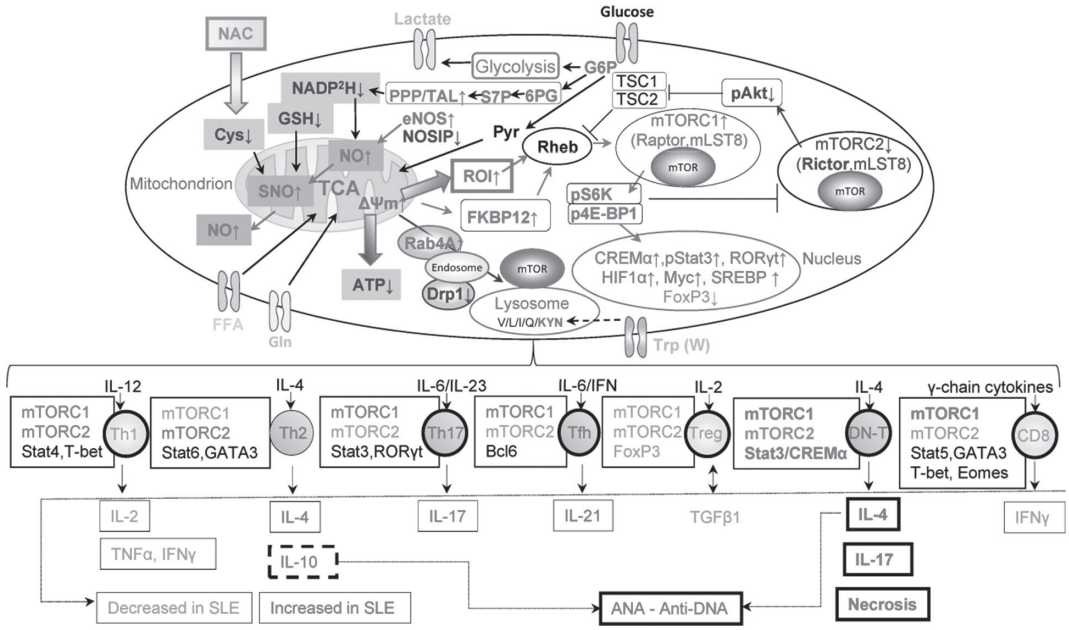


**Abstract BD-02 Figure 1** Metabolic control of pro-inflammatory T-cell lineage specification in SLE. Schematic molecular order of pathways upstream and downstream of activation of the mechanistic target of rapamycin (mTOR) in SLE. mTOR is activated on the surface of lysosomes in a state of amino acid sufficiency (V/L/I/Q/Kyn).[1] Oxidative stress, in particular cysteine oxidation, also activates mTORC1 through association with Rheb.[2] Given the results of our randomized double-blind placebo-controlled clinical trial showing that therapeutically effective reversal of GSH depletion by NAC blocks mTORC1 *in vivo*,[3] GSH depletion will be considered the primary metabolic checkpoint of pro-inflammatory T-cell lineage specification in SLE. The depletion of GSH will be mechanistically connected to the depletion of cysteine (Cys) and NADPH and to the accumulation of kynurenine (Kyn) which have been uncovered by comprehensive metabolome studies of PBL from SLE and healthy subjects matched for age, gender, and ethnicity and processed in parallel.[4] Blockade of mTOR with rapamycin reverses the depletion of effector-memory CD8 T cells and Tregs and the expansion of pro-inflammatory $CD4^-CD8^-$ double-negative T cells in patients with active SLE *in vivo* [5]. Red and blue arrows reflect direction of changes in SLE.

all changes occurred within a range considered safe. Platelet counts were slightly elevated over 12 months. As primary clinical efficacy endpoint, SLEDAI and BILAG disease activity scores were reduced over 12 months in 16/29 patients (55%). 19/29 patients (65.5%) met criteria for SLE Responder Index (SRI). Arthritis, rash, pyuria, and hypocomplementemia improved among SLEDAI components, while cardiopulmonary, musculoskeletal, mucocutaneous, and vasculitis BILAG organ-domain scores also declined. Prednisone use diminished from 24.3±4.7 mg/day to 7.2±2.3 mg/day ($p<0.0009$). Sirolimus expanded $CD4^+CD25^+FoxP3^+$ Tregs and $CD8^+$ memory T cells and inhibited IL-4 and IL-17 production by $CD4^+$ and $CD4^-CD8^-$ double-negative T cells after 12 months. $CD8^+$ memory T cells were selectively expanded in SRI-responders.

**Conclusions** Sirolimus elicits rapid, progressive, and sustained improvement of disease activity by correcting pro-inflammatory T-cell lineage specification in patients with active SLE.

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**Trial registration** Prospective Study of Rapamycin for the Treatment of SLE; ClinicalTrials.gov Identifier: NCT00779194. Treatment trial of SLE with N–acetylcysteine; ClinicalTrials.gov identifier: NCT00775476.

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## BD-03 ADHERENCE TO ANTIMALARIALS AND RISK OF TYPE 2 DIABETES MELLITUS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A POPULATION-BASED COHORT STUDY

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**Background** Aside from their effect on disease activity in systemic lupus erythematosus (SLE) antimalarials have been shown additional benefits such as reducing the risk of diabetes. However, a recent systematic review reported sub-optimal adherence to antimalarials with rates as low as 25%. As medication adherence mediates patient outcomes, our objective was to evaluate the association between adherence to antimalarials

and risk of type 2 diabetes mellitus (T2DM) among SLE patients.

**Methods** Using a population-based database that includes all residents of British Columbia, Canada, we conducted a retrospective, longitudinal cohort study of patients with incident SLE and incident antimalarial use. We established drug courses for antimalarials – defining each new course when a 90 day permissible gap had been exceeded between refills and calculating corresponding proportion days covered (PDC). Our primary exposure was adherence to antimalarials according to three categories: **1)** adherent (PDC $\geq$0.90); **2)** non-adherent (0<PDC<0.90); and **3)** discontinuer (PDC=0, no drug). T2DM outcomes were defined using International Classification of Disease 9th and 10th Revision Codes, and Canadian Drug Identity Codes for anti-diabetic medication (first date of either encounter). We used multivariable Cox's proportional hazards models with time-dependent variables to evaluate the association between adherence to antimalarials and risk of T2DM.

**Results** The study cohort included 1498 patients with incident SLE, with mean age of 44.4±14.8 years and 1360 (90.8%) women. Mean number of antimalarial prescriptions/courses over follow-up was 23.2±37.7/2.1±1.8, with mean course duration of 553.9±820.8 days. Over median 4.62 years of follow-up, we recorded 140 incident cases of T2DM. After adjusting for age, gender, comorbidities, and concomitant medications, the hazard ratio (HR) for those who were adherent to antimalarials was 0.61 (95% confidence interval [CI], 0.40–0.93) as compared to discontinuers, suggesting a protective effect of adherence to antimalarials. In contrast, the HR for those who were non-adherent was 0.78 (95% CI 0.50 to 1.22) as compared to discontinuers. Sensitivity analyses involving permutations of permissible gaps (i.e. 120, 180 days) and PDC cut-off (i.e. 0.80) did not materially change our results.

**Conclusions** These population-based data show a protective effect of adherence to antimalarials on risk of T2DM in SLE patients. Given the effectiveness of antimalarials in treating SLE as well as additional benefits, findings emphasize the need to raise awareness, among health professionals and patients with SLE, of the importance of adherence to these therapies.

## BD-04 CLASSIFICATION OF SLE PATIENTS BASED ON LONGITUDINAL ASSESSMENT OF COMPLEMENT COMPONENT 3 IN RELATION TO COMPLEMENT COMPONENT 4

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**Background** Systemic lupus erythematosus (SLE) disease activity is characterized by tissue deposition of immune complexes and consumption of complement, which contribute to tissue injury. In clinical practice, it is common to encounter patients where either C3 or C4 is low in isolation, though the clinical implications of variation in C3 relative to C4 are unclear. Here we performed relationship-based clustering of SLE patients based on serum C3 and C4 levels to investigate if this could define distinct clinical subgroups of SLE patients.

**Methods** C3, C4 and other clinical and laboratory parameters were obtained from our proprietary database. A total of 151 SLE patients having an average of 38 (range 7–117) measurements of C3 or C4 were studied. To classify SLE patients based on the character of the relationship of C3 vs C4, we performed relationship-based clustering approach by defining linear fit parameters (including alpha, beta, standard error, and p values) followed by hierarchical clustering. The clusters obtained were screened in terms of their dependency to clinical data using Chi square test or Fisher's exact test, as appropriate, with significance defined as $p<0.05$.

**Results** Clustering based on multiple characteristics of the relationship between C3 and C4 identified 6 clusters of patients. Clusters 1 and 6 were small and did not have clear phenotypes. Cluster 2 and cluster 5 were both defined by strong correlations between C3 and C4 (Cluster 2 – r=0.81, p<0.00001, Cluster 5 – r=0.81, p=0.0016), though cluster 5 had a lower median C3 level (Cluster 2 C3=79.5, Cluster 5 C3=74.5). Cluster 3 had higher median levels of C3 and C4 (C3=106.0, C4=20.6), and the correlation between C3 and C4 was far less robust (r=0.60, p=0.44730). Cluster 4 was notable for the lowest median C3 and C4 levels (C3=69.8, C4=12.3), and no significant correlation between C3 and C4 was present (r=0.54, p=0.121143).

Individuals in cluster 2 were more likely to have Jaccoud arthropathy (OR 6.11, CI 1.59 to 24.47), or a history of avascular necrosis (AVN) (OR 4.38, CI 1.55 to 12.34), but less likely to have thrombocytopenia (OR 0.15, CI 0 to 0.98). Cluster 5 patients were more likely to have thrombocytopenia (OR 2.78, CI 1.04 to 7.43) and less likely to have AVN (OR 0.27, CI 0.05 to 0.99).

**Conclusions** C3 and C4 levels vary widely in SLE patients but generally fall into a few general patterns, which are associated with different clinical manifestations, and may provide novel insight into underlying biological differences between SLE patients.

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## BD-05 DISCOVERY OF SERPINA3 AS A CANDIDATE URINARY BIOMARKER OF LUPUS NEPHRITIS CHRONICITY

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**Background** Non-invasive biomarkers of lupus nephritis (LN) damage are needed to guide treatment decisions. Urinary proteomics has advanced as a tool for novel biomarker discovery in recent years. Specifically, isobaric tags for relative and absolute quantification (iTRAQ) is an advanced proteomics technique that quantifies and compares protein expression among samples by mass spectrometry in a single experiment. We used