organized into different discrete niches each with unique characteristics including enrichment for specific cell populations. B cell were often organized into large clusters with CD4 T cells including T follicular helper-like cells. In contrast, the CD4- T cell populations formed small dispersed clusters which, on a per patient basis, predicted progression to ESRD (p=0.004).

Conclusions These data reveal that in LN, specific *in situ* inflammatory states are associated with the failure of conventional therapy and progression to ESRD.

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505 PARENCHYMAL INFγ RESPONSE REGULATES MURINE LUPUS NEPHRITIS

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Background Lupus nephritis is the most common life-threatening end-organ complication of SLE. Interstitial infiltrates, specifically T cells, are major predictors of disease outcomes. We recently determined that kidney-infiltrating T cells (KITs) are suppressed after kidney infiltration and exhibit an exhausted phenotype. Notably, the kidneys of nephritic lupus-prone (MRL.*Fas*^{lpr}) mice upregulate PD-L1, which we hypothesize is one mechanism inducing KIT suppression. IFNγ is the major inducer of PD-L1 and given the known role of IFNγ in lupus nephritis, we postulated that IFNγ induces a protective program in the kidneys of lupus-prone mice, in direct contrast to the proinflammatory role of IFNγ in the hematopoietic compartment.

Methods MRL. *Fas*^{lpr} mice develop autoantibodies, proteinuria, dermatitis, and glomerulonephritis. Others have previously shown that global IFNγ receptor deficiency (IFNγR$^{-/-}$) ameliorates disease in this mouse model. To determine if IFNγ signaling on parenchymal cells regulates disease, we generated bone marrow chimeras by transferring congenically labeled WT immune cells into either wild-type (WT) or IFNγR$^{-/-}$ MRL.*Fas*^{lpr} recipients. If our hypothesis is correct, then the IFNγR-/- recipients would have more severe disease than their WT counterparts. Chimerization occurred at 4-6 weeks of age and female and male mice were analyzed for disease pathology at 23 and 27 weeks post-chimerization respectively. Analysis included proteinuria, renal histology for both interstitial and glomerular disease, dermatitis, autoantibody production, and immune cell activation. Survival analysis was performed on female mice. Additional analysis focused specifically on T cell phenotypes.

Results IFNγR$^{-/-}$ MRL.*Fas*^{lpr} recipient mice exhibited more severe and rapid disease onset than WT recipient controls. While proteinuria was not different between the two groups, the IFNγR$^{-/-}$ recipients had more severe glomerulonephritis (p< 0.005) and interstitial disease (p< 0.001). Consistent with these findings, IFNγR$^{-/-}$ recipients had reduced survival (p< 0.05). As expected, IFNγR deficiency resulted in reduced PD-L1 expression. When examining infiltrates, KITs isolated from IFNγR$^{-/-}$ recipients exhibited increased expression of Tim3 and PD-1.

Conclusions These experiments suggest that parenchymal IFNγR signaling results in upregulation of protective mechanisms which reduce kidney disease and alter T cell phenotypes. This contrasts with global IFNγR$^{-/-}$ which ameliorated kidney disease. Overall, this finding argues that suppression of IFNγ, and possible other inflammatory mediators, may have differential effects on specific cell lineages and that global suppression of IFNγR may have both positive and negative effects on disease pathogenesis. This will need to be considered when devising targeted therapies.

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506 BELIMUMAB (BEL) IMPROVES RENAL OUTCOMES IN ACTIVE LUPUS NEPHRITIS (LN): A PHASE 3 RANDOMIZED, PLACEBO (PBO)-CONTROLLED TRIAL

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Background BEL is approved for patients (pts) with systemic lupus erythematosus (SLE). We evaluated intravenous (IV) BEL in active LN.

Methods This 104-week trial (GSK Study BEL114054; NCT01639339) randomized adults with active LN (class III, IV, and/or V) 1:1 to monthly BEL 10 mg/kg IV or PBO, plus standard therapy (ST) with high-dose corticosteroids + either cyclophosphamide (CyC) or mycophenolate mofetil (MMF) for induction at the investigator's discretion. CyC was followed by azathioprine (AZA), and MMF by MMF maintenance. The primary endpoint was Primary Efficacy Renal Response (PERR = urine protein:creatinine ratio [uPCR] ≤0.7; estimated glomerular filtration rate [eGFR] no more than 20% below pre-flare value or ≥60 ml/min/1.73m^2; no rescue therapy) at Week 104. Other endpoints were Complete Renal Response (CRR = uPCR <0.5; eGFR no more than 10% below pre-flare value or ≥90 ml/min/1.73 m^2; no rescue therapy) at Week 104; time to renal event (end-stage kidney disease, doubling of serum creatinine, increased proteinuria and/or impaired renal function, renal disease-related treatment failure) or death. Endpoints were analyzed by ST regimen.

Results 224 pts were randomized to each arm. At Week 104, there were significantly more PERR and CRR responders on BEL vs PBO: (43.0% vs 32.3%, OR [95% CI] 1.6 [1.0, 2.3]; p=0.03) and (30.0% vs 19.7%, OR [95% CI] 1.7 [1.1, 2.7]; p=0.02), respectively. Risk of renal event or death was lower in BEL pts relative to PBO (HR [95% CI] 0.5 [0.3, 0.8]; p<0.01). Week 104 PERR response rates in pts on CyC/AZA were 33.9% with BEL and 27.1% with PBO, and 46.3% with BEL vs 34.1% with PBO in those on MMF. BEL reduced risk of renal event or death on background of CYC/AZA (HR [95% CI] 0.5 [0.2, 1.0]) and MMF (HR [95% CI] 0.5 [0.3,

0.8]) relative to PBO. Adverse events (AEs; ≥1) occurred in 95.5% of BEL and 94.2% of PBO pts, and 25.9% of BEL and 29.9% of PBO pts had ≥1 serious AE.

Conclusions The addition of BEL to commonly used ST for the treatment of LN significantly improved renal responses with no unexpected safety signals.

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Trial Registration NCT0163933. GSK Study BEL114054

507 RNASEQ GENE EXPRESSION CONFIRMS THE IMPORTANCE OF GWAS ASSOCIATED RISK GENES IN LUPUS NEPHRITIS

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Background The era of GWAS studies identified over 90 SLE risk loci, while the genetic risk factors associated with lupus nephritis (LN) require further study. The absence of strong associations might reflect uncertainty about future LN status or insufficient coverage within the array. To highlight the importance of previously identified risk genes and pathways predisposing to LN, we investigated PBMC RNAseq data from a cohort of SLE patients followed for several years with and without biopsy-proven LN.

Methods PBMC RNAseq data, including some longitudinal data, from 46 LN samples (30 patients) and 44 samples from SLE patients without LN (28 patients) were studied. The analysis of differentially expressed genes was performed using the limma R package. The reported LN genetic loci were collected from published data. The regularized logistic regression was used to select the most important genes.

Results Comparing LN and non-LN samples, 109 genes were differentially expressed between groups (logFC 1.5, 5% FDR). The functional analysis identified genes related to glomerular membrane formation (COL4A3, COL9A3, MMP9), WNT signaling (WNT1, WNT7A, TPBG), and cell adhesion (FBLN7, ADAM23, TNFAIP6). To find the most informative genes to distinguish LN patients, we used 3 models based on: (1) differentially expressed genes, (2) GWAS reported genes, (3) a combination of the above. All models were based on the same 67 (70%) training and 23 (30%) testing sample sets and efficiently segregated LN patients (AUC 0.9, 0.8, and 0.9). Despite the equal efficiency of the first and the third model, the inclusion of IKZF1 and PRPF18 genes reduced the number of required predictor genes.

Conclusion LN might be an initial presentation of SLE disease or can have a late-onset. The analysis of longitudinal samples helps classify SLE patients correctly and may be of predictive value. Polymorphism in IKZF1 was reported in association with several autoimmune diseases and found to relate to Th and dendritic cell activation. The PRPF18 gene encodes a pre-mRNA splicing factor. Interestingly, another polymorphism at that locus is highly associated with darker skin color in the African-American population, a group with high risk for severe lupus. As a limitation of our study is the relatively small number of participating SLE patients, additional patient data will be needed to confirm these results.

508 C3D-IMAGING IN LUPUS NEPHRITIS

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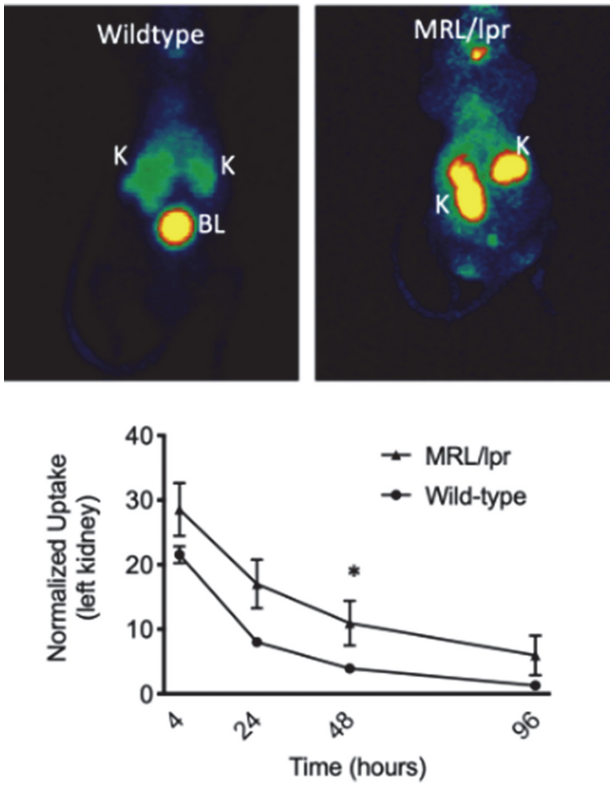
Background We have developed a positron emission tomography (PET)-based imaging probe for detecting inflammation in the kidneys. After immune-complexes deposit in the glomeruli of patients with lupus nephritis (LN), circulating C3 is cleaved and covalently fixed to tissue surfaces. Kidney biopsies are routinely immunostained for deposited C3 fragments as a marker of immunologic activity. Although generally safe, biopsies are invasive procedures, and they are also subject to sampling error. Our new method is based on non-invasive detection of C3d deposits in an animal model of LN and can be translated for use in patients. Furthermore, it will not be limited by the small size of the biopsy or require an invasive procedure.



Abstract 508 Figure 1 C3d-PET of MRL/lpr and wild-type mice. 16-week-old animals were injected with ^{124}I labeled anti-C3d antibody and PET imaging was performed at various timepoints. The kidneys of the MRL/lpr mice revealed higher uptake and retention of ^{124}I-labeled antibody. *P < 0.05. "K" indicates kidney, "BL" indicates bladder.