

by gene ontology (GO) and pathway enrichment analysis that were highly enriched in SLE T cells included mediators of adaptive responses and inflammation, and those regulating co-stimulation. By contrast, negative regulators of cell proliferation and function were found in the healthy control cluster, and diminished in SLE.

**Conclusions** Our data demonstrate altered transcriptional programs of lupus Tfh and Tcm cells, and therapeutic targets in disease. They also represent the first detailed transcriptional profiling, and single cell transcriptional profiling, of Tfh cells, the necessary and critical driver of humoral immunity in SLE.

**Acknowledgements** Supported in part by grants from the NIH/NIAMS (AR40072 and AR053495) and from the Alliance for Lupus Research (to JC).

#### AI-23 MULTIPLEXED MECHANISTIC ASSAYS FOR CHARACTERISING SLE

**Paul J Utz\***. Department of Medicine Division of Immunology and Rheumatology Institute for Immunity, Transplantation and Infection Stanford University School of Medicine Stanford, CA 94305

10.1136/lupus-2016-000179.23

**Background** SLE is a complex disease with very few approved therapeutic options. Unique opportunities exist to characterise blood cells, tissues such as kidney and skin, urine, serum and plasma as part of ongoing longitudinal cohort studies such as Accelerating Medicines Partnership (AMP) and Autoimmunity Centres of Excellence (ACE), and investigator initiated or company-sponsored clinical trials.

**Materials and methods** SLE blood and tissue samples are being studied using a variety of single cell measurements as well as studies of biofluids. Several of these technologies are becoming firmly established in the SLE field, including single cell RNA Seq of blood and dissociated kidney using recently-developed methods in several consortia related to SLE and cancer; low input RNA-Seq of bulk purified cells; Assay of Transposase Accessible Chromatin (ATAC Seq); CyTOF and EpiCyTOF developed through the ACE consortium; transcript profiling using many methodologies; meta analysis of existing transcript profiling datasets; auto-antibody profiling using autoantigen microarrays, and arrays composed of secreted factors such as cytokines and chemokines; multiplexed ion beam imaging (MIBI); and unpublished imaging methods such as CODEX.

**Results** An overview of multiplexed methods will be presented and will focus on efforts by the Stanford ACE and collaborating investigators to develop methods specifically for the study of SLE. Historical methods will be compared, and ACE datasets on human SLE, and mouse models of SLE characterised as part of ALR studies, will be described that demonstrate unique roles for interferons and STAT signalling in lupus.

**Conclusions** Big data analyses and multiplexed assays of samples derived from SLE patients, as well as patients with related autoimmune diseases, have tremendous potential and should be included in all clinical trials, with a goal to better understand pathogenesis and to identify novel therapeutic targets.

**Acknowledgements** Alliance for Lupus Research, NIAID, NIAMS, Henry Gustav Floren Trust, Baxter Foundation, and many patients with SLE who have provided samples

#### AI-24 CALCIUM/CALMODULIN KINASE CONTROLS T AND RENAL CELL FUNCTION

**George C Tsokos\***. Harvard Medical School, Beth Israel Deaconess Medical Centre, Boston, MA

10.1136/lupus-2016-000179.24

**Background** Molecular abnormalities in SLE T cells account for their aberrant function including cytokine production, cytotoxic responses and help to B cells.

**Materials and methods** Use of biochemical, molecular biology and engineered mice; study of kidney tissues and isolated kidney cells.

**Results** Calcium calmodulin kinase IV (CaMK4) is expressed at high levels in T cells from patients with SLE and accounts for the decreased production of IL-2 and the increased production of IL-17. The mechanisms involved modification of transcription factors and epigenetic changes. CaMK4 drives proliferation of mesangial cells in lupus prone mice and the production of IL-6. In parallel CaMK4 suppresses the expression of nephrin in podocytes resulting in proteinuria and also advances the expression of CD86 enabling thus podocytes to provide costimulation to passer-by T cells. Targeted delivery of a CaMK4 inhibitor to CD4 T cells reverses autoimmunity in lupus-prone mice.

**Conclusions** CaMK4 accounts for the abnormal production of cytokines by SLE T cells, the proliferation of mesangial cells and the poor function of podocytes. Targeting CaMK4 and targeted delivery of CaMK4 inhibitors to T cells has proven promising in preclinical studies.

#### AI-25 GLUCOSE OXIDATION IN LUPUS T CELLS

<sup>1</sup>Seung-Chul Choi, <sup>1</sup>Anton A Titov, <sup>1</sup>Yiming Yin, <sup>1</sup>Byron P Croker, <sup>2</sup>Eric S Sobel, <sup>3</sup>Derry C Roopenian, <sup>1</sup>Todd M Brusko, <sup>1</sup>Laurence Morel\*. <sup>1</sup>Departments of Pathology; <sup>2</sup>Medicine, University of Florida, Gainesville, FL, USA; <sup>3</sup>The Jackson Laboratory, Bar Harbour, ME, USA

10.1136/lupus-2016-000179.25

**Background** Autoreactive CD4<sup>+</sup> T cells are essential participants in the pathogenesis of Systemic Lupus Erythematosus (SLE). Immune substrate utilisation, including glucose metabolism, plays a central role in dictating the effector functions of CD4<sup>+</sup> T cells. We hypothesised that 1) SLE T cells have metabolic defects that enhance their pro-inflammatory functions, and 2) Inhibiting glycolytic metabolism in CD4<sup>+</sup> T cell may normalise CD4<sup>+</sup> T cell functions and reduce disease symptoms in SLE mice and in CD4<sup>+</sup> T cells from SLE patients.

**Materials and methods** We utilised four models of spontaneous lupus, B6.NZM2410.Sle1.Sle2.Sle3 Triple Congenic (TC), BWF1, BXSB.YAA and B6.lpr that differ in their genetic background as well as mechanisms of autoimmune activation. C57BL/6 (B6) served as a non-autoimmune control strain. CD4<sup>+</sup> T cells obtained from lupus-prone mice and controls, as well as from SLE patients and healthy controls (HC) were treated with metabolic inhibitors, including metformin, which inhibits mitochondrial complex I and activates AMPK, and the glycolytic inhibitor 2-Deoxy-D-Glucose (2-DG). Lupus-prone mice were treated with these drugs, either before or after disease onset. Glycolysis, oxygen consumption, activation and effector subset distribution were measured in CD4<sup>+</sup> T cells. Disease progression was assessed by measuring standard lupus biomarkers. Gene profiling was performed on CD4<sup>+</sup> T cells from SLE patients and HCs.

**Results** CD4 T cells from lupus mice and patients have a significantly higher metabolism as well as an enhanced mTOR activity