

of family members and improved therapy for patients and families.

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GG-12 ABSTRACT WITHDRAWN

GG-13 'EPI TOF' – A NEW METHOD FOR CHARACTERIZING THE EPIGENETIC LANDSCAPE IN SLE

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**Background** SLE is a complex disease with very few approved therapeutic options. Unique opportunities exist to characterize 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 Centers of Excellence (ACE), and investigator initiated or company-sponsored clinical trials. The epigenome, in particular, is an area of great interest.

**Materials and methods** We have recently published a new method called Epigenetic Time of Flight (EpiTOF), a mass cytometry based method that enables broad characterization of posttranslational modifications (PTMs) of histones in health and disease. Our initial studies demonstrated marked heterogeneity in younger vs older healthy adults. Twin studies showed that ~70% of variation is related to environment. Twenty-two different populations of blood cells were profiled, and the PTMs alone were sufficient to identify cell populations, even in the absence of cell surface markers.

**Results** Blood derived from multiple diseases was provided through the ACE Collaborative Network and local Stanford investigators and subjected to EpiTOF analysis followed by complex computational analysis. I will present ongoing studies in SLE, SSc, RA, IBD, JIA, vaccines, and infectious diseases using EpiTOF.

**Conclusions** EpiTOF and other multiplexed assays (such as autoantibody profiling) 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.

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## Innate Immunity

II-01 TLR9-DEFICIENCY EXACERBATES AUTOIMMUNE DISEASE IN MODELS OF SLE AND CUTANEOUS LUPUS THROUGH B CELL INDEPENDENT MECHANISMS

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**Background** TLR9 appears to play both a protective and a disease-promoting role in animal models of SLE. Even though TLR9 is required for the production of anti-dsDNA and anti-nucleosome autoantibodies, TLR9-deficient autoimmune-prone mice invariably develop more severe disease than their TLR9-sufficient counterparts. Molecular mechanisms that account for this paradoxical function of TLR9 have mainly been explored in cell lines to a large extent have focused on competition between TLR7 and TLR9 for binding to Unc93B1 and the ability to access to the appropriate signaling compartment. Our own *in vitro* comparison of bone marrow derived macrophages and bone marrow derived dendritic cells, obtained from TLR9-sufficient vs TLR9-deficient mice and stimulated with TLR7 ligands, suggested that the impact of TLR9-deficiency might be highly cell type specific, and led us to focus on primary cells obtained from animal models of systemic autoimmunity.

**Methods** We initially used pristane-injected BALB/c mice as a model of SLE, and found that TLR9-deficiency led to exacerbated renal disease and the accumulation of an unusual myeloid subset in the kidneys of these mice. We have directly examined the contribution of TLR9-deficient and TLR-sufficient cells in these mice using a mixed bone marrow chimera strategy. We have also developed an inducible rapid onset model of cutaneous lupus that depends on the injection of OVA-specific T cells into mice that express an OVA fusion protein on class II+ cells; here, TLR9-deficient and TLR7-sufficient recipients develop cutaneous lesions with many of the features of discoid lupus within 4 weeks of T cell injection. Cells isolated from the kidneys of the BALB/c pristane mice and the skin of the cutaneous lupus mice have been further characterized by flow cytometry and gene expression.

**Results** These studies have identified a myeloid subset present at sites of inflammation and in normal peripheral blood that appears to be uniquely impacted by the loss of TLR9. Functional properties of these cells will be discussed.

**Conclusions** TLR9 deficiency impacts very specific myeloid subsets apart from its effects on B cell development and differentiation.

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