Background Lupus nephritis (LN) affects ~70% of systemic lupus erythematosus (SLE) patients and is one of the main contributors to morbidity and mortality. While defective clearance of apoptotic cells (AC), immune complexes, and type 1 interferons (IFN) are strongly implicated in lupus pathogenesis, the precise way that each impacts kidney protection and injury is unknown.

Methods To investigate mechanisms of kidney injury in a lupus-like disease model, we created C57BL/6 mice with defective clearance of AC (Mfge8-/-) and anti-chromatin antibodies (sle1) that were also deficient in either C1q [C1q Triple mutant (C1qTM)] or C3 (C3TM). Kidney injury was evaluated by urine albumin/creatinine ratio (UCAR), PAS staining, and immunofluorescence (IF) staining. The effect of IFN-I on disease was studied in C3TM mice by a single injection of an adenovirus expressing IFNα (AdV-IFNα).

Results Sle1 mice deficient in MFGE8 developed significantly higher titers of autoantibodies directed at lupus antigens compared to sle1 mice alone. When MFGE8-/- Sle1 mice also had C1q or C3 deficiency, a further increase in anti-DNA (figure 1A) and other autoantibodies was observed. Both TM strains showed AC accumulation in the kidneys (figure 1B) and C1qTM mice had decreased survival. Remarkably, we detected glomerular deposition of C3/C3d in C1qTM and the membrane attack complex (MAC) in C3TM mice. To dissociate the effects of complement on B cells versus effects on the kidney, we studied antibody mediated kidney injury (Nephrotoxic Nephritis, NTN) in mice deficient in AC clearance and complement proteins [double knockout (DKO) (Mfge8-/-C1q-/- or Mfge8-/-C3-/-) mice]. NTN in C1q DKO and C3 DKO mice revealed a significantly elevated UACR compared to the single mutants. IF analyses also revealed glomerular C3/C3d deposition in C1qDKO mice and MAC deposition in C3DKO mice. A single injection of AdV-IFNα accelerated kidney damage in C3TM mice, resulting in increased anti-dsDNA IgG titers, UACR, and PAS staining.

Conclusions These findings demonstrate that early component complement deficiencies have two distinct effects: they promote enhanced B cell autoreactivity and they protect against kidney disease. Increased glomerular C3/C3d deposition in C1qTM and NTN C1qDKO mice suggest activation of the lectin or alternative complement pathways. Increased MAC deposition in C3TM and NTN C3DKO mice indicates that a C3-independent mechanism leads to distal complement activation and MAC formation. These data prompt models of tissue injury in low complement states that will require assessment in human SLE and provide rationale for targeted therapeutics that are not currently used.
accurately capture cell shape. We postulated that this might be important as T cells adopt different shapes when scanning for antigen and after recognizing MHC class II-restricted peptides.

**Methods** We implemented a deep convolutional neural network (DCNN) that accurately identified both cell position and shape. The DCNN output was then analyzed with a tuned convolutional neural network (TNN) to identify distance and cell shape features that best discriminated between different T cell populations relative to dendritic cells (DCs). We refer to this analysis pipeline as CDM.

**Results** In mice, CDM3 discriminated between cognate and non-cognate T cell interactions with DCs with a sensitivity and specificity similar to most TPEM measures. In human lupus nephritis, CDM both confirmed that myeloid DCs present antigen to CD4+ T cells in situ and identified plasmacytoid DCs as an important antigen presenting cell in severe inflammation.

**Conclusions** CDM provides a novel tool for quantifying in situ adaptive immune cell networks broadly applicable to the study of human diseases including autoimmunity and cancer.

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**TD-04 PLAQUENIL DISCONTINUATION IS ASSOCIATED WITH INCREASED DAMAGE ACCUMULATION IN SLE**

1Caroline Siegel, 2Jennifer Grossman, 1Sarah Chen, 1Los Sahakian, 1Michael Gorin, 1Maureen McMahon*, 1Divisions of Rheumatology, UCLA David Geffen School of Medicine, Los Angeles, CA, USA; 2Ophthalmology, UCLA David Geffen School of Medicine, Los Angeles, CA, USA

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**Background** There is ample evidence demonstrating that hydroxychloroquine (HCQ) prevents lupus flares, increases long-term survival, and protects against irreversible organ damage in SLE (Pons-Estel Arch Care Res 2010). However, in recent years, ophthalmology guidelines have encouraged providers to limit cumulative HCQ exposure to prevent ocular toxicity. We examined whether a) HCQ use in our UCLA cohort has changed over time and b) whether patients who discontinue HCQ accumulate damage at a different rate than continuous or never users.

**Methods** SLE subjects participating in our longitudinal ‘Biomarkers of Atherosclerosis’ carotid ultrasound cohort were evaluated. Medication use (and reasons for disuse) were recorded at cohort entry, and at each subsequent study visit.


For continuity, SLICC Damage Index (SDI) was measured at baseline, 3 years, and 5 years after cohort entry.

**Results** At baseline, 69.8% of patients were taking HCQ, 62.1% at first follow-up, and 58.6% at second follow-up (p=ns). Patient preference and physician preference were the most common reasons for HCQ non-use. Less than 3% of subjects who discontinued HCQ did so due to concern for eye toxicity at baseline and first follow-up, but this increased to 7.4% at second follow-up.

We compared SDI at baseline in patients who were never HCQ users (n=29), vs previous users (n=93), vs continuously users (n=181). We found evidence of SLE-related damage (SDI≥1) in 75.9% of never HCQ users, 74.1% of previous users, and 52.4% of subjects on HCQ at baseline (p=0.001, Chi-Square). At 5 years, we found SDI≥1 in 94.7% of never HCQ users, 82.7% of previous users vs 68.2% of subjects on HCQ at baseline (p=0.004, Chi-Square).

**Conclusions** Although the frequency HCQ use in our longitudinal SLE cohort has decreased slightly over the last 13 years, the percentage of subjects who discontinued HCQ due to eye-related eye toxicity has increased recently. Further studies will be required to determine whether this increase is due solely to cumulative HCQ dose vs more frequent detection because of adherence to ophthalmology testing guidelines vs earlier detection due to more sensitive testing modalities. Our data also demonstrate that damage accumulation is similar in subjects who previously used HCQ and those who never used, and higher compared to continuous users, suggesting continuous HCQ use may be important for damage prevention in SLE.