease or SLICC-DI >0.

Raw data will be processed by Whole Exome Sequencing using Illumina HiSeq2500. Bioinformatic analysis will be performed at NIH. We will develop an SLE specific bioinformatics pipeline to process data and analyse variants. Results will be filtered against known variants and parental samples.

Results We currently have access to 50 pSLE patients in the US, 75 pSLE patients in SA, 200 pSLE patients in Mexico, and 500 pSLE patients in Canada from which to recruit patients.

We anticipate analysis of 160 samples (20 patient/parent trios at NIH, 50 in Canada) to be complete at the time of presentation. We expect to recruit 30 SA trios, 135 Mexican trios, 40 US trios, and 200 Canadian trios during the total course of the study. Novel rare variants identified will be reviewed.

Conclusions Novel rare variants identified will be reviewed.