patients who are more likely to have ongoing disease activity or subsequent flares.

206 INFLAMMATION CRITICALLY REGULATES ANTIBODY PRODUCTION

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Antibodies are generated through two distinct pathways following B cell activation: the rapid generation of short-lived antibody-secreting plasma blasts and plasma cells (so called extrafollicular responses, EFRs) and the slower development of germinal center reactions (GCs). During the latter, B cells undergo clonal expansion, diversification and affinity maturation, and the generation of long-lived plasma cells as well as memory B cells that often respond to a repeat challenge with EFRs. The mechanisms regulating the differentiation of B cells along one or the other response type are incompletely understood, but critical for understanding how to intervene in ineffective or harmful humoral responses. Using a mouse model of influenza infection we demonstrate that the development of EFRs is dependent on B cell intrinsic and extrinsic, inflammatory, Toll-like receptor (TLR) signals. B cell-intrinsic TLR signals supported antigen-stimulated B cell survival, clonal expansion, and the differentiation of B cells via induction of IRF4, the master regulator of B cell differentiation, through activation of NF-kB c- Rel. Provision of sustained TLR4 stimulation after immunization altered the fate of virus-specific B cells towards EFRs instead of GCs. Thus, acute inflammatory signals enhance antibody production as a means to provide rapidly protective antibodies in infections. During chronic inflammation, the same signals may drive a continued and potentially harmful autoantibody response, indicating that control of inflammation may curb pathogenic antibody responses.

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B Cell Biology

207 ABC AND EXTRAFOLLICULAR RESPONSES: MECHANISTIC INSIGHTS FROM MURINE MODELS OF LUPUS AND INFECTION

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Background Animal models and more recently studies in humans have implicated the "extrafollicular" (EF) B cell response—rather than the germinal center (GC) response—as being prominent and possibly pathogenic in lupus. This response can also generate so-called "age- associated B cells" (ABC, known also as "DN2" in humans) under some conditions, a type of inflammatory B cell the frequency of which is elevated in some lupus patients and animal models of lupus. However, the basic biology that underlies why some immune responses are directed toward the EF mode and others to the GC mode is not well-understood. Nor are the identities and functions of ABC well-defined, particularly in lupus. ABC have been termed memory B cells, implying a quiescent or resting state, which seems incompatible with an ongoing inflammatory disease like lupus and raising the question of how these cells could contribute to pathogenesis

To understand the programming of B cell responses, we studied the response to Salmonella infection, which suppressed GCs while promoting strong EF responses. We discovered a particular cytokine network that suppressed the differentiation of GC B cells and T follicular helper cells, while at the same time enhancing the generation of EF plasmablasts and inflammatory T cells. I will present data on how this network functions as a molecular switch. To understand the role of ABC we studied them in both the immune response to Ehrlichia muris and in the MRL/lpr murine model of lupus, with contrasting results. I will present these data emphasizing that ABC in lupus are a dynamic and heterogeneous population that undergoes clonal expansion and contributes directly to pathogenesis.

Lay abstract I will present data showing how certain types of immune responses that promote lupus are controlled by the immune system. This in turn gives basic insight into lupus pathogenesis and may eventually help in categorizing types of lupus patients and designing and selecting appropriate therapies.

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301 THE LUPUS RISK INDEX (LRI) AS A BIOMARKER IN PATIENTS WITH LUPUS NEPHRITIS

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Background Identification of prognostic and predictive biomarkers in lupus nephritis (LN) is an area of intense study and interest. Non-invasive laboratory markers that associate with the likelihood of responding to therapy and/or assess clinical response in patients with active LN remains an unmet need. The Lupus Risk Index is a score that associates with the risk of developing SLE.[1] It is lowest in Caucasian females and increases in populations with increased risk of developing SLE (African American, Sister's of patients with SLE), and is highest in SLE. Its components (IgM and IgG anti-DNA antibodies and C1q) are each associated with renal disease (or protection from renal disease).

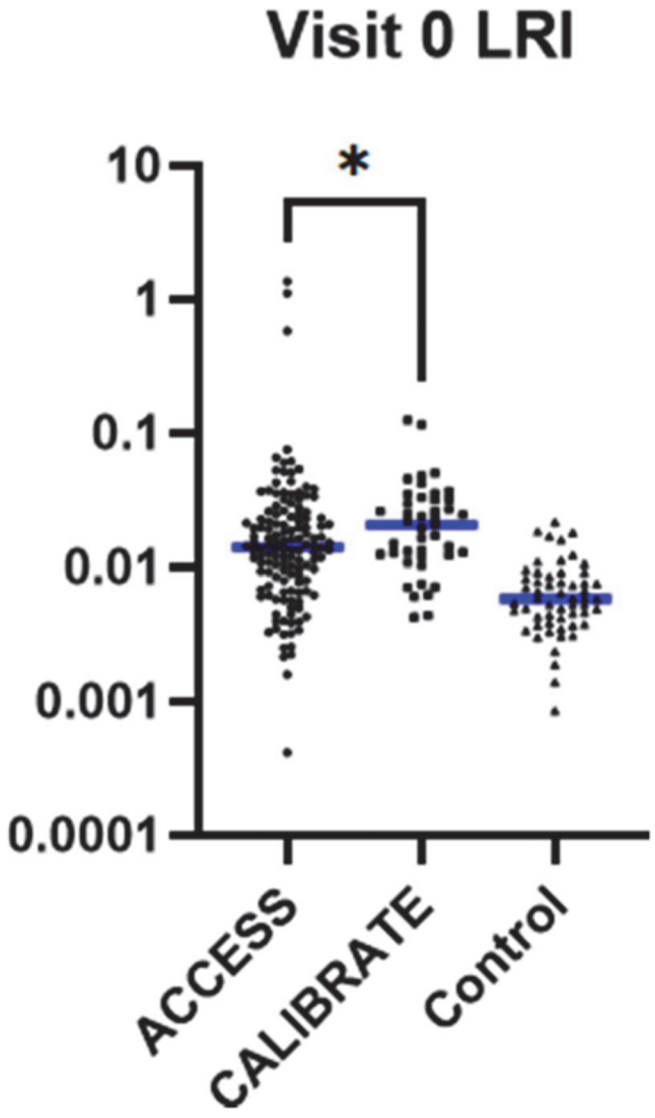
LRI

$$\frac{\text{IgG } \alpha\text{DNA}}{\text{IgM } \alpha\text{DNA} \times \text{C1q}}$$

Objective To assess the LRI as a LN biomarker that predicts a clinical response to induction therapy, or whose early changes may precede a clinical response, or that associates with a clinical therapeutic response.

Methods The LRI was determined on retrospective specimens collected from two LN clinical trials sponsored by the Immune Tolerance Network (ITN): CALIBRATE (n=43) and ACCESS (n=134) as well as healthy controls (n=70). Both trials enrolled subjects with active proliferative LN (Class III,

IV, ± Class V). All subjects participating in CALIBRATE received rituximab (coupled with cyclophosphamide) and half received open-label belimumab through week 48 of the study.



Abstract 301 Figure 1 LRI at baseline in participants enrolled in ACCESS, CALIBRATE and healthy controls

In ACCESS, all participants received the Euro-lupus cyclophosphamide protocol and subjects were randomized to receive either placebo or abatacept infusions. Sera obtained at weeks 0, 12, 24, and 48/52 (CALIBRATE/ACCESS) were studied. Levels of IgG αDNA, IgM αDNA and C1q were determined by ELISA. Response at 24 weeks was defined using the ITN's definitions of renal response. This is a categorical assessment; a Complete Response (CR) requires a Urine protein:creatinine ratio (UPCR) ≤0.5 and creatinine normal or no greater than 125% of baseline, and a prednisone (or equivalent) dose ≤10 mg/d. 2), Partial Response (PR): UPCR ≥50% reduction from baseline plus identical creatinine and steroid criteria as CR, or 3) Non-response (NR) all others.

Results Baseline LRI determined from ACCESS and CALIBRATE samples were both significantly higher than normal controls. Baseline LRI from CALIBRATE which recruited non-naïve disease LN patients, i.e., patients who were resistant to current therapy, or had a repeat LN episodes was significantly greater than those from ACCESS which allowed subjects with new onset lupus nephritis (Figure 1A). Neither the LRI at baseline nor the change of the LRI from baseline to week 12 predicted a subsequent renal response at 24 weeks (figure 2A and 2B).

Moreover, the LRI at week 24 did not associate with a renal response at that timepoint (figure 2C). These results were confirmed when samples from ACCESS and CALIBRATE were assessed separately, or if only subjects receiving the active comparator (abatacept in ACCESS or belimumab in CALIBRATE) were examined.

Conclusions The LRI, a measure associating with the risk of developing SLE, is not a predictive or prognostic biomarker in patients with active LN.

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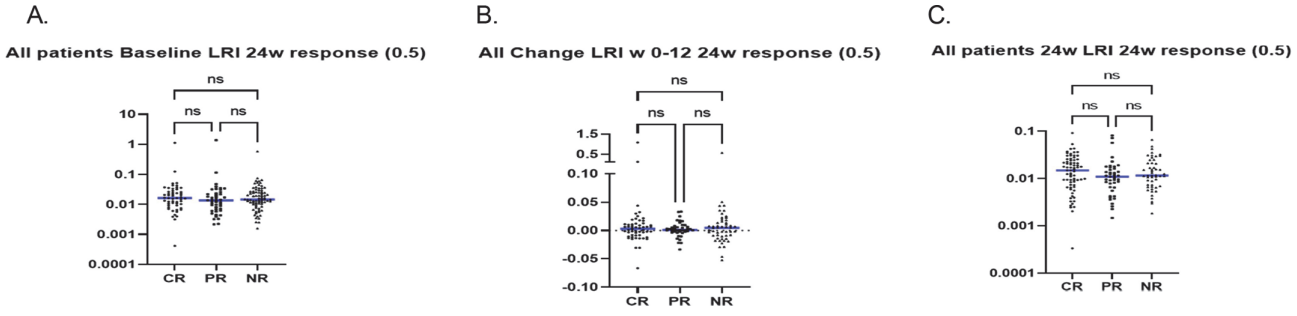

Abstract 301 Figure 2 A. LRI at baseline and response status at week 24; B. Change of LRI from baseline to Week 12 and response status at Week 24, C. Week 24 LRI and response status at Week 24