antibodies to a gene expressed on demethylated but not normal T cells may treat lupus flares.

Footnotes Dept of Medicine, University of Michigan, Ann Arbour MI

GG-02 EPIGENETIC REPROGRAMMING IN NAÏVE CD4+ T CELLS FAVOURING T CELL ACTIVATION AND NON-TH1 EFFECTOR T CELL IMMUNE RESPONSE AS AN EARLY EVENT IN LUPUS FLARES

[1#]Patrick Coit, [2#]Mikhail G Dozmorov, [3]Joan T Merrill, [1]W Joseph McCune, [4]Kathleen Maksimowicz-McKinnon, [5,6]Jonathan D Wren, [1,7]**Amr H Sawalha***. *[1]Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbour, Michigan, USA; [2]Department of Biostatistics, Virginia Commonwealth University, Richmond, Virginia, USA; [3]Clinical Pharmacology Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA; [4]Division of Rheumatology, Henry Ford Health System, Detroit, Michigan, USA; [5]Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA; [6]Department of Biochemistry and Molecular Biology, The University of Oklahoma Health Sciences Centre, Oklahoma City, Oklahoma, USA; [7]Centre for Computational Medicine and Bioinformatics, University of Michigan, Ann Arbour, Michigan, USA*

[#]These two authors equally contributed to this work

10.1136/lupus-2016-000179.54

Background Systemic lupus erythematosus is a relapsing autoimmune disease that affects multiple organ systems. T cells play an important role in the pathogenesis of lupus, however, early T cell events triggering disease flares are incompletely understood. We studied DNA methylation in naïve CD4+ T cells from lupus patients to determine if epigenetic remodelling in CD4+ T cells is an early event in lupus flares.

Materials and methods A total of 74 lupus patients with disease activity ranging from 0–18 as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) were included in this study. Naïve CD4+ T cells were isolated from peripheral blood samples and DNA extracted for genome-wide methylation assessment. RNA was also extracted from a subset of patients to determine the relationship between epigenetic changes and transcriptional activity using RNA sequencing and microRNA arrays.

Results We demonstrate that naïve CD4+ T cells in lupus undergo an epigenetic pro-inflammatory shift implicating effector T cell responses in lupus flare. This epigenetic landscape change occurs without expression changes of corresponding genes, and poises naïve CD4+ T cells for Th2, Th17, and Tfh immune responses, and opposes inhibitory TGF-β signalling. Bioinformatics analyses indicate that the epigenetic modulator EZH2 might be playing an important role in shifting the epigenetic landscape with increased disease activity in lupus naïve CD4+ T cells. Further, the expression of miR26a and miR101, which are sensitive to glucose availability and target EZH2, negatively correlated with disease activity in lupus patients.

Conclusion An epigenetic landscape shift in naïve CD4+ T cells that favours T cell activation and non-Th1 immune responses predates transcriptional activity and correlates with lupus activity. A role for EZH2 dysregulation in triggering lupus flares warrants further investigation. The proposed T cell epigenetic model of disease flare in lupus patients is depicted in Figure 1.

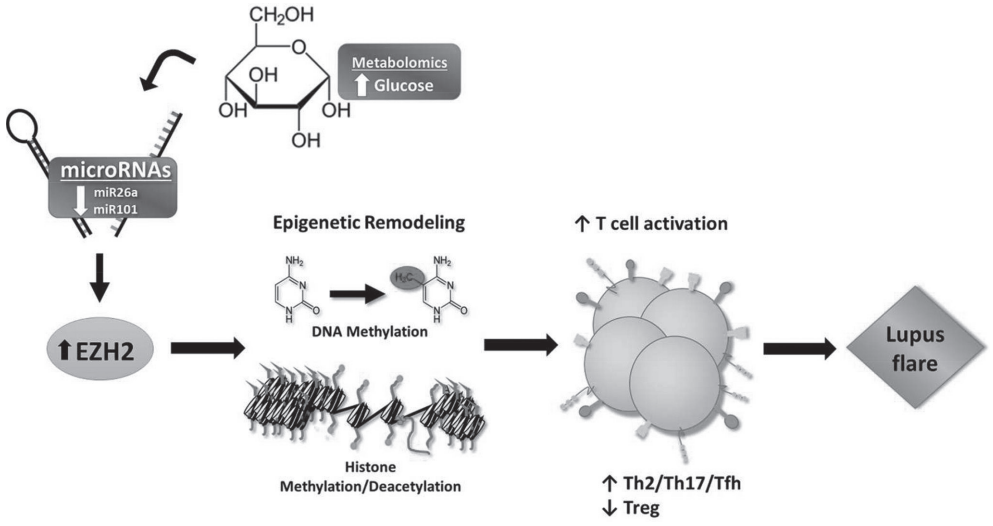
Acknowledgements This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award number R01AI097134.

GG-03 STAT1-STAT4 ASSOCIATION WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

[1]Zubin Patel, [1]Matt Weirauch, [1]Leah C Kottyan, [1,2]**John B Harley***. *[1]University of Cincinnati and the Centre for Autoimmune Genomics and Aetiology (CAGE), Cincinnati Children's Hospital Medical Centre, Cincinnati, OH; [2]US Department of Veterans Affairs Medical Centre, Cincinnati, OH*

10.1136/lupus-2016-000179.55

Background Signal Transduction and Activation of Transcription (STAT) transcription factors are evolutionarily ancient, mediating signals from the cytoplasm to the nucleus in eukaryotic life for the past 400 million years. The STAT protein sits quiescent in the cytoplasm until phosphorylated whereupon it dimerizes with another STAT protein. The phosphorylated STAT dimer is then transported to the nucleus and becomes a transcription factor activating or suppressing gene expression. The *STAT1–STAT4*



Abstract GG-02 Figure 1 T cell epigenetic model of disease flares in lupus

locus has powerful common variant associations with SLE risk with odds ratio = 1.5 and $p < 10^{-20}$ in all human ancestries and also has an association, though not necessarily identical to SLE, with rheumatoid arthritis, primary biliary cirrhosis, Behcet's Disease, Sjögren's syndrome, progressive systemic sclerosis, and type I diabetes.

Methods Genome wide association studies of SLE, Bayesian and frequentist fine mapping methods, DNA affinity purification assays, and electrophoretic mobility shift assays.

Results We are attempting to identify the causal variants and determine the mechanism for SLE disease risk at this locus. Our data suggest that the risk haplotype alters the expression of mRNA from both *STAT1* and *STAT4*. Application of frequentist and Bayesian methods restrict the plausibly causal variants to four possibilities in introns 4 and 5 of *STAT4* under the assumption that the association observed across human ancestries is being driven by the same causal variants. Three of these four polymorphisms are predicted to alter the binding of a specific transcription factor, leading to the hypothesis that the same transcription factor is operating at multiple sites in a risk haplotype. We have data suggesting differential and allele preferential binding of the transcription factor at one variant with evaluation of the others in process. This may possibly be the first discovered example of the phenomenon of multiple transcription factor binding on multiple variants of a risk haplotype.

Conclusion In general, genome wide association studies (GWASs) provide powerful evidence of the presence of a genetic variation altering phenotype risk without revealing what the specific responsible variant is among those in a statistical dead heat for causation, in which cell type(s) or stage(s) of differentiation in which the risk difference is relevant, or what the molecular mechanism might be. We have work underway to reveal these details for lupus loci, initially concentrating on *IRF5*, *STAT1-STAT4*, and *ETS1*. The STAT1-STAT4 association with SLE can be isolated to involve only a few variants, which are predicted to have curiously similar transcription factor binding behaviour.

GG-04 A MISSENSE MUTATION IN NEUTROPHIL CYTOSOLIC FACTOR 1 (*NCF1*) IS ASSOCIATED WITH SUSCEPTIBILITY TO MULTIPLE AUTOIMMUNE DISEASES

[**1,2]Jian Zhao, [**3]Jianyang Ma, [1,2]Yun Deng, [4]Jennifer A Kelly, [5]Kwangwoo Kim, [5]So-Young Bang, [7]Hye-Soon Lee, [8]Quan-Zhen Li, [8]Edward K Wakeland, [4,7]Kathy Moser Sivils, [1]Bevra H Hahn, [1]Jennifer M Grossman, [5]Sang-Cheol Bae, [4]Patrick M Gaffney, [3,8,9,10,11]Nan Shen, [1,2]**Betty P Tsao***. *[1]Division of Rheumatology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California 90095, USA; [2]Division of Rheumatology and Immunology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina 29425, USA; [3]Shanghai Institute of Rheumatology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200001, China; [4]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma 73104, USA; [5]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul 133-792, Korea; [6]Department of Immunology, University of Texas Southwestern Medical Centre, Dallas, Texas 75235, USA; [7]Department of Pathology, University of Oklahoma Health Sciences Centre, Oklahoma City, Oklahoma 73104, USA; [8]Institute of Health Sciences, Shanghai Institutes for Biological Sciences (SIBS) and Shanghai Jiao Tong University School of Medicine (SJTUSM), Chinese Academy of Sciences (CAS), Shanghai 200025, China; [9]State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200001, China; [10]The Centre for Autoimmune Genomics and Aetiology (CAGE), Cincinnati Children's Hospital Medical Centre, Cincinnati, Ohio 45229, USA; [11]Collaborative Innovation Centre for Translational Medicine at Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China; [**]These authors contributed equally to this work*

10.1136/lupus-2016-000179.56

Background Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with a strong genetic component. Dozens of SLE-associated loci have been identified by genome-wide associated studies (GWAS) and included in the ImmunoChip for fine-mapping.

Materials and methods Using ImmunoChip, we assessed case-control subjects including Chinese, European Americans (EA) and African Americans (AA) for association with SLE. Subsequently, we carried out trans-ancestral mapping and resequenced the complex *GTF2IRD1-GTF2I-NCF1* region on 7q11.23 to identity underlying causal variant.

Results The strongest association signal in Chinese was unexpectedly detected at rs73366469 (OR = 2.88, $P = 3.6\times10^{-29}$) within the *GTF2IRD1-GTF2I* intergenic region on 7q11.23 rather than SLE-associated GWAS loci. This association was confirmed in EA (OR = 1.37, $P = 2.5\times10^{-3}$) but not in AA. By trans-ancestral mapping and sequencing, we identified R90H of *NCF1*, a neighbouring gene of *GTF2I* encoding the p47phox subunit of NADPH oxidase, as a highly plausible causal variant. R90H was associated with SLE in East Asians (OR = 3.47, $P_{meta} = 3.0\times10^{-105}$), EA (OR = 2.11, $P_{meta} = 7.0\times10^{-8}$) and AA (OR = 1.91, $P = 7.2\times10^{-3}$), and in conditional test R90H eliminated SLE-associated signals within the *GTF2IRD1-GTF2I* region including rs73366469. Furthermore, R90H was dose-dependently associated with early age of onset in Korean ($P = 0.011$) and EA ($P = 0.012$) patients with SLE. In addition to SLE, R90H was associated with seropositive rheumatoid arthritis (RA) in Koreans (OR = 1.66, $P = 1.2\times10^{-8}$) and primary Sjögren's syndrome (SS) in EA (OR = 1.72, $P = 5.8\times10^{-3}$). The conserved arginine 90 to histidine substitution located in the PX-binding domain of p47phox is predicted deleterious, which is supported by a report showing R90H results in reduced reactive oxygen species (ROS) production.

Conclusions We identified R90H of *NCF1* as a novel risk variant for multiple autoimmune diseases, highlighting the pathogenic role of reduced ROS production in developing autoimmune diseases.

GG-05 ATAC-SEQ PROFILING REVEALS CELL-TYPE SPECIFIC EPIGENETIC FEATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Richard C Pelikan, Neelakshi Jog, Melissa Bebak, Joel Guthridge, Judith James, **Patrick Gaffney***. *Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA*

10.1136/lupus-2016-000179.57

Background Genetics studies have now identified over 80 SLE risk loci that influence predisposition to SLE with the majority of risk variants altering regulatory elements that govern gene expression. Precise understanding of how risk variants in regulatory elements influence gene expression in different cell types and cell states is critical for defining the molecular networks leading to autoimmunity. To begin to address this issue, we profiled the chromatin accessibility landscape of three distinct, albeit heterogeneous, compartments of the immune system across three clinical states.

Materials and methods Primary B and T lymphocytes and monocytes from 5 SLE subjects with high disease activity (SLEDAI $\geq$3) and 4 SLE subjects with low disease activity (SLEDAI $\leq$2) and 5 healthy controls were collected and processed for high-throughput open chromatin profiling by ATAC-seq. Reads were aligned to the hg19 genome and regions of enriched