Background T cell activation depends upon a calcium signalling cascade that is regulated by voltage-gated potassium channels. Effector memory T cells (T EM), which are implicated in the immunopathogenesis of autoimmune diseases, express relatively high levels of the potassium channel Kv1.3. Dalaizate is a potent peptide inhibitor of the Kv1.3 channel that has recently shown safety and efficacy in a Phase I b plaque psoriasis trial. Evidence suggests that inflammatory cytokine producing T EM cells might be involved in the immunopathology of lupus nephritis. The objective of this study is to provide proof-of-principle ex vivo data for therapeutically targeting chronic T cell activation in systemic lupus erythematosus (SLE).

Materials and methods Peripheral blood mononuclear cells from paediatric and adult SLE patients as well as healthy controls were studied. T lymphocyte subsets were assayed ex vivo for Kv1.3 expression by flow cytometry. The effect of dalaizate on inflammatory cytokine expression by T EM cells activated by thapsigargin/phorbol myristate acetate (PMA) or ionomycin/PMA was evaluated by intracellular cytokine staining.

Results Kv1.3 expression by CD8⁺ T EM cells was significantly higher in patients with active lupus nephritis when compared to patients with inactive SLE or healthy controls. Dalaizate inhibited IFN-γ, IL-17 and TNF-α production by both CD4⁺ and CD8⁺ T EM cells from SLE patients in a dose-dependent manner. Dalaizate-mediated inhibition was more significant in IFN-γ and TNF-α-expressing CD4⁺ T EM cells from patients with active SLE compared to cells from patients with inactive disease.

Conclusions Ex vivo studies suggest that dalaizate inhibition of Kv1.3 on T EM may be an effective strategy for treating SLE. In addition, Kv1.3 expression may be a useful biomarker of SLE disease activity.

Background Patients with systemic autoimmune rheumatic diseases (SARD) often have a prolonged pre-clinical phase during which they are anti-nuclear antibody (ANA)⁺ but lack clinical symptoms. Here we sought to determine whether ANA⁺ individuals who lack sufficient symptoms for a SARD diagnosis share the B cell phenotypic changes seen in SARD.

Materials and methods Healthy controls (HC) and ANA⁺ individuals who: 1) lacked clinical symptoms of SARD (ANS); 2) had at least one clinical symptom of SARD (UCTD); or 3) had recently diagnosed steroid and immunosuppressive naïve SARD (SLE, SS, SSc, MCTD, DM) were recruited. PBMCs were stained with various combinations of fluorescently labelled antibodies and analysed by flow cytometry. Anti-nuclear antibodies were measured through the hospital laboratory. Whole blood IFN signature and BAFF RNA levels were measured by NanoString.

Results B cell phenotypes were examined for 32 HC, 38 ANS, 28 UCTD, and 59 early SARD patients. Patients with early SARD had a number of changes in their naïve and memory B cell subsets including: increased proportions of mature naïve (SSc) and T1T2 cells (SLE and SS), and decreased proportions of switched memory cells (all SARD). Similar decreases in the proportion of switched memory B cells were seen in ANS and UCTD patients, and as seen for the SARD patients, these cells were activated with elevated levels of CD86 as compared to HC. Significantly increased activation of the CD27⁺1Gδ⁺ memory compartment was also seen in ANS, UCTD, SLE and SjD patients. Although significantly increased proportions of plasmablasts and/or CD138⁺ plasma cells were seen in early SARD patients, these were not seen in ANS and UCTD patients. Nevertheless, in pre-SARD individuals (ANS + UCTD) there was a significant positive correlation between the size of these cell subsets and ANA titer as well as the number of different anti-nuclear antibody specificities. As observed for early SARD patients, there was a trend to increased BAFF levels as compared to HC in pre-SARD individuals, which achieved statistical significance in UCTD patients. However, there was no association between the levels of BAFF and any of the B cell phenotypes, whereas the IFN signature was positively associated with the proportion of T1T2 cells.

Background T cell activation depends upon a calcium signalling cascade that is regulated by voltage-gated potassium channels. Effector memory T cells (T EM), which are implicated in the immunopathogenesis of autoimmune diseases, express relatively high levels of the potassium channel Kv1.3. Dalaizate is a potent peptide inhibitor of the Kv1.3 channel that has recently shown safety and efficacy in a Phase I b plaque psoriasis trial. Evidence suggests that inflammatory cytokine producing T EM cells might be involved in the immunopathology of lupus nephritis. The objective of this study is to provide proof-of-principle ex vivo data for therapeutically targeting chronic T cell activation in systemic lupus erythematosus (SLE).

Materials and methods Peripheral blood mononuclear cells from paediatric and adult SLE patients as well as healthy controls were studied. T lymphocyte subsets were assayed ex vivo for Kv1.3 expression by flow cytometry. The effect of dalaizate on inflammatory cytokine expression by T EM cells activated by thapsigargin/phorbol myristate acetate (PMA) or ionomycin/PMA was evaluated by intracellular cytokine staining.

Results Kv1.3 expression by CD8⁺ T EM cells was significantly higher in patients with active lupus nephritis when compared to patients with inactive SLE or healthy controls. Dalaizate inhibited IFN-γ, IL-17 and TNF-α production by both CD4⁺ and CD8⁺ T EM cells from SLE patients in a dose-dependent manner. Dalaizate-mediated inhibition was more significant in IFN-γ and TNF-α-expressing CD4⁺ T EM cells from patients with active SLE compared to cells from patients with inactive disease.

Conclusions Ex vivo studies suggest that dalaizate inhibition of Kv1.3 on T EM may be an effective strategy for treating SLE. In addition, Kv1.3 expression may be a useful biomarker of SLE disease activity.

Background T cell activation depends upon a calcium signalling cascade that is regulated by voltage-gated potassium channels. Effector memory T cells (T EM), which are implicated in the immunopathogenesis of autoimmune diseases, express relatively high levels of the potassium channel Kv1.3. Dalaizate is a potent peptide inhibitor of the Kv1.3 channel that has recently shown safety and efficacy in a Phase I b plaque psoriasis trial. Evidence suggests that inflammatory cytokine producing T EM cells might be involved in the immunopathology of lupus nephritis. The objective of this study is to provide proof-of-principle ex vivo data for therapeutically targeting chronic T cell activation in systemic lupus erythematosus (SLE).

Materials and methods Peripheral blood mononuclear cells from paediatric and adult SLE patients as well as healthy controls were studied. T lymphocyte subsets were assayed ex vivo for Kv1.3 expression by flow cytometry. The effect of dalaizate on inflammatory cytokine expression by T EM cells activated by thapsigargin/phorbol myristate acetate (PMA) or ionomycin/PMA was evaluated by intracellular cytokine staining.

Results Kv1.3 expression by CD8⁺ T EM cells was significantly higher in patients with active lupus nephritis when compared to patients with inactive SLE or healthy controls. Dalaizate inhibited IFN-γ, IL-17 and TNF-α production by both CD4⁺ and CD8⁺ T EM cells from SLE patients in a dose-dependent manner. Dalaizate-mediated inhibition was more significant in IFN-γ and TNF-α-expressing CD4⁺ T EM cells from patients with active SLE compared to cells from patients with inactive disease.

Conclusions Ex vivo studies suggest that dalaizate inhibition of Kv1.3 on T EM may be an effective strategy for treating SLE. In addition, Kv1.3 expression may be a useful biomarker of SLE disease activity.