to therapeutic applications. Finally, we have shown that IRS can prevent skin lesions following mechanical injury by blocking PDC activation in the skin environment. The lead IRS inhibitor, called DV1179, has entered a human clinical trial and its safety was assessed in multiple ascending doses in healthy volunteers and lupus patients, however no effect on IFN response was observed in lupus patients.

**Conclusions** These data provide a new understanding of the role of self-recognition of DNA and RNA by TLR as an important parameter during inflammatory response. These data also stress the potential of blocking PDC activation to increase patient’s response to corticosteroid treatment although the use of oligonucleotide based inhibitors did not reduce the IFN signature in lupus patients. Other approaches could be tested as well.

PROTECTION OF LUPUS NEPHRITIS BY I RHOM2 DEFICIENCY IN FCyRIIB+-/ MICE

Xiaoping Qing, Yuri Chinenov, Michael Madaio, Patricia Redecha, Priya D Issuree, David McIlwain, Tak W Mak, Carl P Blobel, Jane E Salmon.

**Background** Lupus nephritis (LN) is a major cause of morbidity and mortality in lupus. A disintegrin and metalloprotease 17 (ADAM17), is a principal membrane-anchored metalloprotease that cleaves a large spectrum of membrane-bound proteins into their soluble forms. Inactive rhomboid protein 2 (iRhom2), a newly identified regulator of ADAM17, controls maturation and function of ADAM17. Interestingly, in iRhom2+-/ mice, loss of ADAM17-dependent shedding activity is limited to the immune organs. Accumulating evidence has shown increased protein shedding and possibly activation of ADAM17 in lupus. Among ADAM17 substrates, tumour necrosis factor α (TNF-α) and heparin-binding EGF (HB-EGF) have been reported to play important roles in mediating renal damage in lupus. We hypothesised that the activation of iRhom2/ADAM17 pathway plays a role in the pathogenesis of lupus nephritis.

**Materials and methods** We crossed iRhom2+-/ mice with the well-established FcγRIIB+-/- lupus-prone mice, and assessed development of lupus-like syndrome in these mice.

**Results** We found that iRhom2 deficiency protects FcγRIIB+-/- mice from severe kidney damage (Figure 1), with minimal impact on the production of anti-double stranded (ds) DNA antibodies and renal deposition of immune complex and complement C3. In the absence of iRhom2, glomerular and tubule-interstitial structures were preserved, and massive inflammatory infiltrates including myeloid and CD4+ T cells were alleviated in the lupus kidneys. Protection of kidney injury by iRhom2 deficiency is associated with reduced EGFR signalling and ERK1/2 activation in the kidneys of FcγRIIB+-/- mice. Transcriptome analysis of the whole kidneys as well as kidney macrophages from FcγRIIB+-/- mice identified genes encoding pro-inflammatory cytokine/chemokines, fibrosis and tissue remodelling highly upregulated, and many of these genes were significantly reduced in the absence of iRhom2. In addition, kidney biopsies from patients with lupus nephritis show intense staining for HB-EGF, an EGFR ligand, in areas of crescents.

**Conclusions** Our findings here provide the first evidence that iRhom2, a major regulator of ADAM17, plays a critical role in the pathogenesis of LN. The role of iRhom2 in a spontaneous chronic mouse model of LN, FcγRIIB+-/- mice, appears to be targeting at the effector arm of the disease, rather than affecting the process of autoimmunity development. iRhom2 may be a potential therapeutic target in LN.

Abstract II16 Figure 1 iRhom2 deficiency protects FcγRIIB+-/- mice from developing severe kidney injury. FcγRIIB+-/- mice crossed with iRhom2+-/- mice were assessed for survival and kidney injury. Survival (A) and proteinuria (B) were plotted at each age. Pathological scores were illustrated for glomerular (C) and tubular-interstitial area (D) respectively. (A) survival, Chi square test. (B) proteinuria, student t-test. (C, D) pathological scores, non-parametric Mann Whitney test. **P < 0.005, ****P < 0.0001
LUPUSHDL PROMOTES PRO-INFLAMMATORY CELL-BASED THERAPY IN SYSTEM LUPUS

Abstract II-18 Figure 1

Neutrophil elastase colocalized with extracellular DNA. Control neutrophils were isolated from peripheral blood and stimulated with 10nM PMA for 2 hr at 37°C. Cells were fixed and stained for detection of neutrophil elastase (green) and DNA was labeled with Hoechst 33342 (blue).