
# POSTER TOUR PRESENTATIONS

**PT002 / #417**

**Topic:** ***AS09 - Emerging Approaches in SLE Management***

**POSTER TOUR 01: CLINICAL OUTCOMES IN SLE**
**22-05-2025 10:00 AM - 10:40 AM**

# COMPLEMENTARY LUPUS-SPECIFIC INDEXES INFORMED BY SELECT IMMUNE MEDIATORS CHARACTERIZE RISK OF CONCURRENT DISEASE ACTIVITY AND FUTURE IMPENDING FLARE IN SYSTEMIC LUPUS ERYTHEMATOSUS

Melissa Munroe[1,2], Daniele Defreese[1], Adrian Holloway[1], Bernard Rubin[1], Mohan Purushothaman[1], Wade Dejager[2], Susan Macwana[2], Joel Guthridge[2], Stan Kamp[2], Nancy Redinger[2], Teresa Aberle[2], Eliza Chakravarty[2], Cristina Arriens[2], Yanfeng Li[3], Hu Zeng[3], Uma Thanarajasingam[3], Judith James[2,4], Eldon Jupe[1]
[1]Progentec Diagnostics, Inc., Oklahoma City, United States of America, [2]Oklahoma Medical Research Foundation, Oklahoma City, United States of America, [3]Mayo Clinic, Rochester, United States of America, [4]University of Oklahoma Health Sciences Center, Oklahoma City, United States of America

**Background/Purpose:** Systemic lupus erythematosus (SLE) is driven by immune dysregulation, with increased risk for heightened clinical disease activity and flare that lead to permanent end-organ damage, morbidity, and early mortality. Capturing immune dysregulation as lab-based screening tests would help prioritize SLE patients for early intervention. This study assesses the utility of employing a Lupus Flare Risk Index (L-FRI) and Lupus Disease Activity Index (L-DAI) in parallel to assess simultaneous risk of future disease flare and concurrent disease activity to guide therapy.

**Methods:** We assessed levels of 17 SLE-associated plasma mediators to calculate L-FRI and L-DAI scores in 80 preflare vs. 76 prenonflare visits, as well as 49 flare vs. 51 nonflare follow-up visits with available samples, from a unique cohort of prospectively followed SLE patients. Hybrid SLEDAI (hSLEDAI) scores, clinical features, medication usage, and the presence of SLE-associated autoantibody specificities, including dsDNA, chromatin, Ro/SSA, La/SSB, Sm, SmRNP, and RNP, were also compared. The L-FRI algorithm reflects the sum of 11 log-transformed, standardized immune mediators, weighted by the Spearman r correlation coefficient for each preflare (PF)/pre-nonflare (PNF) analyte vs. subsequent hSLEDAI scores at the time of *future* flare/nonflare, [1.-2.]. The L-DAI algorithm reflects the sum of 10 log-transformed, standardized immune mediators, weighted by the Spearman r correlation coefficient of each active (hSLEDAI ≥4)/low (hSLEDAI<4) disease activity analyte vs. the composite of *concurrent* hSLEDAI scores and number of SLE-associated autoantibody specificities, [3.].

**Results:** Forty of 80 (50%) preflare vs. 24 of 76 (32%) pre-nonflare visits were associated with concurrent active disease (hSLEDAI≥4; *p=0.0230*). The L-FRI differentiated preflare

vs. pre-nonflare visits and subsequent flare vs. nonflare visits, irrespective of disease activity state (**Figure 1A**), with severe flare visits present above the high risk cut-off (decision curve analysis, [1.-2.]). The L-DAI differentiated concurrent active vs. low (hSLEDAI<4) disease activity, irrespective of preflare/pre-nonflare or flare/nonflare status (**Figure 1B**), with renal manifestations present above the high risk cut-off (decision curve analysis, [3.]). All SLE groups had significantly higher L-FRI and L-DAI scores than demographically matched healthy Ctrl (n=71, $p<0.0001$, **Figure 1A-B**). Plasma levels of BLyS (L-FRI, L-DAI), as well as L-FRI informing mediators MCP-3, TNFRI, and TNFRII were highest in preflare visits with concurrent active disease ($p<0.05$), while IL-17A levels were highest in preflare visits with concurrent low disease activity ($p<0.05$), **Figure 1C**. IL-7 (L-FRI, L-DAI) levels were increased with both flare and disease activity risk ($p<0.05$), while L-DAI informing mediators IFN-α and IP-10 were highest in active disease, with preflare increased over pre-nonflare levels ($p<0.05$), **Figure 1C**. Of interest, although the L-FRI and L-DAI performed well at assessing flare and disease activity risk, respectively (AUC>0.9), parallel assessment of L-FRI and L-DAI performed better than either alone to identify simultaneous risk of concurrent active disease and imminent flare risk, **Table 1**.

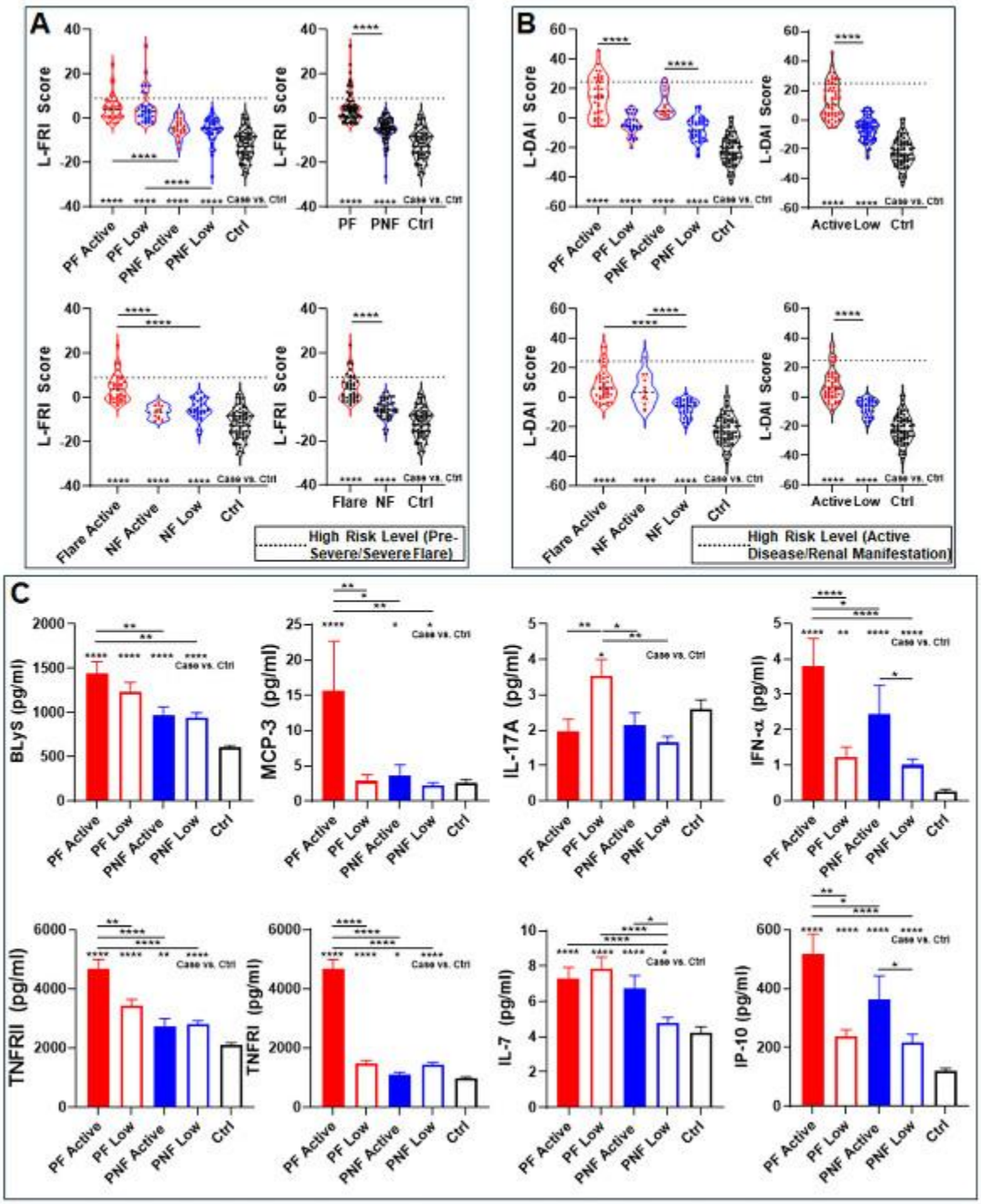



**Figure 1**. Using Lupus Flare Risk Index (L-FRI, **A**) and Lupus Disease Activity Index (L-DAI, **B**) to evaluate combination of impending flare and concurrent disease activity risk. Select L-FRI and L-DAI informing mediators reflect flare and/or disease activity risk (**C**). PF=Preflare; PNF=PreNonflare; Active (hSLEDAI≥4); Low (hSLEDAI<4); *$p<0.05$; **$p<0.01$, ****$p<0.0001$ by Kruskal-Wallis test with Dunn's multiple comparison.

**Table 1. Combination of L-FRI and L-DAI Tests Optimally Informs *Future* Flare and *Concurrent* Disease Activity Risk**

| Comparison | Variables | Test | AUC | 95% CI | *p-value* |
|---|---|---|---|---|---|
| Flare Risk Status | Pre-Flare (PF) vs. Pre-Nonflare (PNF)[a] | L-FRI[b] | 0.923 | 0.884-0.963 | ***<0.0001*** |
| | | L-DAI[c] | 0.644 | 0.553-0.735 | ***0.0034*** |
| | | L-FRI + L-DAI | 0.942 | 0.907-0.977 | ***<0.0001*** |
| Disease Activity Risk Status | Active (Act) vs. Low Disease Activity[d] | L-FRI | 0.554 | 0.461-0.646 | *0.2593* |
| | | L-DAI | 0.920 | 0.877-0.963 | ***<0.0001*** |
| | | L-FRI + L-DAI | 0.918 | 0.875-0.962 | ***<0.0001*** |
| Active Disease Flare Risk | PF/Act vs. PNF/Act | L-FRI | 0.926 | 0.860-0.991 | ***<0.0001*** |
| | | L-DAI | 0.607 | 0.464-0.750 | *0.1759* |
| | | L-FRI + L-DAI | 0.940 | 0.882-0.998 | ***<0.0001*** |
| Low Disease Activity Flare Risk | PF/Low vs. PNF/Low | L-FRI | 0.916 | 0.860-0.971 | ***<0.0001*** |
| | | L-DAI | 0.599 | 0.473-0.725 | *0.1314* |
| | | L-FRI + L-DAI | 0.932 | 0.881-0.998 | ***<0.0001*** |
| Moderate Flare/Disease Activity Risk | PF/Low vs. PNF/Act | L-FRI | 0.909 | 0.836-0.982 | ***<0.0001*** |
| | | L-DAI | 0.899 | 0.820-0.978 | ***<0.0001*** |
| | | L-FRI + L-DAI | 0.971 | 0.936-1.00 | ***<0.0001*** |
| Highest vs. Lowest Flare/Disease Activity Risk | PF/Act vs. PNF/Low | L-FRI | 0.938 | 0.892-0.984 | ***<0.0001*** |
| | | L-DAI | 0.923 | 0.868-0.977 | ***<0.0001*** |
| | | L-FRI + L-DAI | 0.993 | 0.980-1.00 | ***<0.0001*** |

[a]Pre-Flare/Pre-Nonflare visits occurred within 12 weeks of SELENA-SLEDAI Flare Index (SFI) defined Flare/Comparable Nonflare

[b]Lupus Flare Risk Index (L-FRI) informs flare risk within next 12 weeks

[c]Lupus Disease Activity Index (L-DAI) informs concurrent SLE disease activity risk

[d]Disease Activity: Active (hSLEDAI≥4); Low (hSLEDAI<4)

**Conclusions:** The L-FRI used with the L-DAI optimally identified risk of imminent lupus disease flare and concurrent active disease, including severe flare and renal manifestations. A subset of mediators consistently enhanced the L-FRI and L-DAI tests to identify SLE patients who may benefit from early intervention strategies. Such an approach would improve disease management and be advantageous in prospective clinical trials for study participant recruitment and assessment. [1.] Munroe M. Arthritis Rheumatol 2023; 75: 723-725. [2.] Munroe M. Annal Rheum Dis 2024; 83:402-403. [3.] Munroe M. Annal Rheum Dis 2024; 83: 19-20.

**PT003 / #262**

**Topic:** ***AS11 - Epidemiology and Public Health***

**POSTER TOUR 01: CLINICAL OUTCOMES IN SLE**
**22-05-2025 10:00 AM - 10:40 AM**

# LONG-TERM INFECTION RISK IN MODERATE-SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS FROM THE BRITISH ISLES LUPUS ASSESSMENT GROUP BIOLOGICS REGISTER (BILAG-BR): A PROSPECTIVE LONGITUDINAL STUDY

Sheilla Achieng[1,2], Sarah Dyball[1], Mia Rodziewicz[1], Emily Sutton[1], Ben Parker[1], Dan Wootton[2], Rebecca Lenihan[2], Lance Turtle[2], Ian Bruce[1,3], British Isles Lupus Assessment Group Biologics Register (Bilag-Br) Clinical Consortium[4]
[1]The University of Manchester, Centre For Musculoskeletal Research, Division Of Musculoskeletal And Dermatology Sciences, Faculty Of Biology, Medicine And Health, Manchester, United Kingdom, [2]University of Liverpool, Department Of Clinical Infection, Microbiology And Immunology, Institute Of Infection, Veterinary And Ecological Sciences, Liverpool, United Kingdom, [3]Queen's University Belfast, Centre For Public Health, Faculty Of Medicine, Health And Life Sciences, Belfast, United Kingdom, [4]British Isles Lupus Assessment Group Biologics Register (BILAG-BR), manchester, United Kingdom

**Background/Purpose:** Patients with systemic lupus erythematosus (SLE) are at increased risk of infection relative to the general population. A previous analysis from our cohort found a crude incidence rate of serious infections at 117.7 (95% CI 98.3–141.0) per 1000 person-years in the first 12 months from cohort entry. We aimed to establish the long-term risk of serious infections in patients with moderate-to-severe SLE in a large national observational cohort.

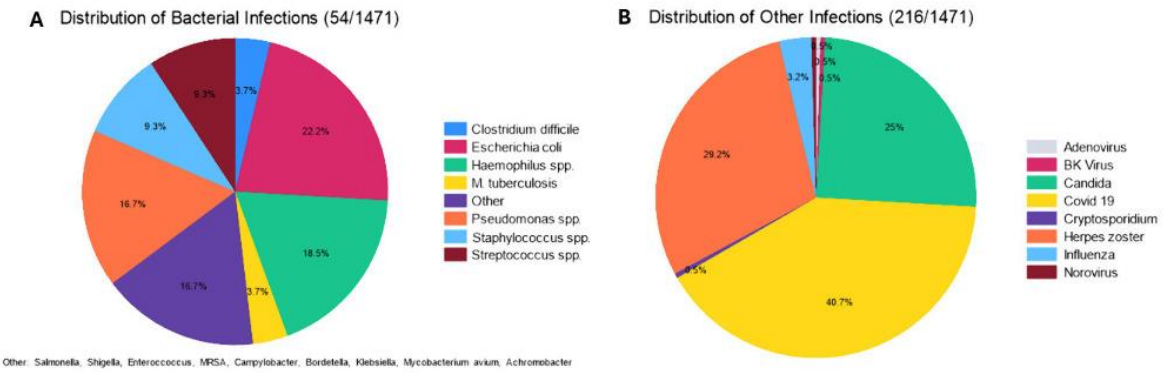
**Methods:** The British Isles Lupus Assessment Group Biologics Register (BILAG-BR) is a UK-based prospective register of patients with SLE. We included patients starting a new biological (rituximab or belimumab) within the previous 12 months or a new standard of care DMARD drug within the last month. Our primary outcome was the long-term incidence of infections, and infections of special interest including herpes zoster. Infections occurring within 28 days of the initial infection were classified as relapses, whereas after 28 days were considered reinfections. Infections involving distinct organ systems or resulting in systemic dissemination within 28 days were recorded separately, unless pathogen identification confirmed they were related to a single infection event. Serious infections were those requiring intravenous antimicrobial treatment, hospital admission, or resulting in morbidity or death. Infection and mortality data were collected from study centres and the UK Office for National Statistics.

**Results:** Between July 2010, and January 2023, 1342 individuals contributed 7073.4 person-years of follow-up. This included 929 (69.2%) participants on rituximab, 209(15.6%) on belimumab, and 204 (15.2%) receiving standard of care. The median age at cohort entry was 45 years (IQR 35–55),1206 (89.9%) were women, 670/1172 (57.2%) were White, 207 (17.7%) were South Asian, 202 (17.2%) were Black, and 93 (7.9%) were of East Asian, mixed or other ethnic backgrounds. In total, 1471 infections occurred in 545 (40.6%) individuals. Of these, 303 infections in 186 (13.9%) were classified as serious [Table 1]. The crude incidence rate of all infections and serious infections were 208.0 (95% CI 197.3 -218.6) and 42.8 (95% CI 38.0– 47.7) per 1000 person-years, respectively. In the 186 individuals with serious infection, 126 (67.7%) experienced one serious infection,42 (22.6%) had two, and 18 (9.7%) had three or more (max 11) serious infections. Herpes zoster occurred in 4.7% of the 1,342 participants at risk (incidence rate 8.9 cases per 1000 person-years, (95% CI 6.96 – 11.4)). Two cases of tuberculosis were reported, both required hospitalisation; one was a TB recurrence 153 days after the second rituximab cycle (cumulative dose 3 grams), the other was diagnosed during pre-treatment screening. Bacterial pathogens were identified by culture in 54 cases [Figure 1a]. Figure 1b shows the distribution of other infectious agents in the cohort. There were 22 infection-related deaths at a median of 2783 days (IQR 1343 – 3709) following initiation of therapy. There were no safety signals indicating an increased risk of atypical or opportunistic infections, as these occurrences were rare.

| Site / Type of Infection | Total No. of Serious Infections (%) | Total No. of Deaths (%) |
|---|---|---|
| Respiratory tract and lung infections | 121 (39.9%) | 12 (54.5%) |
| Covid-19 | 19 /121 | 5/12 |
| Tuberculosis | 2 /121 | 0 |
| Sepsis, bacteraemia, and septicaemia | 38 (12.5%) | 9 (40.9%)<br>1 *Staphylococcus aureus* septicaemia<br>1 *Pseudomonas spp.* septicaemia<br>1 *Campylobacter jejuni* septicaemia<br>No pathogen reported in 6 cases |
| Skin and soft tissue infections | 35 (11.6%) | 0 |
| Genitourinary tract infections | 33 (10.9%) | 1 (4.5%) |
| Abdominal and gastrointestinal infections | 30 (9.9%) | 0 |
| Infection source not specified | 23 (7.6%) | 0 |
| Iatrogenic (secondary to indwelling device) | 13 (4.3%) | 0 |
| Bone and joint infections | 4 (1.3%) | 0 |
| Herpes zoster | 2 (0.7%) | 0 |
| CNS infections | 1 (0.3%) | 0 |
| Dental and oral soft tissue infections | 1 (0.3%) | 0 |
| Infective endocarditis | 1 (0.3%) | 0 |
| Ocular infections | 1 (0.3%) | 0 |
| **Total** | **303** | **22** |

Table 1: Distribution of 303 serious infections which occurred in 186 individuals

Figure 1: Pie charts showing **A** Proportion of causative bacterial infectious agents, **B** other infectious agents




**Conclusions:** Our longer-term analysis shows a lower crude incidence rate of serious infections than in the first 12 months of follow-up suggesting potential adaptation or mitigation of risk over time. We also noted the occurrence of pathogens that are potentially vaccine-preventable and so further work is required to understand vaccine protocols as well as the quality and durability of vaccine responses in this high-risk cohort.

**PT004 / #704**

**Topic:** ***AS13 - Guidelines and Recommendations***

**POSTER TOUR 01: CLINICAL OUTCOMES IN SLE**
**22-05-2025 10:00 AM - 10:40 AM**

# EULAR RECOMMENDATIONS FOR A CORE DATA SET TO SUPPORT CLINICAL CARE AND TRANSLATIONAL AND OBSERVATIONAL RESEARCH IN SYSTEMIC LUPUS ERYTHEMATOSUS

Johanna Mucke[1], George Bertsias[2], Martin Aringer[3], Laurent Arnaud[4], Carina Boström[5], Ricard Cervera[6], Gamal Chehab[1], Laszlo Czirjak[7], Lene Dreyer[8], Luís Inês[9], Soren Jacobsen[10], Charite Kjaerside Nielsen[11], Emiliano Marasco[12], Marta Mosca[13], Kirsi Myllys[11], Cristina Pamfil[14], José María Pego-Reigosa[15], Jutta Richter[1], Savino Sciascia[16], Farah Tamirou[17], Michel Tsang-A-Sjoe[18], Edward Vital[19], Ronald Van Vollenhoven[18], Chris Wincup[20], Matthias Schneider[1]
[1]Heinrich-Heine University, Clinic For Rheumatology, Dusseldorf, Germany, [2]University Hospital of Heraklion, Rheumatology And Clinical Immunology, Heraklion, Greece, [3]University Medical Center and Faculty of Medicine, Division Of Rheumatology, Department Of Medicine Iii, Dresden, Germany, [4]Department of Rheumatology, National Reference Center for Autoimmune Diseases (RESO), University Hospitals Strasbourg, Strasbourg, France, [5]Karolinska Institute, Department Of Neurobiology, Care Sciences And Society, Stockholm, Sweden, [6]Hospital Clinic de Barcelona. IDIBAPS. University of Barcelona, Autoimmune Diseases, Barcelona, Spain, [7]University of Pecs, Department Of Rheumatology And Immunology, Pecs, Hungary, [8]Center of Rheumatic Research Aalborg, Department Of Rheumatology, Aalborg, Denmark, [9]Rheumatology Department, Centro Hospitalar Universitário de Coimbra - ULS Coimbra, coimbra, Portugal, [10]Copenhagen University Hospital Center for Rheumatology and Spine Diseases, Copenhagen, Denmark, [11]Lupus Europe, Brussels, Belgium, [12]Bambino Gesu Children's Hospital, Division Of Rheumatology, Rome, Italy, [13]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy, [14]Iuliu Hatieganu University of Medicine and Pharmacy, Department Of Rheumatology, Cluj-Napoca, Romania, [15]Complejo Hospitalario Universitario de Vigo. Grupo IRIDIS. Instituto de Investigación Sanitaria Galicia Sur (IISGS), Rheumatology, Vigo, Spain, [16]University of Turin, San Giovanni Bosco Hub Hospital, Department Of Clinical And Biological Sciences, Turin, Italy, [17]Cliniques Universitaires Saint Luc, Brussels, Belgium, [18]Amsterdam Rheumatology and Immunology Center, Department Of Rheumatology And Clinical Immunology, Amsterdam, Netherlands, [19]University of Leeds, Leeds Institute Of Rheumatic And Musculoskeletal Medicine, Leeds, United Kingdom, [20]King's College Hospital, London, United Kingdom

**Background/Purpose:** To enhance clinical and multicenter research outcomes in systemic lupus erythematosus (SLE), standardised documentation of patient- and disease-related features is important. The aim of this EULAR taskforce was to define a core set of essential items for the comprehensive care of SLE patients in clinical practice, with an extension for vital elements required for translational and observational research.

**Methods:** A multidisciplinary EULAR task force group engaged in a multistep approach including a four round Delphi survey and a face-to-face meeting.

**Results:** Twenty-five stakeholders from 14 different countries participated. During the process, the initial list of 99 items was reduced to 73 items for inclusion in the clinical core data set and 8 additional items for research extension. The items were grouped in the domains ‘general’, ‘disease activity’, ‘disease history’, ‘disease damage’, ‘comorbidities’, ‘patient reported outcomes’, ‘laboratory markers’, ‘outcomes’, and ‘treatment’, with suggested frequencies of assessment. (Figue 1)

| First visit & on demand | | Regularly | | Yearly |
|---|---|---|---|---|
| Demographics | Date of birth<br>Sex<br>Race/ethnicity<br>Height<br>Weight<br>Date of death | Treatment | Lupus specific<br>Antiplatelet & anticoagulants<br>Drug toxicities & intolerance<br>Adherence<br>Other medication | |
| Disease onset | Year of first SLE symptom<br>Year of diagnosis<br>Fulfillment of classification criteria at diagnosis | Lab | Routine lab<br>C3, C4<br>dsDNA antibodies | |
| Basic lab | ANA & ENA profile<br>aPL antibodies | Outcomes | Hospitalization<br>Flares<br>PGA<br>Remission<br>LDA | |
| | | PRO | Fatigue<br>Pain<br>HRQoL<br>Work productivity | |

| | Disease history | Disease activity | Damage | Comorbidities |
|---|---|---|---|---|
| Skin/ mucocutaneous | X | X | X | |
| Renal | X | X | X | X |
| Cardiovascular | X | X | X | X |
| Respiratory | X | X | X | X |
| Neuropsychiatric | X | X | X | X |
| Peripheral vascular | X | X | X | X |
| Hematology | X | X | X | |
| Musculoskeletal | X | X | X | |
| Ophthalmic | X | X | X | |
| Constitutional | X | X | | |
| Gastrointestinal | X | X | X | X |
| Sec. Aps | X | | | |
| History of pregnancy morbidity | X | | | |
| Premature gonadal failure | | | X | |
| Diabetes | | | X | X |
| Cancer | | | X | X |
| Hypertension | | | | X |
| Vaccinations | | | | X |
| Other autoimmune diseases | | | | X |

ANA antinuclear antibodies, aPL antiphospholipid, APS antiphospholipid syndrome, C3/C4 complement 3/4, dsDNA double stranded DNA, ENA extractable nuclear antigen, HRQoL health related quality of life, LDA low disease activity, PRO patient reported outcome, Sec. secondary

Figure 1. Core Data Set for SLE to support clinical care and research extension for observational and translational research (research extension in red)

**Conclusions:** The presented clinical core data set and its research extension are designed to improve SLE patient care and facilitate collaborative research by ensuring the comparability of datasets and cohort descriptions. This initiative lays the foundation for the establishment of a global SLE data space, and has the potential to expedite the implementation of personalized medicine in SLE care. This work was funded by a EULAR grant and was submitted on behalf of Taskforce for development of EULAR recommendations for a core data set to support clinical care and translational and observational research in systemic lupus erythematosus,

**PT005 / #801**

**Topic: *AS17 – Miscellaneous***
**Late-Breaking Abstract**

**POSTER TOUR 01: CLINICAL OUTCOMES IN SLE**
**22-05-2025 10:00 AM - 10:40 AM**

# RECOMBINANT HERPES ZOSTER VACCINE (RZV) IN A LARGE COHORT OF AUTOIMMUNE RHEUMATIC DISEASES PATIENTS: A PROSPECTIVE DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED PHASE 4 STUDY

Nadia Aikawa[1], Ana Medeiros-Ribeiro[1], Sandra Pasoto[1], Leonard Kupa[1], Luciana P.C. Seguro[1], Ana Paula Assad[1], Eduardo F. Borba[1], Carla Saad[1], Emily F. N. Yuki[1], Danieli Andrade[1], Andrea Shimabuco[1], Karina Bonfiglioli[1], Diogo Domiciano[1], Julio Moraes[1], Samuel Shinjo[1], Percival Sampaio-Barros[1], Henrique Giardini[1], Joao Oliveira[1], Isabele Antonelli[1], Renata Mello[1], Thais Gorayeb[1], Lucas Farias[1], Andrea Negrini[1], Fernanda Chaer[1], Ana Praxedes[1], Marta Lopes[2], Clovis Silva[1], Eloisa Bonfá[1]
[1]Rheumatology Division, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil (BR), Sao Paulo, Brazil, [2]Infectious Diseases Division, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil (BR), Sao Paulo, Brazil

**Background/Purpose:** Patients with autoimmune rheumatic diseases (ARDs) are at high risk of herpes zoster (HZ) and the new recombinant vaccine against HZ (RZV) offers safety improvements. This study evaluates disease safety, overall safety and humoral immunogenicity of RZV in ARD patients compared to non-vaccinated ARDs and non-immunosuppressed control group (CG).

**Methods:** This prospective double-blind randomized placebo-controlled phase 4 study evaluated ARD patients at high risk of HZ. Participants aged >18 years were randomized into two groups: P1 (vaccine) and P2 (placebo), with non-immunosuppressed individuals serving as CG. Both P1 and CG received two intramuscular doses of RZV administered 6 weeks apart (D0 - V1 and D42 - V2), while P2 received placebo. Disease activity was evaluated using specific scores and adverse events (AEs) were assessed through a standardized questionnaire. Blood samples were collected prior to the 1st dose (V1) and 6 weeks following the 2nd dose (V3) with humoral immunogenicity measured via anti-gE antibody serum concentrations (ELISA).

**Results:** A total 1,012 ARD patients (P1:529 and P2:483) and 393 CG completed the study. ARDs included nine different chronic conditions, mainly rheumatoid arthritis (n = 290) and systemic lupus erythematosus (n = 302). At baseline, treatments included prednisone (39%), hydroxychloroquine (31%), sulfasalazine (6%), immunosuppressive drugs (79%) [mycophenolate mofetil (24%), methotrexate (23%), leflunomide (20%),

azathioprine (18%) and cyclosporine (2%), tacrolimus (2%) and cyclophosphamide (3%)], biologic therapy (44%) [TNFi (17%), tocilizumab (8%), rituximab (7%), belimumab (6%), secukinumab (5%) and anifrolumab (1%)] and JAK inhibitors (4%). P1(vaccine) and P2 (placebo) groups were balanced for age [50 (IQR 39.8 - 61) vs. 51 (IQR 40 - 61.8) years, $p = 0.543$], female sex (77% vs. 80%, $p = 0.314$), ARD diagnoses and therapies ($p > 0.05$), except for lower frequency of mycophenolate mofetil (MMF) in P1 ($p = 0.047$). The primary endpoint showed comparable flare frequencies in P1 and P2 at V2 (4.1% vs. 6.2%, $p = 0.142$) and V3 (10.2% vs. 11.6%, $p = 0.506$). Secondary endpoints revealed no moderate/severe AEs, but AEs were less frequent in P1 (78% vs 90%, $p < 0.0001$), including both local (72% vs. 85% $p < 0.0001$) and systemic reactions (50% vs. 62%, $p = 0.001$), mainly headache (24% vs. 33%, $p=0.005$), fatigue (16% vs. 24%, $p = 0.008$), drowsiness (16% vs. 23%, $p = 0.015$), myalgia (16% vs. 21%, $p = 0.034$), chills (15% vs. 21%, $p = 0.012$) and fever (11% vs. 19%, $p=0.002$ after 1st RZV dose. Although humoral response was adequate, it was lower in P1 compared to CG (92% vs. 99%, $p < 0.0001$). Baseline GMT was similar ($p = 0.674$), but the GMT increase after two doses was lower in P1 than in CG [35.09 (95%CI 30.49-40.4) vs. 64.52 (95%CI 55.97-74.38); $p < 0.001$]. Multivariate analysis identified rituximab [OR 0.152 (95%CI 0.059-0.393), $p < 0.0001$] and MMF [OR 0.0460 (95%CI 0.224-0.946), $p = 0.035$] as major deleterious factors for reduced vaccine response. No HZ case were confirmed by RT-PCR up to week 12.

**Conclusions:** RVZ demonstrated a strong disease safety profile and adequate short-term immunogenicity in highly immunosuppressed ARD patients, including those with active diseases, with no severe adverse events and no significant impact on disease activity. Our findings highlight MMF and rituximab as key factors impairing vaccine immunogenicity, suggesting that a booster dose may be beneficial for patients on these therapies.

**PT001 / #268**

**Topic:** ***AS04 - Biomarkers***

**POSTER TOUR 02: RECENT INSIGHTS ON THE PATHOGENESIS OF LUPUS NEPHRITIS**
**23-05-2025 10:00 AM - 10:40 AM**

## A PRELIMINARY STUDY OF THE RELATIONSHIP BETWEEN PLASMA MICROBIAL CELL FREE DNA AND DISEASE ACTIVITY IN PATIENTS WITH LUPUS

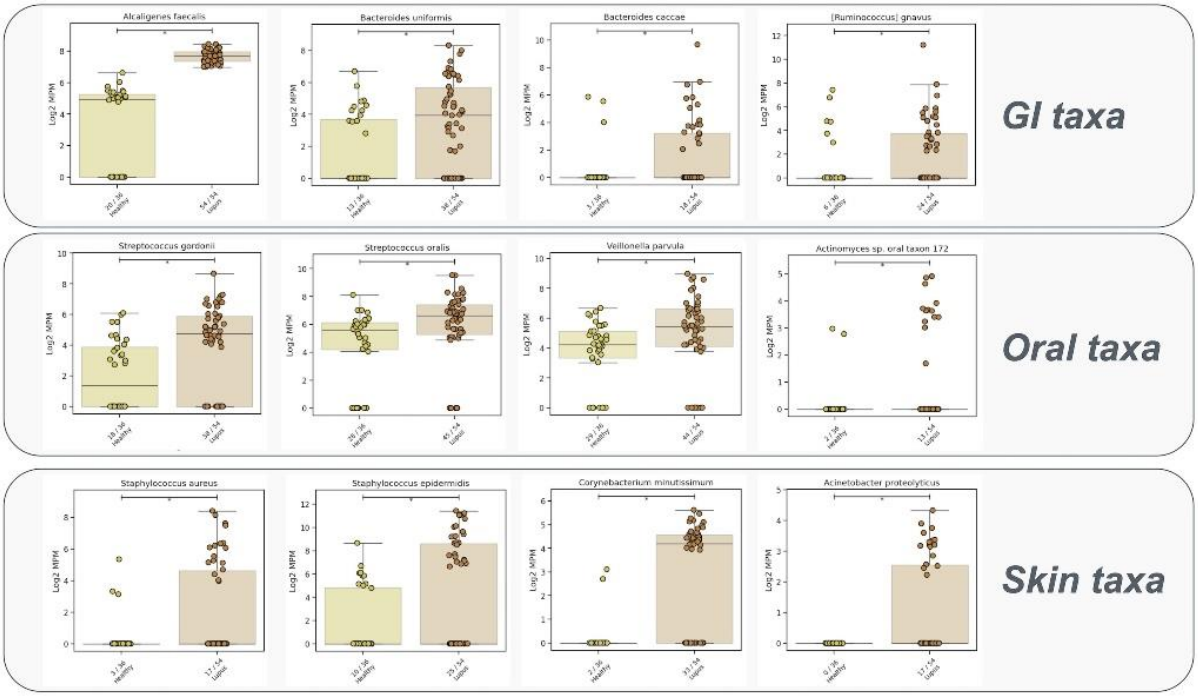
Shiv Kale[1], Paul Babb[1], Roberto Caricchio[2], Amanda Eudy[3], David Pisetsky[3], Jennifer Rogers[3], Sivan Bercovici[1]
[1]Karius, Biomarker Discovery, Redwood City, United States of America, [2]UMass Chan Medical School, Worcester, United States of America, [3]Duke University School of Medicine, Durham, United States of America

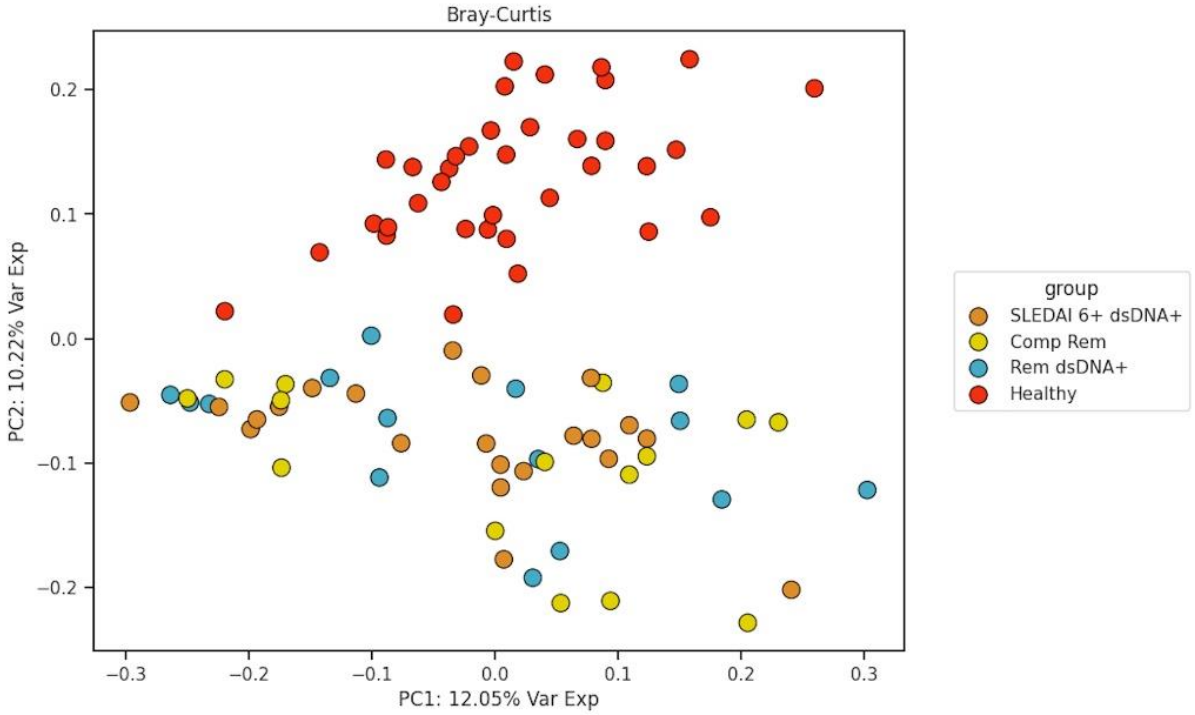
**Background/Purpose:** Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by widespread tissue inflammation and damage in association with antinuclear antibody production. Emerging research suggests that disturbances in the microbiome (dysbiosis) can interact with the immune system to drive pathogenesis. Microbial cell-free DNA (mcfDNA) in plasma, analogous to human cell-free DNA, is thought to originate from microbial organisms undergoing cellular turnover. These microbial derived DNA fragments can transverse into the bloodstream and may be processed by circulating DNases. However, these degraded fragments may also be readily detected, identified, and quantified in plasma using advanced molecular and bioinformatics methodologies. The purpose of this pilot study was to explore a possible relationship between plasma mcfDNA and disease activity in patients with lupus.

**Methods:** Plasma samples from patients with lupus were collected at two clinical centers. Patients were clustered into three groups: complete remission, remission with a positive anti-dsDNA titer, and active disease (SLEDAI greater > 6) with a positive anti-dsDNA titer. Specimens from a healthy cohort were derived from an independent collection center. Plasma was collected, processed, and stored in K2-EDTA tubes. Cell-free DNA was extracted from plasma via the Karius Discovery assay and sequenced at a depth of 400M paired-end reads per sample. A set of analytical filters was applied to control for contamination, separating biological signals from background. Differential abundance analysis, correlation analysis, and principal coordinate analysis were conducted to identify microbial signatures that discriminated between the healthy and lupus patient populations as well as the disease activity groupings. Identified features were incorporated into a gradient-boosted machine learning classifier to assess their predictive power.

**Results:** Our study included 54 patients with SLE (median age 37.5 years, 46% had a history of lupus nephritis, 85% female) and 36 healthy controls (median age 45 years,

61% female). Our analysis indicated specific elevated microbial species, estimated in molecules per microliter (MPM), with concordant findings observed across both clinical centers. The mcfDNA that were identified were associated with the oral (Streptococcus, Prevotella, Porphyromonas, and Veillonella species); gastro-intestinal (Bacteroides, Alcaligenes, Streptomyces, and Campylobacter species); and skin (Staphylococcus, Corynebacterium, and Acintobacter species) microbiomes (Figure 1). Principal coordinate analysis and preliminary machine learning classifiers suggested a possible partition between the healthy individuals and those with lupus (Figure 2). The analysis also indicated that a subset of the microbial signatures may differentiate between disease activity groupings.




**Conclusions:** Our pilot study provides preliminary data suggesting an increase in mcfDNA concentration from signature microbial species that can distinguish patients with SLE from controls and differentiate between disease subgroups. Further studies, including longitudinal analyses of larger and more diverse patient cohorts, will be needed to determine the utility of plasma mcfDNA as a biomarker for disease activity and delineate mechanisms by which increased mcfDNA may arise and contribute to pathogenesis.

**PT006 / #521**

**Topic:** ***AS15 - Lupus Nephritis-Clinical***

**POSTER TOUR 02: RECENT INSIGHTS ON THE PATHOGENESIS OF LUPUS NEPHRITIS**
**23-05-2025 10:00 AM - 10:40 AM**

## NON-INVASIVE HIGH-THROUGHPUT SERUM PROTEOMICS FOR DISTINGUISHING SUBTYPES OF LUPUS NEPHRITIS

Rufei Lu[1], Andrea Fava[2], Benjamin Jones[3], Peter Izmirly[4], Jennifer Anolik[5], Chaim Putterman[6], David Wofsy[7], Diane L Kamen[8], Maria Dall'Era[9], Kenneth Kalunian[10], Michael H Belmont[4], Richard Furie[11], Susan Macwana[3], Wade Dejager[3], Catriona Wagner[1], Michael Weisman[12], Mariko Ishimori[13], Paul J. Utz[12], Betty Diamond[11], Jill Buyon[4], Michelle Petri[14], Judith James[3], Joel Guthridge[3]
[1]Oklahoma Medical Research Foundation, Arthritis And Clinical Immunology, Oklahoma City, United States of America, [2]Johns Hopkins University, Rheumatology, Baltimore, United States of America, [3]Oklahoma Medical Research Foundation, Oklahoma City, United States of America, [4]New York University School of Medicine, Medicine, New York, United States of America, [5]University of Rochester's Lupus Clinic, Rochester, United States of America, [6]Albert Einstein College of Medicine, Department Of Medicine, Bronx, United States of America, [7]University of California San Francisco, San Francisco, United States of America, [8]Medical University of South Carolina, Charleston, United States of America, [9]University of California San Francisco, Department Of Rheumatology, San Francisco, United States of America, [10]University of California San Diego, San Diego, United States of America, [11]Institute of Molecular Medicine, Feinstein Institutes for Medical Research, Manhasset, United States of America, [12]Stanford University, Palo Alto, United States of America, [13]Cedars-Sinai Medical Center, Los Angeles, United States of America, [14]John Hopkins University, Baltimore, United States of America

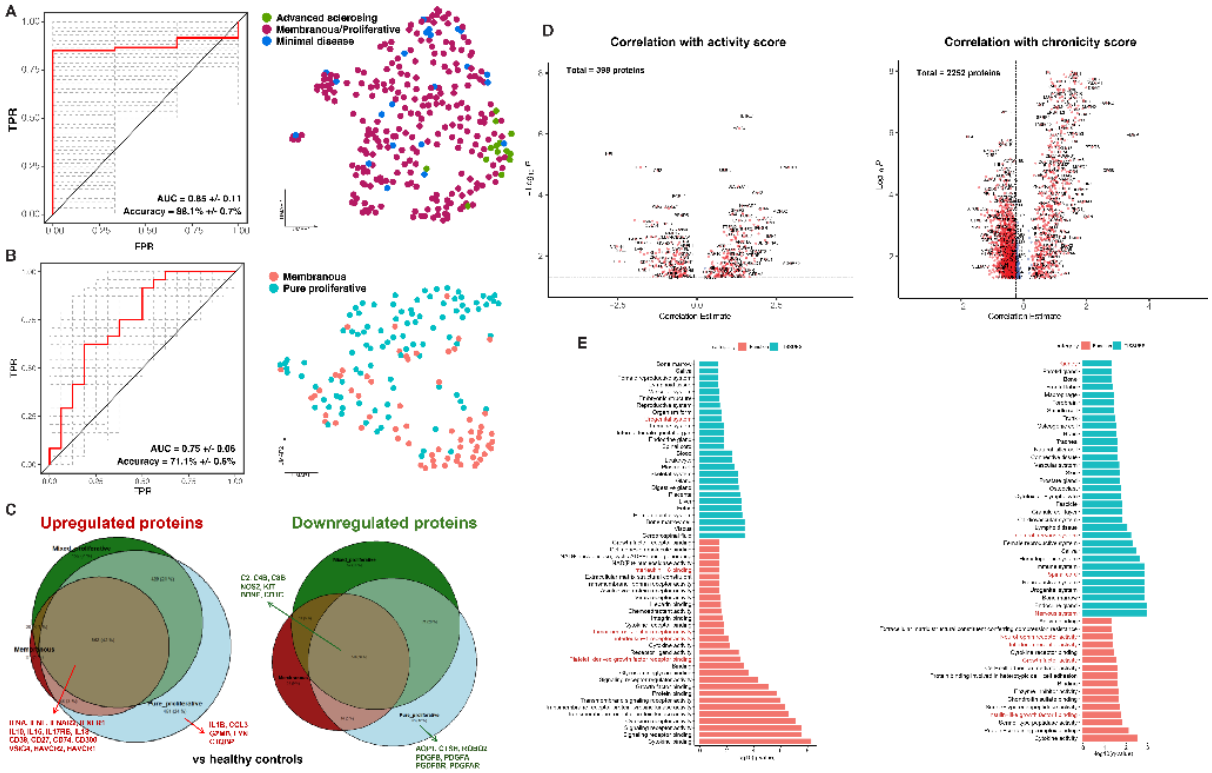
**Background/Purpose:** Lupus nephritis (LN) treatment decisions are commonly guided by histopathological classifications based on the ISN/RPS and NIH activity and chronicity indices. Since LN class and activity may shift over time, treatment adjustments are often necessary. However, repeated kidney biopsies are invasive and impractical, highlighting the need for noninvasive biomarkers to inform LN classification and guide therapy. In this study, we analyzed serum proteomic profiles to identify noninvasive biomarkers reflective of histological class, activity, and chronicity indices.

**Methods:** This study recruited 196 SLE patients with lupus nephritis (LN) as part of the AMP RA/SLE network. Each patient underwent a kidney biopsy evaluated by a renal pathologist for LN classification using the ISN/RPS system and NIH activity and chronicity indices. Serum samples were collected at biopsy to explore non-invasive biomarkers. High-throughput proteomic analysis was conducted using the Olink

Explore HT platform to identify protein expression patterns linked to LN class, activity, and chronicity. Multivariate logistic regression, adjusted for age, gender, and genetic ancestry, along with random forest algorithms, were used to pinpoint potential biomarkers to guide LN treatment decisions.

**Results:** Compared to healthy controls, LN patients upregulated multiple pathways related to the innate and adaptive immune systems, including TNF, IL-10, efferocytosis, and antigen processing and presentation pathways. Patients with pure proliferative LN (class III or IV) showed further upregulation in B cell receptor signaling, Th1/Th2 differentiation, neutrophil degranulation, Th17 differentiation, and leukocyte chemotaxis pathways compared to those with minimal disease (class I/II), membranous (V), or mixed proliferative (III/IV+V) LN. Machine learning models using a decision-tree-based boost algorithm achieved high accuracy for distinguishing healthy controls (95.3% [86.9%-99%]) and LN patients (99.5%, [97% - 100%]), as well as advanced sclerosing (class VI), compared to other classes (AUC, 0.85 ± 0.11; accuracy, 88.1% ± 0.7%). When distinguishing membranous vs pure proliferative classes, the ML model showed a modest prediction performance with an AUC of 0.75 ± 0.06 with a cross-validation accuracy of 71.1% ± 0.6%. When compared to healthy controls, there are 862 upregulated proteins, including interferons, IL-10, and lymphocyte surface receptors, shared among patients with membranous, proliferative, and mixed classes and 92 downregulated proteins, including C2, C4, and C8 (Figure 1C). In addition, the expression of 398 and 2252 proteins was associated with the NIH activity and chronicity indices, respectively (Figure 1D). Specifically, proteins involved in IL-18, TNF, and IL-1 pathways and intracellular proteins from multiple organ systems with prominent enrichment in immune cells positively correlated with the activity index (Figure 1D). Interestingly, proteins enriched in interferon, growth factor and neurotrophin receptor pathways and intracellular proteins from multiple organ systems, particularly the nervous system, correlated with the chronicity index (Figure 1E).

**Conclusions:** This study revealed that lupus nephritis (LN) patients exhibited significant upregulation of immune pathways, including TNF and IL-10, compared to healthy controls, particularly in proliferative LN. A machine learning model effectively distinguished LN patients from healthy controls and showed moderate performance in differentiating membranous from proliferative LN. Proteomic analysis identified proteins associated with NIH activity and chronicity indices, underscoring the potential of serum proteomics as a non-invasive tool for LN classification and monitoring.


A
TPR
FPR
AUC = 0.85 +/- 0.11
Accuracy = 88.1% +/- 0.7%
Advanced sclerosing
Membranous/Proliferative
Minimal disease
B
TPR
FPR
AUC = 0.75 +/- 0.06
Accuracy = 71.1% +/- 0.6%
Membranous
Pure proliferative
C
Upregulated proteins
Downregulated proteins
vs healthy controls
D
Correlation with activity score
Total = 398 proteins
Correlation with chronicity score
Total = 2252 proteins
E

**PT007 / #602**

**Topic:** ***AS15 - Lupus Nephritis-Clinical***

**POSTER TOUR 02: RECENT INSIGHTS ON THE PATHOGENESIS OF LUPUS NEPHRITIS**
**23-05-2025 10:00 AM - 10:40 AM**

## INTEGRATING GENETIC RISK SCORES AND TRADITIONAL RISK FACTORS TO PREDICT DEVELOPMENT OF LUPUS NEPHRITIS BASED ON (CSTAR) COHORT

Jiuliang Zhao[1], Xinzhuang Yang[1], Mengtao Li[2], Xiaofeng Zeng[2]
[1]Peking Union Medical College Hospital, Beijing, China, [2]Peking Union Medical College Hospital, Rheumatology And Clinical Immunology, Beijing, China

**Background/Purpose:** Lupus nephritis (LN) is one of the most common and severe manifestations of systemic lupus erythematosus (SLE). However, identifying patients at high risk of LN remains challenging. This multicenter prospective cohort study aimed to evaluate the utility of clinical risk factors and genetic susceptibility for predicting new-onset LN in SLE patients.

**Methods:** Based on Chinese SLE treatment and research (CSTAR), SLE patients without LN at SLE diagnosis were consecutively enrolled. Clinical characteristics were recorded, and blood samples were collected for genotyping. The contribution of 112 non-HLA SLE susceptible variants was taken together as a genetic risk score (GRS).

**Results:** A total of the 2441 SLE patients without LN at baseline, 215 (8.8 %) developed LN within a mean follow-up of 2.9±1.6 years. Age < 30 years old, absence of arthritis, serositis, hypocomplementemia, and positive anti-dsDNA antibodies emerged as significant predictors of LN. We further enrolled 451 patients and performed genotyping. The five traditional risk factors were validated and the utility of GRS in affecting LN development was assessed. The hazard ratio of GRS was 3.19 after adjusting for the five clinical risk factors ($p=4.36\times10\text{-}5$). Furthermore, integrating GRS improved the classification of new-onset LN risk compared to compositing traditional risk factors alone (AUC 0.838 vs. 0.799). Patients in the clinical low-risk group but with high GRS quartiles showed significantly higher LN probability than those without (18.5% vs. 1.9%), similar to that in the clinical high-risk group (29.4%).

**Conclusions:** Our study gave further evidence to the role of traditional risk factors, including younger age, serositis, absence of arthritis, hypocomplementemia, and anti-dsDNA antibodies, in new-onset LN risk prediction. The integration of GRS and the four clinical risk factors may play a pivotal role in the individualized management of SLE.

**PT008 / #89**

**Topic:** ***AS15 - Lupus Nephritis-Clinical***

**POSTER TOUR 02: RECENT INSIGHTS ON THE PATHOGENESIS OF LUPUS NEPHRITIS**
**23-05-2025 10:00 AM - 10:40 AM**

# A RETROSPECTIVE STUDY ON LUPUS NEPHRITIS: EXAMINING CLINICAL, SEROLOGICAL, AND PROGNOSTIC DIFFERENCES BETWEEN PEDIATRIC AND ADULT-ONSET PATIENTS IN A TERTIARY MEDICAL CENTER

Esra Firat Senturk[1], Yagmur Ersoy[2], Kaan Demirbas[3], Talal Ammar[4], Mesude Ozluk[5], Isin Kilicaslan[6], Nur Canpolat[7], Sezgin Sahin[8], Ozgur Ksapcopur[8], Serdal Ugurlu[1]
[1]Cerrahpasa Medical Faculty, Internal Medicine-rheumatology, istanbul, Turkey, [2]Cerrahpasa Medical Faculty, Internal Medicine, istanbul, Turkey, [3]Cerrahpasa Medical Faculty, Pediatrics, istanbul, Turkey, [4]Cerrahpasa Medical Faculty, Pyhsiology, istanbul, Turkey, [5]Istanbul Medical Faculty, Pathology, Istanbul, Turkey, [6]Istanbul Medical Faculty, Istanbul, Turkey, [7]Cerrahpasa Medical Faculty, Pediatric Nephrology, istanbul, Turkey, [8]Cerrahpasa Medical Faculty, Pediatric Rheumatology, istanbul, Turkey

**Background/Purpose:** Renal involvement occurs in about 40-50% of adult SLE patients. Pediatric-onset SLE nephritis is more common and severe than in adults. This study evaluates the differences in renal involvement and clinical outcomes between childhood-onset and adult-onset SLE.

**Methods:** This retrospective study at a rheumatology center included 177 biopsy-proven nephritis cases. Demographic, clinical, and lab data were collected. Renal pathology was assessed using the 2018 ISN/RPS criteria, comparing various pathological features and thrombotic microangiopathy between adult and pediatric SLE nephritis. Pre-2018 biopsies were re-evaluated by an experienced pathologist. Treatment protocols and therapeutic goals were compared, and correlations between clinicopathologic parameters and chronic kidney disease were analyzed."

**Results:** In this study, 168 biopsy-proven nephritis cases (128 adults, 40 children) were analyzed. The female-to-male ratio was similar in both groups. The median time from SLE diagnosis to biopsy was shorter in children than adults. ISN/RPS Class IV was the most common pathology in both groups. Chronicity scores were higher in adults, while activity scores were similar. Rituximab was more commonly used in adults, but cyclophosphamide and mycophenolate mofetil usage did not differ. More children achieved prednisolone-free status with low proteinuria compared to adults. End-stage renal failure was more frequent in adults. Regression analysis showed a negative correlation between CKD and childhood-onset lupus nephritis, with fibrinoid necrosis negatively correlated and endocapillary hypercellularity and glomerular sclerosis positively correlated with CKD. APL positivity was higher in adults but not linked to CKD.

| | | Adult-onset (N=128) | Childhood-onset (N=42) | p |
|---|---|---|---|---|
| Gender, [Female-N (%)] | | 99 (77.3%) | 32 (76.2%) | 0.93 |
| Age at lupus nephritis diagnosis, [median-(min-max)] | | 29.00 (18-78) | 13.00 (3-17) | - |
| The time interval from SLE-to-SLE nephritis (months), [median-(interquartile range)] | | 10 (0-60) | 1.75(0-17.04) | 0.09 |
| Follow-up time (months) [median-(min-max)] | | 84 (0-360) | 59 (8-263) | 0.04 |
| Mucocutaneous, [N (%)] | | 69 (59.0%) | 32(78.0%) | 0.02 |
| Hematological, [N (%)] | | 32 (27.6%) | 27(65.9%) | 0.000 |
| Neuropsychiatric, [N (%)] | | 11 (9.6%) | 10(24.4%) | 0.01 |
| Cardiopulmonary, [N (%)] | | 39 (33.6%) | 16 (39.0%) | 0.53 |
| Joint, [N (%)] | | 70 (59.8%) | 24(58.5%) | 0.88 |
| APL (positive cases), [N (%)] | | 45 (35.2%) | 5 (11.6%) | 0.005 |
| Anti-dsDNA (positive cases), [N (%)] | | 35 (81.4%) | 35 (81.4%) | 0.36 |
| Anti-Sm (positive cases), [N (%)] | | 16 (12.5%) | 7 (16.3%) | 0.000 |
| Renal pathology classification | II | 13 (10.2%) | 9 (22.5%) | 0.07 |
| | III | 27 (21.1%) | 6 (15.0%) | |
| | IV | 38 (29.7%) | 20 (50.0%) | |
| | V | 18 (14.1%) | 3 (7.5%) | |
| | III+V | 15(11.7%) | 1(2.5%) | |
| | IV+V | 9 (7.0%) | 0 (0.0%) | |
| | III+IV | 3 (2.3%) | 1 (2.5%) | |

Table 1. Comparison of Demographic, Laboratory, and Clinical Modalities in Adult-Onset versus Childhood-Onset Systemic Lupus Erythematosus Patients.

Chronic kidney disease (N = 38/164)

| | Regression coefficient (r2) | p |
|---|---|---|
| Childhood-onset, (N=3) | -0.21 | 0.006 |
| Endocapillary hypercellularity (N = 79/99) | 0.20 | 0.05 |
| Fibrinoid necrosis (N = 28/100) | -0.23 | 0.02 |
| Glomerular sclerosis (N = 46/99) | 0.25 | 0.017 |

Table 2. Significant Parameters Identified in Correlation Analysis for Chronic Kidney Disease.

**Conclusions:** As opposed to current literature, our study reveals that childhood-onset lupus nephritis has a lower likelihood of progressing to end-stage renal disease with a more favorable treatment response, while the clinical manifestations are not different from adult-onset SLE nephritis. Additionally, endocapillary hypercellularity and glomerular sclerosis are slightly correlated with CKD, while the presence of fibrinoid necrosis is negatively correlated with CKD

**PT009 / #712**

**Topic:** ***AS20 - Precision Medicine***

**POSTER TOUR 02: RECENT INSIGHTS ON THE PATHOGENESIS OF LUPUS NEPHRITIS**
**23-05-2025 10:00 AM - 10:40 AM**

# SIMILARITY AND DIVERSITY IMMUNOLOGICAL ABERRATIONS IN STABLE BENIGN IMMUNITY AND TOWARD ANA-RELATED AUTOIMMUNE DISEASES IN ANA-POSITIVE AT-RISK POPULATIONS

Porntip Intapiboon[1,2], Lucy Marie Carter[1,3], Jack Arnold[1,3], Md Yuzaiful Md Yusof[1,3], Edward Vital[1,3]
[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]Allergy and Rheumatology Unit, Faculty of Medicine, Prince of Songkla University,, Hat Yai, Thailand, [3]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

**Background/Purpose:** Previous genetic and transcriptome studies revealed shared immune dysregulation in ANA-at-risk individuals. Upregulation of interferon-stimulated genes signature while mitochondrial oxidative phosphorylation downregulation is linked to disease progression. However, functional protein studies in this population are limited. This study aims to investigate baseline functional protein dysregulation in ANA-at-risk individuals and discriminate an immune aberration between the groups.

**Methods:** Stored samples from 103 ANA-at-risk individuals (progressors = 32, non-progressors = 67) were included in a proteome study using the EXPLORE Inflammation I and II panel, Proximity Extension Assay (PEA) technology (Olink®, Uppsala, Sweden). The module eigengenes (MEs) were constructed from 193 proteins with greater than 0.5 differential expression proteins (DEPs) when compared to healthy control (HC) by using Weighted Gene Co-expression Network Analysis (WGCNA) from R package version 4.3.1. Exclusively, the modular analysis from IFN-inducible proteins was computed to improve validity and reliable interpretation. The module trait correlation was analysed using the Pearson correlation. Enrichment analysis was performed to determine the biological significance of identified modules. The false positivity was mitigated using the Benjamini-Hochberg multiple testing method; an adjusted $p$-value < 0.05 was considered statistically significant. Cytoscape and bioinformatics platforms were employed for data visualisation.

**Results: Results:** The unique and overlapping significant protein number was demonstrated in the Venn diagram (Fig 1A). Seven co-expressed protein modules were constructed, and two modules showed significant correlations with RMD progression, independent of age, gender, or antibody status. The grey module exhibited a positive correlation (r = 0.23, p = 0.02), while the green module showed a negative correlation (r

= -0.22, p = 0.02) (Fig 1B). Proteins in the grey module were enriched in innate immunity pathways, particularly IFN and B cell signalling, and were highly elevated in progressors (Fig 2A). In contrast, higher in non-progressors, the green module proteins were associated with viral processes and cell-cycle regulation (Fig 2B). Figure 2C shows the four IFN modules constructed from WGCNA; only the cyan module, containing both IFN-I and IFN-II inducible proteins, overlapped with the proteins in the grey module and had a significant positive correlation with RMD progression (Fig 2D). In non-progressors, the IFN-I negative regulators YY1, PTPN6, and YTHDF3 were elevated, and an inverse relationship between positive and negative IFN-inducible protein DEPs was demonstrated (Fig 2E). Besides this, the proteins included in the remaining five modules had significantly higher DEPs when compared to HC (Fig 1C), implicating biological processes such as cellular stress response, apoptosis, protein phosphorylation, and cytokine signalling (Fig 1D).

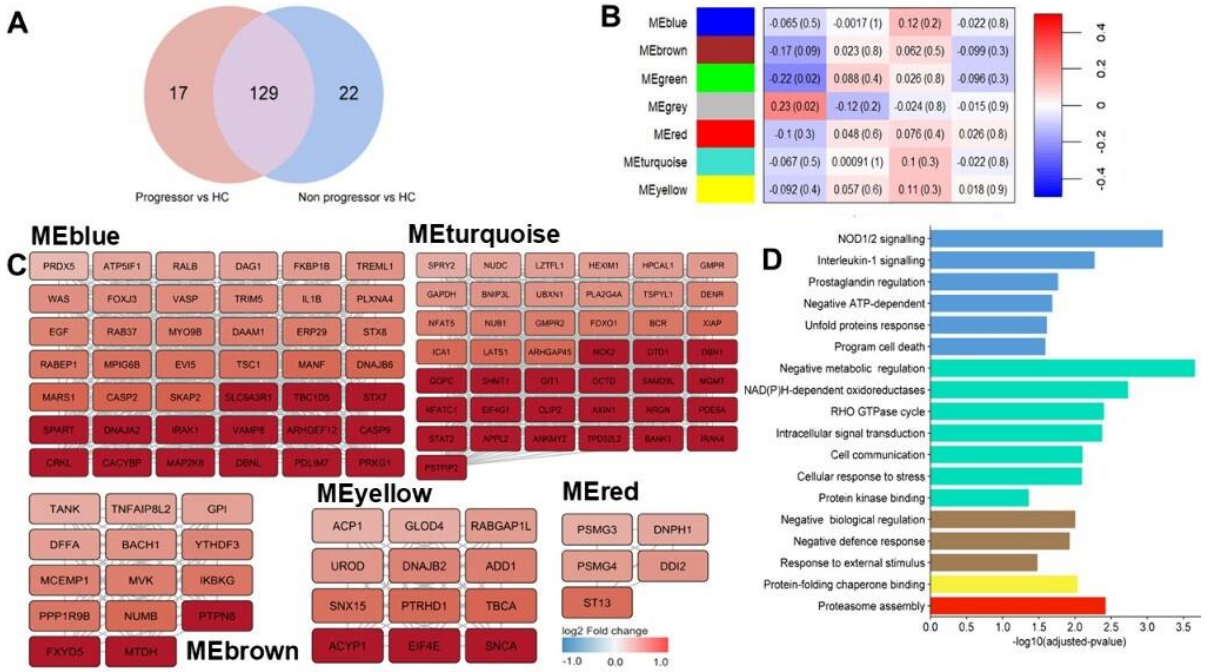



Figure 1 The significant protein numbers between ANA+ and HC (A), Proteomic modular from weighted gene co-expression network analysis and trait correlation (B), the DEPs between ANA+ and HC from five non-significant modules (C), and biological function (D).

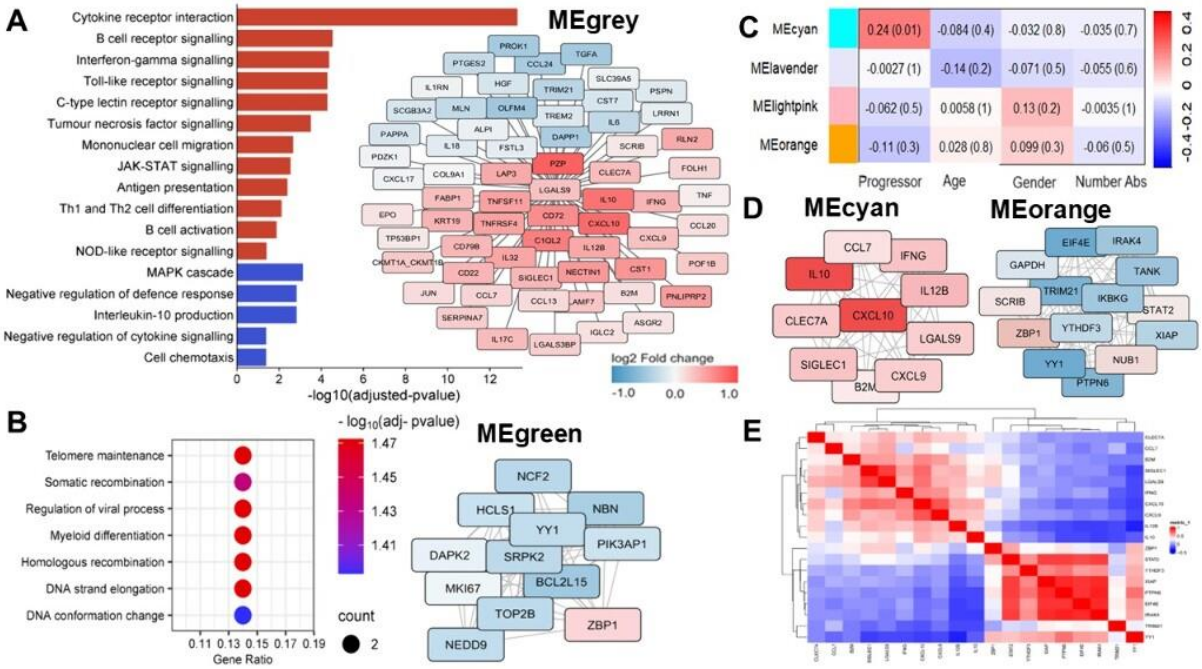



Figure 2 The significant RMDs progression modules (A) and IFN inducible proteins modules (B-F).

**Conclusions: Conclusion:** This comprehensive proteomic study revealed robust immunological and cellular metabolism disequilibrium among ANA at-risk individuals regardless of progression to RMDs. IFN play a crucial role in ANA positivity. However, it might only be a surrogate marker of cellular response to external (e.g. viral infection) or internal stressors (e.g. DNA damage response). This finding underscores the influence of IFN-I, and a dual IFN and B cell regulation aberration promotes the progression to RMDs. Identifying the biomarkers involved in these pathways might have resulted in higher RMD progression predictive accuracy than conventional ANA.

**PT010 / #726**

**Topic: *AS04 – Biomarkers***
**Late-Breaking Abstract**

**POSTER TOUR 02: RECENT INSIGHTS ON THE PATHOGENESIS OF LUPUS NEPHRITIS**
**23-05-2025 10:00 AM - 10:40 AM**

# SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE COURSE CLASSIFICATION FROM IMMUNOGLOBULIN-G-DERIVED N-GLYCANS ANALYZED VIA THE GLYCOTYPER™ LIQUID BIOPSY PLATFORM

Klaus Lindpaintner[1], Gray Huffman[1], Grace Grimsley[1], Aaron Angerstein[1], Tammy Nowling[2], Richard Drake[2], Stephen Castellino[1]
[1]Bruker, Billerica, United States of America, [2]MUSC, Charleston, United States of America

**Background/Purpose:** Systemic lupus erythematosus (SLE) is a chronic autoimmune condition characterized by autoantibody-driven immune-complex formation. Lupus nephritis (LN), a kidney disease caused by SLE, develops due to immune-complex deposition in the glomeruli. The immune activation caused by these glomerular aggregates leads to inflammation, tissue damage, and potentially kidney failure. Early diagnosis and treatment of LN with immunosuppressants are of critical importance to prevent end-stage renal disease. While renal biopsy is the current standard of care for LN diagnosis, alternative liquid-biopsy-based approaches are urgently needed to avoid biopsy-associated complications.

**Methods:** In order to characterize changes in immunoglobulin N-glycan expression as a function of lupus disease course, we applied the GlycoTyper™ platform, a MALDI-MS-based method for N-glycan analysis, to urine samples from 114 healthy controls (HC), 116 SLE patients, and 210 LN patients. In this study, anti-IgG antibody arrays were printed on amine-reactive slides; multi-well modules were then applied to enable the analysis of 16 patient samples per slide. N-glycans were released from captured IgG using PNGase F before being embedded in a chemical matrix for analysis by MALDI-MS (Bruker timsTOF fleX). A quality strategy consisting of pre-acquisition system suitability tests and on-slide QC arrays was employed to ensure the robustness of the platform

**Results:** Using N-glycan profiles and two demographic characteristics (age and sex), a multiclass random forest classifier was generated with an area under the receiver operating characteristic curve of 0.87 for differentiating LN patients from HCs and SLE patients without kidney disease. This model demonstrated a sensitivity of 0.9 and specificity of 0.88 on a validation data set in a one-vs-all classification scheme with LN treated as the positive case. For model generation, N-glycan intensities were normalized and transformed to centered log ratios (CLRs). While the classifier

performed well in differentiating patients with LN from HC or SLE using IgG-derived N-glycans from urine samples, N-glycan profiles from HC and SLE patient samples showed no statistically significant differences. A subsequent longitudinal analysis of LN patients randomly sorted into three immunosuppressant treatment groups identified 4 N-glycans whose abundances were associated at statistically significant levels with an improved urine protein-to-creatinine ratio (UPCR), a key marker of LN treatment response.

**Conclusions:** We conclude that glycoproteomic characterization of IgG provides a novel and powerful analytical tool to differentiate SLE with and without renal involvement, potentially predict likelihood of progression from SLE to lupus nephritis, and may allow prediction of treatment response in lupus nephritis.

**PT011 / #594**

**Topic:** ***AS15 - Lupus Nephritis-Clinical***

**POSTER TOUR 03: RECENT ADVANCEMENTS IN SLE CLINICAL OUTCOMES AND THERAPY**
**23-05-2025 10:00 AM - 10:40 AM**

## IMPACT OF BELIMUMAB ON EFFICACY, SAFETY AND IMMUNE PHENOTYPES IN REFRACTORY AND ACTIVE LUPUS NEPHRITIS IN REAL-WORLD LOOPS REGISTRY

Hidenori Sakai[1], Yusuke Miyazaki[1], Shingo Nakayamada[1], Satoshi Kubo[2], Ippei Miyagawa[1], Masanobu Ueno[1], Hiroaki Tanaka[1], Yasuyuki Todoroki[2], Yurie Kanda[1], Yuya Fujita[1], Yoshiya Tanaka[1]
[1]The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Department of Molecular Targeted Therapies, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

**Background/Purpose:** Belimumab (BEL) is a human monoclonal antibody against soluble B cell activating factor (BAFF). The BLISS-LN trial demonstrated the efficacy and safety of induction therapy combined with BEL in patients with active lupus nephritis (LN). In this study, we aimed to reveal how BEL alters the peripheral blood immune phenotype and to identify the immunophenotypic characteristics of patients with active LN suitable for BEL.

**Methods:** In this retrospective multicenter study, patients with biopsy-proven ISN/RPS class III or IV LN who received standard of care (SoC: glucocorticoid [GC] and either mycophenolate mofetil [MMF] or cyclophosphamide [CYC]) were included. The efficacy and safety of BEL combined with SoC (BEL+SoC group, n = 38) were compared with SoC alone (SoC group, n = 35). Based on a comprehensive eight-color flow cytometric analysis for human immune system termed “the Human Immunology Project” by NIH and FOCIS, we performed peripheral blood immunophenotyping to compare patients with active LN (n = 73) with age- and sex-matched healthy controls (HC, n = 120), and compared patients with LN pre- and post-treatment.

**Results:** The baseline patient characteristics were not significantly different between the SoC and BEL+SoC groups. The BEL+SoC group showed significantly higher complete renal response (CRR) (SoC vs. BEL+SoC = 37.1% vs. 73.0%, P = 0.004) at 52 weeks. GC dosage (mg/day) (SoC vs. BEL+SoC = 6.8 ± 2.7 vs. 4.7 ± 1.9, P < 0.001), SLICC Damage Index (SoC vs. BEL+SoC = 0.5 ± 0.7 vs. 0.2 ± 0.4, P = 0.009) and the rate of all adverse events (SoC vs. BEL+SoC = 65.7% vs. 37.8%, P = 0.021) at 52 weeks were significantly lower in the BEL+SoC group. Immunophenotyping revealed that, compared with HC, patients with active LN had significantly higher percentages of

$CD3^+CD4^+CD38^+HLA\text{-}DR^+$ activated T helper cells (HC vs. LN = 0.7 ± 0.5 vs. 2.0 ± 1.8, P < 0.001), $CD3^+CD8^+CD38^+HLA\text{-}DR^+$ activated cytotoxic T cells (HC vs. LN = 1.1 ± 3.1 vs. 6.3 ± 5.6, P < 0.001), $CD3^-CD19^+CD27^-IgD^-$ double-negative (DN) B cells (HC vs. LN = 0.5 ± 0.4 vs. 1.6 ± 2.0, P < 0.001) and $CD3^-CD19^+CD27^+CD20^-CD38^+$ plasmocytes (HC vs. LN = 0.3 ± 0.5 vs. 1.7 ± 1.6, P < 0.001) at baseline. There were no significant differences in baseline immunophenotypes between the SoC and BEL+SoC groups. The BEL+SoC group had significantly higher reduction rates of DN B cells (SoC vs. BEL+SoC = +2.9 ± 102.2 vs. −44.6 ± 58.3, P = 0.033) at 52 weeks than the SoC group. In the BEL+SoC group, patients who achieved CRR had a significantly higher percentage of pre-treatment plasmocytes (non-responders vs. responders = 1.0 ± 0.8 vs. 2.5 ± 2.0, P = 0.041) than those who did not. No immunophenotypic characteristics were associated with CRR in the SoC group.

**Conclusions:** In induction therapy for patients with active LN, combination therapy with BEL (BEL+SoC) significantly reduced the proportion of DN B cells compared to SoC alone (GC+MMF/CYC). BAFF inhibition by BEL may prevent differentiation of transitional/naïve B cells into self-reactive DN B cells, thereby controlling disease activity, enabling early GC reduction, and potentially reducing organ damage and adverse events. BEL may be particularly effective in patients with increased peripheral blood plasmocytes before treatment. Given that BAFF promotes plasmocyte differentiation, increased plasmocytes indicate elevated BAFF levels, which may explain the enhanced effectiveness of anti-BAFF therapy.

**PT012 / #274**

**Topic:** ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

**POSTER TOUR 03: RECENT ADVANCEMENTS IN SLE CLINICAL OUTCOMES AND THERAPY**
**23-05-2025 10:00 AM - 10:40 AM**

## RHEUMATOLOGY DIAGNOSTICS UTILIZING ARTIFICIAL INTELLIGENCE FOR ANA PATTERN IDENTIFICATION AND TITRE QUANTIFICATION

Farbod Moghaddam[1], Javad Sajadi[1], Ann Clarke[1], Sasha Bernatsky[2], Karen Costenbader[3], Irene Chen[4], Murray Urowitz[5], John Hanly[6], Caroline Gordon[7], Sang-Cheol Bae[8], Juanita Romero-Diaz[9], Jorge Sanchez-Guerrero[10], Daniel J Wallace[11], David Isenberg[12], Anisur Rahman[13], Joan . Merrill[14], Paul R Fortin[15], Dafna D Gladman[5], Ian Bruce[16], Michelle Petri[17], Ellen Ginzler[18], Mary-Anne Dooley[19], Rosalind Ramsey-Goldman[20], Susan Manzi[21], Andreas Jönsen[22], Graciela S. Alarcón[23], Ronald Van Vollenhoven[24], Cynthia Aranow[25], Meggan Mackay[26], Guillermo Ruiz-Irastorza[27], S. Sam Lim[28], Murat Inanc[29], Kenneth Kalunian[30], Soren Jacobsen[31], Christine Peschken[32], Diane L Kamen[33], Anca Askanase[34], Marvin Fritzler[1], Mina Aminghafari[1], May Choi[1]
[1]University of Calgary, Calgary, Canada, [2]McGill University, Medicine, Montreal, Canada, [3]Brigham and Women's Hospital, Rheumatology, Boston, United States of America, [4]Berkeley, Berkeley, United States of America, [5]University of Toronto, Toronto, Canada, [6]Dalhousie University, Halifax, Canada, [7]University of Birmingham, Birmingham, United Kingdom, [8]Hanyang University Hospital for Rheumatic Diseases,, Seoul, Korea, Republic of, [9]The National Institute of Medical Sciences and Nutrition, Mexico City, Mexico, [10]Krembil Research Institute, Toronto, Canada, [11]Cedars-Sinai Medical Center, Los Angeles, United States of America, [12]Department of Ageing, Rheumatology and Regenerative Medicine, Division of Medicine, University College London, London, United Kingdom, [13]University College London, London, United Kingdom, [14]Oklahoma Medical Research Foundation, Clinical Immunology Program, Oklahoma City, United States of America, [15]Universite Laval, Quebec City, Canada, [16]Queen's University Belfast, Belfast, United Kingdom, [17]John Hopkins University, Baltimore, United States of America, [18]SUNY Downstate Medical Center, New York, United States of America, [19]University of North Carolina at Chapel Hill, Chapel Hill, United States of America, [20]Northwestern University, Chicago, United States of America, [21]Allegheny Singer Research Institute, Allegheny Health Network, Pittsburgh, United States of America, [22]Lund University Faculty of Medicine, Lund, Sweden, [23]The University of Alabama at Birmingham, Rheumatology, Oakland, United States of America, [24]Amsterdam University Medical Centers, Department Of Rheumatology And Clinical Immunology, Amsterdam, Netherlands, [25]Feinstein Institute for Medical Research, Manhasset, United States of America, [26]Feinstein Institutes for Medical Research, Northwell Health, New York, United States of America, [27]Biobizkaia

Health Research Institute, Bilbao, Spain, [28]Emory University, Division Of Rheumatology, Atlanta, United States of America, [29]Istanbul University, Istanbul, Turkey, [30]University of California San Diego, San Diego, United States of America, [31]Copenhagen University Hospital Center for Rheumatology and Spine Diseases, Copenhagen, Denmark, [32]University of Manitoba, Winnipeg, Canada, [33]Medical University of South Carolina, Charleston, United States of America, [34]Columbia University Medical Center, New York, United States of America

**Background/Purpose:** Antinuclear antibody (ANA) immunofluorescence (IFA) patterns and titers are a key part of rheumatology diagnostics, however, there is considerable intra- and inter-laboratory variability with manual interpretation. Replacing manual interpretation with a standardized and automated approach could help reduce variability, increasing laboratory accuracy and efficiency. We developed machine learning (ML) models (ANA Reader©) to aid laboratories in ANA pattern and titer interpretation, including a model for the nuclear dense fine-speckled (DFS) ANA pattern (AC-2), a rare pattern among systemic autoimmune rheumatic disease (SARD) patients that decreases the likelihood of these conditions.

**Methods:** 13,671 ANA images from SLE patients enrolled in the Systemic Lupus International Collaborating Clinics Inception Cohort (SLICC, n=2,825 images), non-SLE subjects enrolled in the Ontario Health Study (OHS, n=10,639 images), and the International Consensus on ANA Patterns (ICAP, n=207 images) were analyzed. All SLICC and OHS ANA were performed in one central laboratory using IFA on HEp-2 cells (NovaLite, Werfen, SD) and read on a digital IFA microscope (NovaView, Werfen, SD). As the reference standard, one laboratory technologist (HH) with >30 years of experience in ANA studies interpreted 13 ANA patterns and titre for each image. We developed and compared the performance of eight ML models for ANA pattern recognition. To evaluate ANA titre, we used an ML technique for imaging processing that identified individual HEp-2 cells in the ANA images and then calculated the cell illuminance and cut-offs corresponding to each titre (1:80-1:5120). Fifty images were randomly selected to compare the titre classification based on image processing with the lab technologist as the reference standard.

**Results:** 6,307 images containing at least one ANA pattern (>=1:80) from SLICC (n=2,806 images), OHS (n=3339 images), and ICAP (n=162 images) were included. We identified one ML model (ANA Reader©) with the best performance for ANA pattern identification compared to the reference with a high area under the curve (AUC) score of 83.4%, modest weighted accuracy of 68.4%, precision of 67.1%, sensitivity of 70.1%, and F1 score of 67.2%. The AUC for individual ANA patterns ranged from 0.71 to 0.97 (Figure 1). There was a strong correlation between titres reported by the ANA Reader© and the technologist's interpretation (Spearman rank 0.93, p <0.0001), where the titres reported were identical or differed by only one dilution in most cases (96.0%).

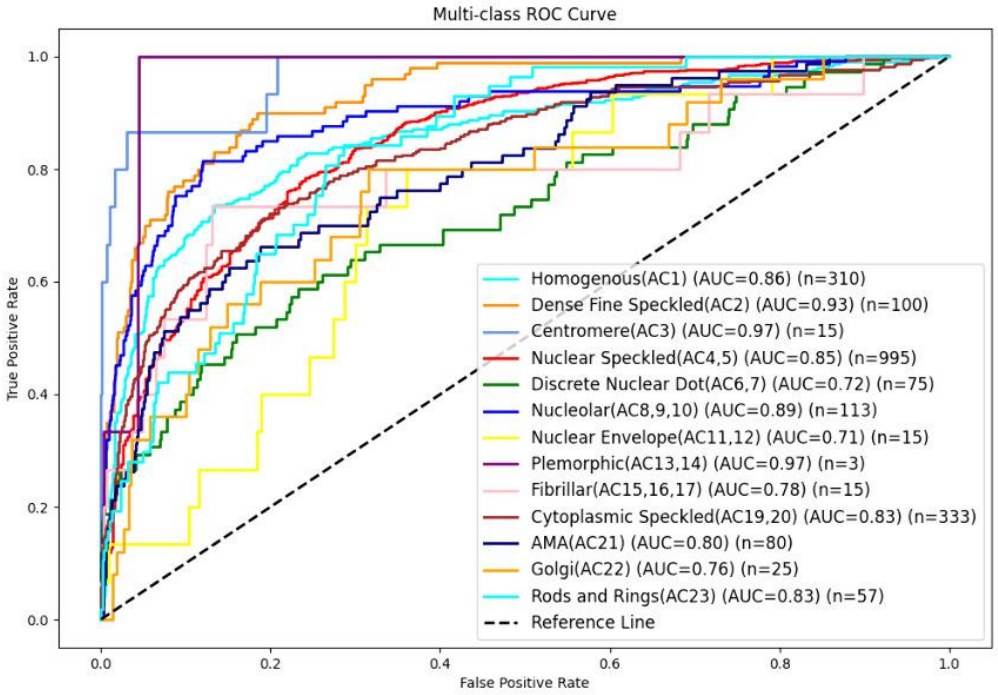



**Figure 1. Area-under-the-curve (AUC) scores for the thirteen anti-nuclear antibody (ANA) patterns using the ANA Reader© model, which had the best performance compared to seven other machine learning techniques.** The ANA patterns with the best performance were centromere (AUC 0.97) and pleomorphic patterns (AUC 0.97). On average, there were five images per patient sample for SLICC, three images per patient sample for OHS, and one image per patient from ICAP. 80% of the images were used for model training and the remaining 20% for validation. In total, there were 512 patients in the SLICC cohort, 3,559 individuals in the OHS cohort, and 207 patients from ICAP who were included in the study.

**Conclusions:** ML has the potential to become a highly effective and efficient approach to evaluating ANA patterns and titres. The performance of our ANA Reader© is expected to improve as we continue to train our models with more ANA images. Future external validation studies and the development of other ML models to predict more complex and multiple ANA patterns and titres are also underway.

**PT013 / #74**

**Topic:** ***AS23 - SLE-Diagnosis, Manifestations, & Outcomes***

**POSTER TOUR 03: RECENT ADVANCEMENTS IN SLE CLINICAL OUTCOMES AND THERAPY**
**23-05-2025 10:00 AM - 10:40 AM**

# BRIDGING THE GAP BETWEEN PATIENT'S PERCEPTION ON QUALITY OF LIFE AND DISEASE ACTIVITY AND DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOUS PATIENT.

Coral Mouriño[1], David Fernandez[1], Ivonne Lourdes Mamani[1], Íñigo Rúa-Figueroa[2], Karen Roberts[3], Irene Altabás González[1], Raúl Menor[4], Julia Martínez-Barrio[5], Alejandro Olive[6], Paula Rubio-Munoz[6], María Galindo-Izquierdo[7], Antonio Fernández Nebro[8], Jaime Calvo[9], Celia Erausquin[2], Eva Tomero[10], Esther Uriarte[11], A Pecondon-Espanol[12], Mercedes Freire[13], Ricardo Blanco[14], Lorena Expósito[15], M Ibanez-Barceló[16], Carlos Montilla-Morales[17], José Rosas[18], María Jesús García-Villanueva[19], Paloma Vela-Casampere[20], Oihane Ibarguengoitia-Barrena[21], Francisco Javier Toyos Sáenz De Miera[22], Ja Hernandez-Beriain[23], Clara Moriano[24], Gemma Bonilla[25], Javier Narváez[26], Jose Luis Andreu-Sanchez[27], Marta Arévalo[28], Loreto Horcada[29], Tatiana Cobo-Ibanez[30], Nuria Lozano-Rivas[31], Cristina Bohórquez[32], Carlota Iñiguez[33], Eva Salgado[34], Vicenç Torrente-Segarra[35], Tarek Salman-Montes[36], Jose Eloy Oller[37], José María Pego-Reigosa[1]
[1]Complejo Hospitalario Universitario de Vigo. Grupo IRIDIS. Instituto de Investigación Sanitaria Galicia Sur (IISGS), Rheumatology, Vigo, Spain, [2]Hospital Universitario Doctor Negrín, Rheumatology, Las Palmas, Spain, [3]Instituto de investigación Galicia Sur, External Statistical Advisor, Rheumatology, vigo, Argentina, [4]Hospital General Jerez de la Frontera, Cádiz, Spain, [5]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [6]Hospital Germans Trias i Pujol, badalona, Spain, [7]Hospital 12 de Octubre, Madrid, Spain, [8]Carlos Haya Hospital, Malaga, Spain, [9]Hospital Universitario de Araba, vitoria, Spain, [10]Hospital Universitario de la Princesa, Madrid, Spain, [11]Donosti Hospital, san sebastian, Spain, [12]Hospital Miguel Servet, zaragoza, Spain, [13]Complejo Hospitalario Universitario A Coruña, Coruña, Spain, [14]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [15]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain, [16]Hospital Universitario Son Llàtzer, Palma de Mallorca, Spain, [17]Hospital Clínico Universitario de Salamanca, Salamanca, Spain, [18]Hospital Marina Baixa, Alicante, Spain, [19]Hospital Universitario Ramón y Cajal, Madrid, Spain, [20]Hospital General Universitario de Alicante, Alicante, Spain, [21]Hospital Universitario Basurto, Bilbao, Spain, [22]iHospital Virgen Macarena, Sevilla, Spain, [23]Hospital Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain, [24]Hospital Universitario de León, León, Spain, [25]Hospital Clínico Universitario La Paz, Madrid, Spain, [26]Hospital Belvitge, Barcelona, Spain, [27]Hospital Universitario Puerta de Hierro, Majadahonda, Spain, [28]Hospital Parc Taulí, Barcelona, Spain, [29]Complejo

Hospitalario de Navarra, Navarra, Spain, [30]Hospital Clínico Universitario Vigen de la Arixaca, Murcia, Spain, [31]Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain, [32]Hospital Universitario Príncipe de Asturias,, Madrid, Spain, [33]Hospital Locus Augusti, Lugo, Spain, [34]Hospital Universitario de Ourense, Ourense, Spain, [35]Hospital Moisés Broggi, Barcelona, Spain, [36]Hospital del Mar, Barcelona, Spain, [37]Hospital Universitario Dr Peset, Valencia, Spain

**Background/Purpose:** Systemic Erythematosus Lupus (SLE) is a chronic autoimmune disease affecting multiple organs and systems. It often begins at a young age and can lead to severe complications, prolonged treatments, and emotional challenges, affecting patients' self-perception and quality of life (QoL). Healthcare professionals are increasingly concerned about the impact of SLE on patients' mental and emotional well-being. Tools like the Lupus Impact Tracker (LIT), which consists of 10 questions, assess how patients manage the disease, their self-esteem, psychological status, and family responsibilities. LIT is designed to measure the impact of lupus on QoL (1) and has been linked to disease activity (2). Objectives: To analyze the correlation between SLE activity, accumulated organ damage, and patients' self-perception of QoL, focusing on pain, fatigue, and mental health. To explore the influence of additional factors like comorbidities, socioeconomic status, and chronic treatments on QoL in SLE patients.

**Methods:** The study analyzed data from the RELESSER-PROS cohort at the first annual visit (V1). LIT scores were divided into quartiles, and variables in each group were examined. Chi-square/Fisher tests were used for categorical data, and ANOVA/Kruskal-Wallis for continuous variables. Logistic regression identified factors influencing LIT scores above 50, with a 5% significance level using R software.

**Results:** A total of 1,417 SLE patients were included in the study, with 90% female and 94.2% Caucasian. The average age at diagnosis was 34.7 years, and the median Lupus Impact Tracker (LIT) score at the first visit (V1) was 25. The highest scoring domains were “pain/fatigue” (mean score 1.52 per question) and “emotional health” (1.29), while the lowest were “body image dissatisfaction” (0.87) and “lupus medication side effects” (0.69). At V1, the mean clinical SLEDAI score (disease activity) was 1.92, and the mean SLE Damage Index (SDI) score was 1.42. Patients with higher LIT scores (50-100) had significantly higher SLEDAI and SDI scores (Table 1), indicating more severe disease and damage. These patients were also less likely to be in low disease activity (LLDAS) or 2021 DORIS remission (p=0.04). The study also examined additional factors influencing quality of life (QoL), including educational and laboral status, comorbidities (e.g., pulmonary disease, depression, cardiovascular disease), and therapies (e.g., glucocorticoids, immunosuppressants). A multivariate analysis identified variables significantly associated with higher LIT scores (Table 2), showing that these factors contribute to a greater impact of SLE on patients'
QoL.

Table 1. Disease activity and damage accrual by subgroups according to the LIT (quartile) values

| | [0,10] n=405 | [10,25] n=322 | [25,50] n=408 | [50,100] n=282 | p-value |
|---|---|---|---|---|---|
| **cSLEDAI mean ± SD** | 1.45 ± 2.63 | 1.80 ± 2.97 | 2.20 ± 3.34 | 2.33 ± 4.09 | 0.00378 |
| **SDI mean ± SD** | 1.12 ± 1.46 | 1.20 ± 1.71 | 1.58 ± 1.86 | 1.84 ± 2.00 | <0.001 |

cSLEDAI: clinical (without serology) SLE Disease Activity Index; SD; standard deviation; SDI: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index.

Table 2. Factors associated with a higher impact of SLE on QoL (dependent variable: LIT score >50) in the multivariate analysis.

| Variable | OR | 95% CI | p-value |
|---|---|---|---|
| **Male** | 0.42 | 0.20-0.81 | 0.015 |
| **Higher studies** | 0.51 | 0.33-0.79 | 0.003 |
| **Not active worker** | 1.67 | 1.19-2.35 | 0.003 |
| **Fibromyalgia** | 2.22 | 1.23-3.96 | 0.007 |
| **Depression** | 2.51 | 1.69-3.71 | <0.001 |
| **Thyroid disease** | 2.02 | 1.24-3.24 | 0.004 |
| **GC dose≥ 30mg/day** | 7.39 | 1.12-60.8 | 0.03 |
| **Hydroxychloroquine** | 0.64 | 0.47-0.89 | 0.007 |

GC: glucocorticoid.

**Conclusions:** We observed a positive correlation between LIT values and the activity of SLE (measured by cSLEDAI) and accumulated damage (measured by SDI) in our cohort. We found a correlation between hydroxychloroquine treatment, male sex and higher studies and better outcomes in QoL of SLE patients. The presence of comorbidities such fibromyalgia, depression or thyroid disease was related to a higher negative impact in QoL. High doses of Glucocorticoids are also related to a poor outcome in LIT values. Beyond the activity and damage of the disease, there are other variables that significantly influence patients with SLE and have an impact on their quality of life. These results highlight the relevance of considering these factors when making clinical decisions, with the purpose of optimizing medical care.

**PT014 / #285**

**Topic:** ***AS24 - SLE-Treatment***

**POSTER TOUR 03: RECENT ADVANCEMENTS IN SLE CLINICAL OUTCOMES AND THERAPY**
**23-05-2025 10:00 AM - 10:40 AM**

# ROZIBAFUSP ALFA IN PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS OF A BAYESIAN ADAPTIVE PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE RANGING STUDY

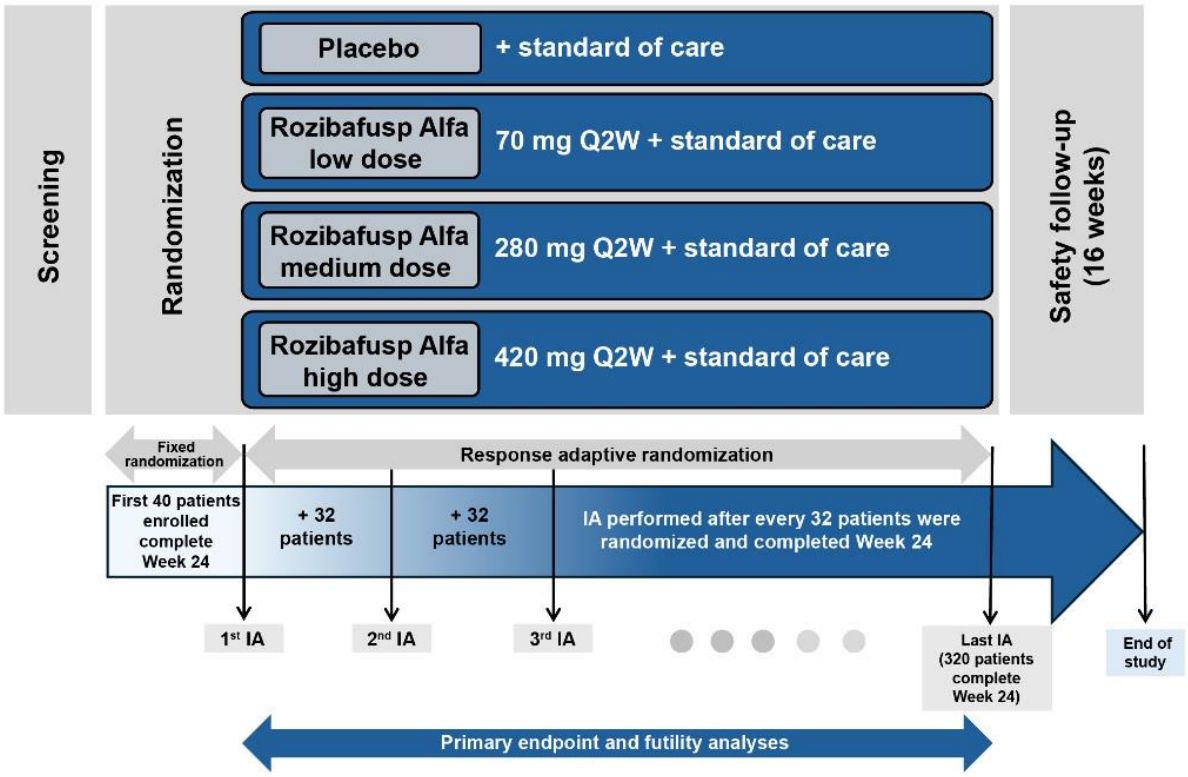
Fatima Barbar-Smiley[1], Fengming Tang[1], Sandra Garces[1], Amit Saxena[2], Bazle Abidi[1], Claudia Pena Rossi[1], Joan . Merrill[3]
[1]Amgen, Thousand Oaks, United States of America, [2]NYU Grossman School of Medicine, Division Of Rheumatology, New York, United States of America, [3]Oklahoma Medical Research Foundation, Oklahoma City, United States of America

**Background/Purpose:** SLE is a multisystem autoimmune disorder driven by diverse immunological mechanisms. Dysregulation of T and B cell interactions results in class-switched immunoglobulin G (IgG) autoantibodies, a hallmark of SLE. SLE disease activity is associated with elevated expression of two key mediators of T and B Cells: inducible costimulatory ligand (ICOSL) and B cell activating factor (BAFF). Rozibafusp alfa is a novel bispecific IgG2 antibody-peptide conjugate that targets dual inhibition of ICOSL and BAFF. This phase 2b study (NCT04058028) evaluated the efficacy and safety of rozibafusp alfa in adults with active SLE.

**Methods:** This was a Bayesian adaptive phase 2b, randomized, double-blind, placebo-controlled, multi-center, dose-ranging study in adult patients with active SLE with Hybrid Systemic Lupus Erythematosus Disease Activity Index (hSLEDAI) score ≥ 6, clinical hSLEDAI score ≥ 4 and inadequate response to standard of care (SOC) therapies. Patients were randomized to receive placebo or rozibafusp alfa 70 mg, 280 mg or 420 mg every two weeks for 52 weeks (Figure). The randomization ratio started as 1:1:1:1, then was adapted using Response Adaptive Randomization to allocate more patients to more efficacious doses and fewer patients to less efficacious doses, with a fixed 25% allocation to placebo based on the clinical efficacy at pre-specified interim analyses (IAs) [1]. The first IA was conducted, blinded to the investigators, when the first 40 enrolled patients completed Week 24. Subsequent IAs were conducted each time 32 more patients reached Week 24. Futility analyses utilized a Bayesian hierarchical model at each IA. The primary endpoint was the achievement of SLE Responder Index 4 (SRI-4) response at Week 52, defined as a ≥ 4-point reduction from baseline in the hSLEDAI score, no new British Isles Lupus Assessment Group (BILAG) 2004 A and no > 1 new BILAG B scores, a < 0.3-point deterioration in Physician's Global Assessment, and no

increase in treatment beyond protocol-allowed therapies. Patients were followed up for a minimum of 16 weeks for safety.

**Figure.** Clinical trial design utilizing response adaptive randomization




IA, interim analysis; Q2W, every two weeks

**Results:** The study met predefined futility criteria at the sixth IA. At the time when the trial was terminated, 244 participants (93.4% female; mean [SD] age: 43.5 [10.9] years) had been enrolled. Among these participants, 134 patients in rozibafusp alfa groups (70 mg: n = 51; 280 mg: n = 35; 420 mg: n = 48) and 43 patients in placebo had the opportunity to complete Week 52 visit. The percentage of participants with an SRI-4 response at Week 52 did not substantially differ between the rozibafusp alfa groups (56.9-72.9%) and placebo (60.5%). A total of 243 patients who received at least one dose of study drug were included in the safety analysis. Treatment-emergent adverse events were observed at similar frequencies between rozibafusp alfa groups (63.9-81.6%) and placebo (67.7%). Serious adverse events occurred comparably in the rozibafusp alfa groups (3.5%-13.9%) and placebo (9.7%) (Table). The discontinuation of this trial was due to pre-specified futility criteria but not related to any safety

concerns.

**Table.** Safety of rozibafusp alfa in patients with active SLE

| | **Placebo** (N=62) | **Rozibafusp Alfa low dose** (70 mg, Q2W) (N=58) | **Rozibafusp Alfa medium dose** (280 mg, Q2W) (N=36) | **Rozibafusp Alfa high dose** (420 mg, Q2W) (N=87) |
|---|---|---|---|---|
| **SAEs[a], n (%)** | **6 (9.7)** | **7 (12.1)** | **5 (13.9)** | **3 (3.5)** |
| **Non-serious AEs[b], n (%)** | **29 (46.8)** | **34 (58.6)** | **20 (55.6)** | **51 (58.6)** |
| *Upper respiratory tract infection* | 8 (12.9) | 6 (10.3) | 6 (16.7) | 8 (9.2) |
| *Urinary tract infection* | 6 (9.7) | 9 (15.5) | 4 (11.1) | 13 (14.9) |
| *Headache* | 3 (4.8) | 5 (8.6) | 3 (8.3) | 8 (9.2) |
| **Fatal AEs, n (%)** | **0** | **0** | **0** | **0** |

[a] None of the reported individual SAE exceeded 3% prevalence.
[b] Included other AEs with a prevalence of approximately 10% or higher.
AE, adverse event; Q2W, dosing every two weeks; SAE, serious adverse event.

**Conclusions:** With high placebo response rates, rozibafusp alfa did not show substantial added benefit over SOC for SLE treatment. Rozibafusp alfa was safe and well tolerated in patients with active SLE. **Reference:** [1.] Garces S, et al. Lupus Sci. Med 2023;10:e000890. doi:10.1136/lupus-2022-000890

**PT015 / #768**

**Topic: *AS24 - SLE-Treatment***
**Late-Breaking Abstract**

**POSTER TOUR 03: RECENT ADVANCEMENTS IN SLE CLINICAL OUTCOMES AND THERAPY**
**23-05-2025 10:00 AM - 10:40 AM**

# FEASIBILITY AND USABILITY OF A CLINICAL DECISION SUPPORT SYSTEM FOR TREAT-TO-TARGET IN SYSTEMIC LUPUS ERYTHEMATOSUS: THE T2T-SLE PILOT STUDY

Agner Parra Sanchez[1], Koen Vos[2], Odile Van Hall[3], Irene Bultink[1], Michel Tsang-A-Sjoe[1], Alexandre Voskuyl[1], Ronald Van Vollenhoven[1]
[1]Amsterdam University Medical Centre, Department Of Rheumatology And Clinical Immunology, Amsterdam, Netherlands, [2]Flevoziekenhuis, Department Of Rheumatology, Almere, Netherlands, [3]Amsterdam Rheumatology and immunology Center, location READE, Department Of Rheumatology, Amsterdam, Netherlands

**Background/Purpose:** The Treat-to-Target (T2T) strategy has been endorsed for systemic lupus erythematosus (SLE) management, yet its implementation remains challenging[1]. A clinical decision support system (CDSS) was developed to assist physicians in applying a T2T approach in clinical practice[2]. This study aimed to assess the feasibility, usability, and acceptability of a CDSS designed to implement a T2T strategy in SLE management from the perspectives of both physicians and patients.

**Methods:** The T2T-SLE study was a 24-week, non-randomized, cluster, multicenter pilot study conducted in North Holland, including two tertiary university medical centers (UMCs) and two regional outpatient clinics. Patients diagnosed with SLE were assigned by treatment center to either routine care or T2T-CDSS-assisted care. The CDSS, developed based on evidence-based guidelines, provided clinical recommendations for disease management. Primary outcomes included feasibility (recruitment, retention, and implementation challenges), usability (physicians perceived ease of use of the CDSS web-app), and acceptability (physician and patient satisfaction). The CDSS was evaluated solely by physicians, with one physician in an UMC and one in a regional center using the tool. In turn, patients reported their satisfaction with the T2T strategy, which involved more frequent outpatient clinic visits and structured discussions on treatment targets. Patient feedback was collected through qualitative questionnaires and patient-reported outcome measures (PROMs). Secondary outcomes included treatment patterns, disease activity measures, and implementation barriers and facilitators.

**Results:** A total of 91 participants were screened, with 38 enrolled (41.8%) and 35 completing the study (92.1% retention). The most common reason for declining participation was unspecified reasons (24.7%) followed by lack of interest (23.1%) and scheduling conflicts due to life events (4.4%). (Fig. 1). The enrolled population was representative of a broad spectrum of SLE severity, with a mix of stable and active disease. Patients in the T2T-CDSS group had slightly lower baseline disease activity scores compared to the routine care group, though both groups exhibited similar demographic characteristics (Table 1). Physicians reported that the CDSS was useful in supporting T2T-based decision-making, but challenges related to workflow integration and time constraints were noted. Patients in the T2T group generally expressed satisfaction with the strategy, highlighting the benefits of increased monitoring and shared treatment goal discussions. However, some reported concerns about the burden of more frequent visits.

Fig 1. *Enrollment Diagram, Inclusion and Exclusion Criteria*

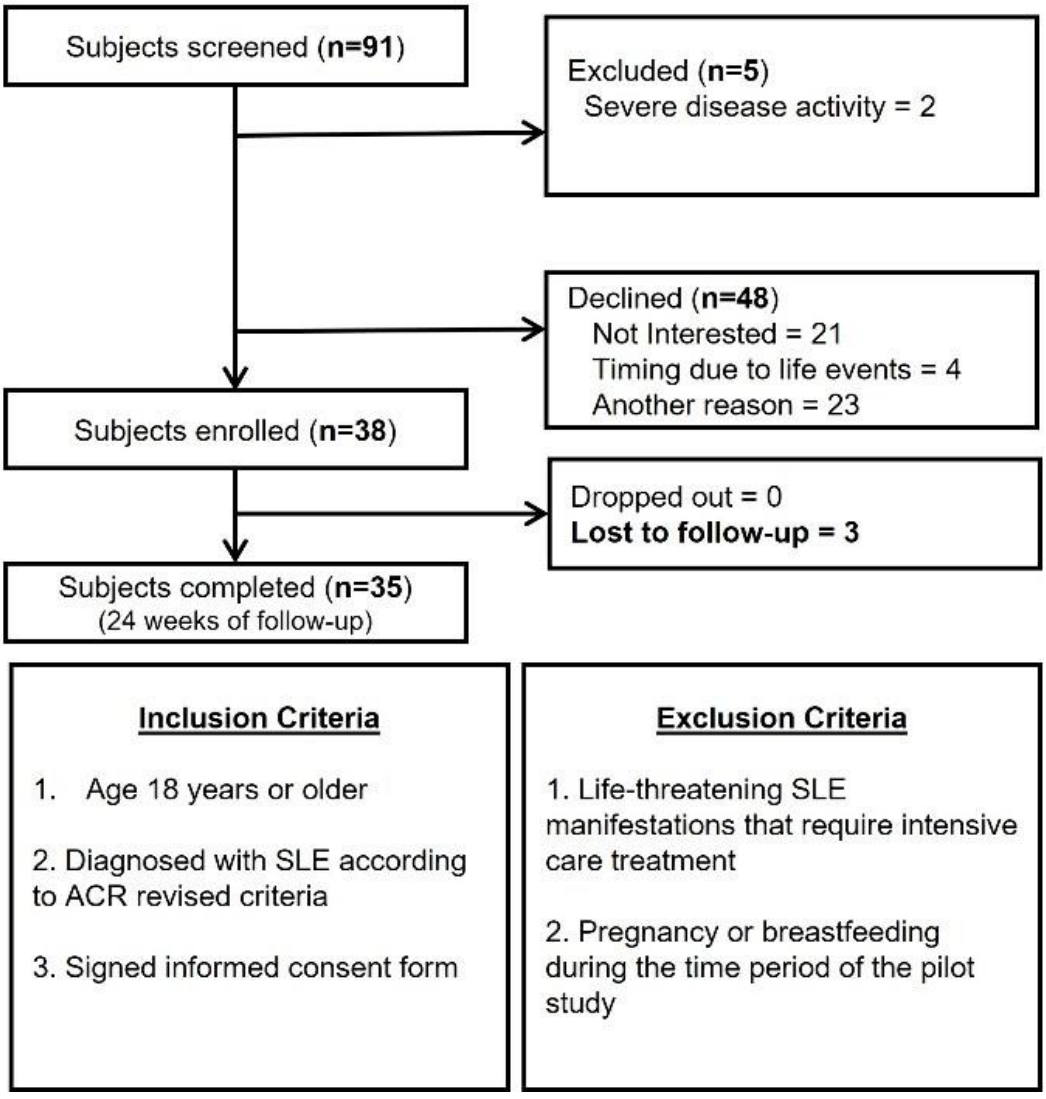


**Table 1. Baseline characteristics in patients from the treat-to-target and the routine care group**

| | Treat to target group (n=18) | Routine care group (n=17) |
|---|---|---|
| Age, mean (S.D.) | 40.2 (11.9) | 46.8 (8.7) |
| Female gender, n (%) | 16 (88.8) | 16 (94) |
| Caucasian ethnicity (%) | 14 (77.7) | 14 (82.3) |
| **Disease activity measures:** | | |
| SLEDAI-2K, (median (IQR)) | 2 (1-6) | 2 (0-5) |
| cSLEDAI-2K, (median (IQR)) | 1 (0-2) | 0 (0-4) |
| PGA (0-3), (median (IQR)) | 0.65 (0.3-1.4) | 0.4 (0.3-0.6) |
| SLICC/ACR damage index, (median (IQR)) | 1 (0-2) | 1 (0-4) |
| **Treatment variables:** | | |
| Glucocorticoids, n (%) | 9 (50) | 11 (64.7) |
| Antimalarials, n (%) | 16 (88.8) | 17 (100) |
| Immunosuppressants, n (%) | 10 (55.5) | 8 (47) |
| Biologics, n (%) | 2 (11) | 0 (0) |
| **PROMs:** | | |
| PaGA (0-10), (median (IQR)) | 3 (1-7) | 4.5 (2-7) |
| FACIT score, (median (IQR)) | 26 (17-42) | 33 (31-47) |
| SF-36 | | |
| PCS, mean (S.D.) | 41.2 (12.7) | 44.5 (11.1) |
| MCS, mean (S.D.) | 50.3 (10.8) | 48.1 (12.3) |

*FACIT, Functional Assessment of Chronic Illness Therapy – Fatigue Scale; PGA, Physician Global Assessment; PaGA, Patient Global Assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SF-36, Short Form 36 Health Survey Questionnaire; cSLEDAI-2K, Clinical Systemic Lupus Erythematosus Disease Activity Index 2000; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.*

**Conclusions:** The T2T-SLE pilot study demonstrated the feasibility of using a CDSS to implement a T2T strategy in SLE management. Physician-reported usability was positive, though workflow integration challenges were noted. Patients valued structured treatment discussions but reported mixed opinions on visit frequency. The study demonstrated feasibility for larger-scale implementation, though recruitment delays and engagement challenges indicate a need for improved patient outreach strategies. Future studies should optimize recruitment strategies and further assess long-term clinical effectiveness.

## References:

1. Parra Sanchez AR, Voskuyl AE, van Vollenhoven RF. Treat-to-target in systemic lupus erythematosus: advancing towards its implementation. Nat Rev Rheumatol 2022;18(3):146-57. doi: 10.1038/s41584-021-00739-3
2. Parra Sanchez AR, Grimberg MG, Hanssen M, et al. Web-based eHealth Clinical Decision Support System as a tool for the treat-to-target management of patients with systemic lupus erythematosus: development and initial usability evaluation. BMJ Health Care Inform 2023;30(1) doi: 10.1136/bmjhci-2023-100811

**PT016 / #756**

**Topic: *AS15 - Lupus Nephritis-Clinical***
**Late-Breaking Abstract**

**POSTER TOUR 03: RECENT ADVANCEMENTS IN SLE CLINICAL OUTCOMES AND THERAPY**
**23-05-2025 10:00 AM - 10:40 AM**

# TRIPLE THERAPY WITH BELIMUMAB IN PROLIFERATIVE LUPUS NEPHRITIS: REAL-WORLD EFFICACY AND GLUCOCORTICOID-SPARING EFFECTS

Paola Vidal-Montal[1], Aina Fabregat[1], Sergi Heredia[2], Julia Bernardez[3], Berta Paula Magallares[3], José Gómez-Puerta[4], Beatriz Frade-Sosa[4], Joan M. Nolla[1], Javier Narváez[1]
[1]Bellvitge University Hospital, Rheumatology, Barcelona, Spain, [2]Hospital Moisès Broggi,, Rheumatology, Barcelona, Spain, [3]Hospital de la Santa Creu i Sant Pau, Rheumatology, Barcelona, Spain, [4]Hospital Clinic Barcelona, Rheumatology, Barcelona, Spain

**Background/Purpose:** The newly published ACR guidelines recommend initiating triple therapy for all patients with proliferative lupus nephritis (LN). In alignment with EULAR and KDIGO recommendations, treatment goals include achieving the 2019 EULAR/ERA-EDTA targets: a reduction in proteinuria by ≥25% at 3 months, ≥50% at 6 months, and <500–700 mg/day at 12 months, while maintaining an estimated glomerular filtration rate (eGFR) within 10% of baseline. The ultimate objective is to achieve complete renal response (CRR) within 12 months of initiating therapy. Additionally, these guidelines emphasize the importance of achieving these targets with the lowest possible glucocorticoid (GC) dose, aiming for a progressive reduction to a maintenance dose of ≤5 mg/day of prednisone, and ultimately discontinuing GC. The aim of this study is to assess the efficacy of triple therapy with belimumab (BEL) added to standard of care (SoC) within the first 6 months of LN onset in achieving renal response, meeting EULAR/ERA-EDTA targets, and evaluating its GC-sparing effect in a real-world clinical setting.

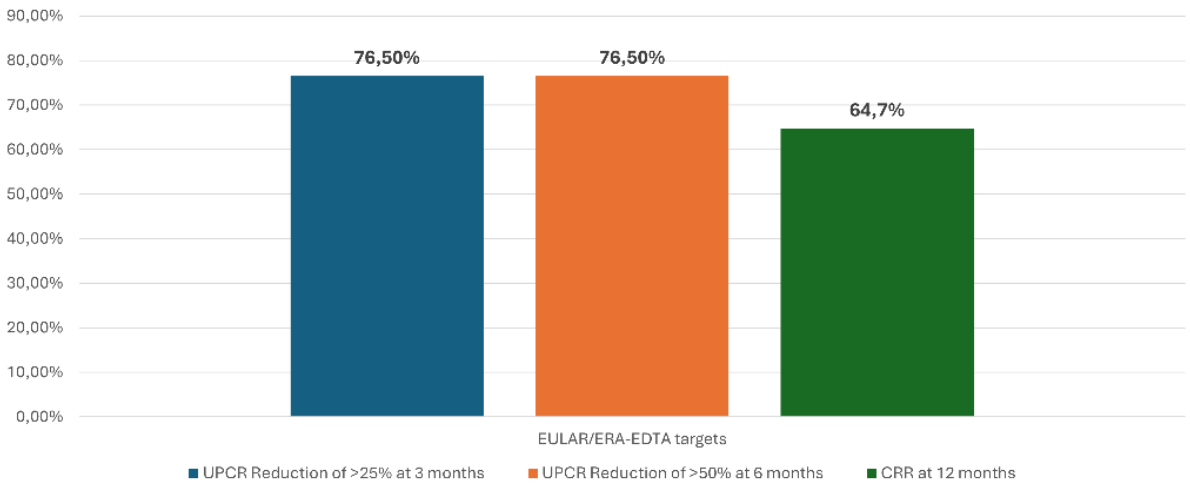
**Methods:** This retrospective, multicenter study was conducted across four hospitals in Barcelona. Patients with biopsy-proven proliferative LN (ISN/RPS class III, IV, or mixed III/IV+V) who received triple therapy including BEL within the first 6 months after LN onset were included. The primary endpoint was the achievement of CRR at one year.

**Results:** A total of 17 patients (82.4% women, mean age at renal biopsy 39.7 ± 14 years) were analyzed. The majority were Caucasian (58.9%), followed by Hispanic (29.4%) and Asian (11.8%). A history of previous LN episodes was present in 35.3% of patients, with two patients experiencing two prior flares. All patients had proliferative LN: 23.5% class III, 35.2% class IV, and 41.2% mixed (III/IV + V). The mean activity index was 8.1 ± 3.3

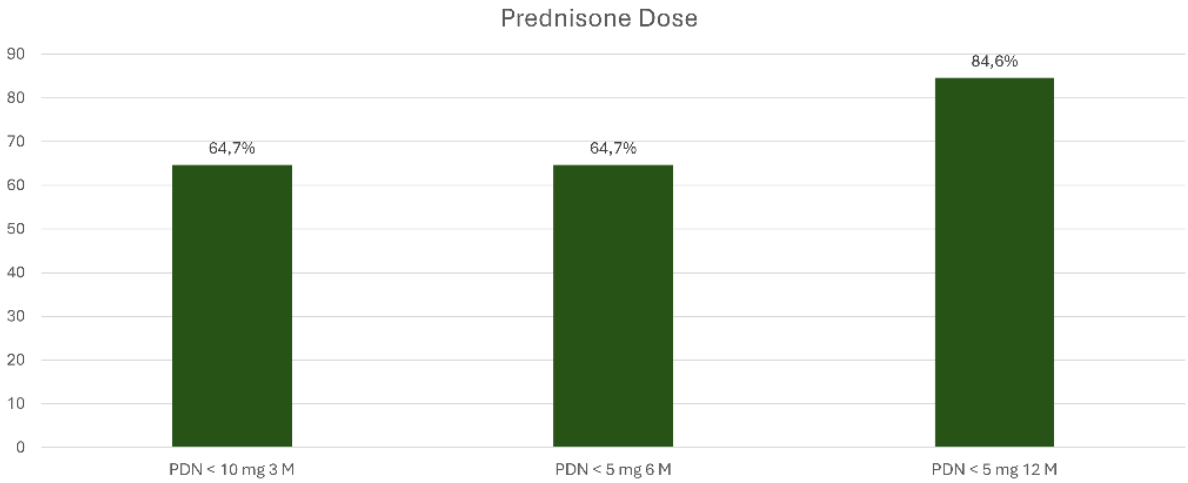
and the chronicity index 2.33 ± 2.3; one patient had thrombotic microangiopathy. Induction therapy included three methylprednisolone pulses in 52.9%, with a mean initial oral prednisone dose of 37.9 ± 14.9 mg/day. Most patients (76.5%) received MMF, while 23.5% were treated with CYC. For maintenance, 94.1% remained on MMF, with one patient receiving azathioprine. At renal flare, mean proteinuria was 3.3 ± 3.2 g/day, eGFR 68 ± 23.1 mL/min/1.73m$^2$, and serum creatinine 144 ± 156 µmol/L.Their evolution is summarized in Table 1.

| | Renal flare | 3 months | 6 months | 12 months (15 patients) | 24 months (13 patients) | Last visit |
|---|---|---|---|---|---|---|
| Proteinuria (g/24h, mean ± SD) | 3.3 ± 3.2 | 1.7 ± 1.6 | 0.82 ± 0.6 | 0.66 ± 0.5 | 0.53 ± 0.5 | 0.34 ± 0.3 |
| Glomerular filtration (eGFR, mL/min/1.73 m², mean ± SD) | 68.5 ± 23 | 73.4 ± 22.3 | 79.1 ± 14.2 | 76 ± 14.6 | 82.7 ± 10.6 | 83±18 |
| Serum creatinine (µmol/L, mean ± SD) | 144.35 ± 156.2 | 123.23 ± 153.4 | 108.76 ± 105.5 | 123.00 ± 141.5 | 126.00 ± 146 | 108.63 ± 119.9 |
| Prednisone dose (mg/day, mean ± SD) | 37.9 ± 14.9 | 11.9 ± 6.8 | 6.5 ± 2.9 | 5.1 ± 3.8 | 6 ± 6.4 | 4.2 ± 4.7 |

By 12 months or earlier, 64.7% (11/17) of patients achieved CRR, with a median time to response of 6 months (IQR 4–12) ( Figure 1). Among the six remaining patients, one achieved CRR at 26 months , three experienced renal relapse (13.6%) while on treatment, one progressed to end-stage renal disease (this patient had a chronicity index of 8 and a history of two prior LN episodes), and one discontinued BEL at 8 months due to an extrarenal flare.




BEL demonstrated a significant GC-sparing effect: at 3 months, 64.7% required <10 mg/day of prednisone; by 6 months, 64.7% needed <5 mg/day, and at 12 months, 84.2% achieved doses <5 mg/day.




When comparing early (<3 months) versus late (3–6 months) initiation of BEL, early initiation was associated with a significantly higher likelihood of achieving CRR, with a hazard ratio of 4.34 (95% CI: 1.06–17.76; p = 0.041). Additionally, the median time to CRR was significantly shorter in the early initiation group (6 months vs. 13 months).

**Conclusions:** In our experience, triple therapy with BEL achieved EULAR/ERA-EDTA targets while significantly reducing glucocorticoid requirements, particularly with early initiation.

**PT017 / #649**

**Topic:** ***AS12 - Genetics, Epigenetics, Transcriptomics***

**POSTER TOUR 04: SLE PATHOGENESIS**
**24-05-2025 10:00 AM - 10:40 AM**

## SLE-DISEASOME: A WIDE SPECTRUM DATABASE OF SYSTEMIC LUPUS ERYTHEMATOSUS RELEVANT FUNCTIONAL PATHWAYS

Daniel Toro Dominguez[1], Ivan Ellson-Lancho[2], Jordi Martorell-Marugán[2,3], Pedro Carmona-Saez[2,4], Marta Alarcón-Riquelme[1,2]
[1]Karolinska Institutet, Institute Of Environmental Medicine, Stockholm, Sweden, [2]GENYO. Centre for Genomics and Oncological Research: Pfizer, University of Granada, Andalusian Regional Government, Granada, Spain, [3]Fundación para la Investigación Biosanitaria de Andalucía Oriental-Alejandro Otero (FIBAO), Granada, Spain, [4]University of Granada, Departament Of Statistics, Granada, Spain

**Background/Purpose:** Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by unpredictable patterns of flares and remissions, affecting a wide range of tissues and organs. SLE causes significant suffering and mortality, and treatment efficacy varies enormously among patients. The main contributing factor to treatment failure and the broad clinical spectrum observed is the heterogeneity in dysregulated molecular mechanisms across patients. Therefore, the use of personalized therapies based on molecular information is considered a promising strategy to address disease heterogeneity, although their practical implementation still faces substantial challenges (1). Transcriptomics offers a powerful tool for understanding molecular profiles, but its reproducibility is strongly affected by batch effects across studies, and its high dimensionality makes interpretation difficult for clinical practice. Pathway-based single-sample scoring approaches emerge as a potential solution by translating gene expression into standardized activity measurements using small sets of functional pathways (2). The key step is to define the disease-relevant biological pathways. There are numerous databases of biological functions available. However, using a single pathway database may lead to biased results based on the knowledge collected in that particular database, while using multiple databases could result in redundant findings. Additionally, selecting significant pathways using one specific study can yield cohort-dependent results, many of which may not be reproducible in other studies. Therefore, in this study, we defined a comprehensive collection of disease-relevant gene-signatures, called the SLE-diseasome, based on a multi-cohort approach and integrating multiple layers of database-derived biological knowledges.

**Methods:** For the development of the SLE-diseasome (Figure 1), a total of 16 SLE datasets, comprising about 5500 SLE patient data and 900 healthy samples were used as well as11 different pathway databases. The different pathways were divided into sub-

pathways, or gene-signatures, using a co-occurrence-based k-means clustering across datasets, to get molecular and functional granularity. Redundancy across all these gene-signatures was reduced by filtering pathways based on similarity, using the Jaccard index. Upon each step, the pathway database was re-annotated. Next, each pathway and patient was scored from each study using m-score-based single-sample molecular scoring. Significance with respect to healthy distribution at patient and pathway level was also calculated and incorporated. Disease relevant pathways were defined as pathways that were significant in at least 10 percent of the patients when compared to healthy controls, and significant across 7 different studies. These two parameters were internally optimized to keep the data structure and minimizing false positive results. Significant pathways were clustered and re-annotated.

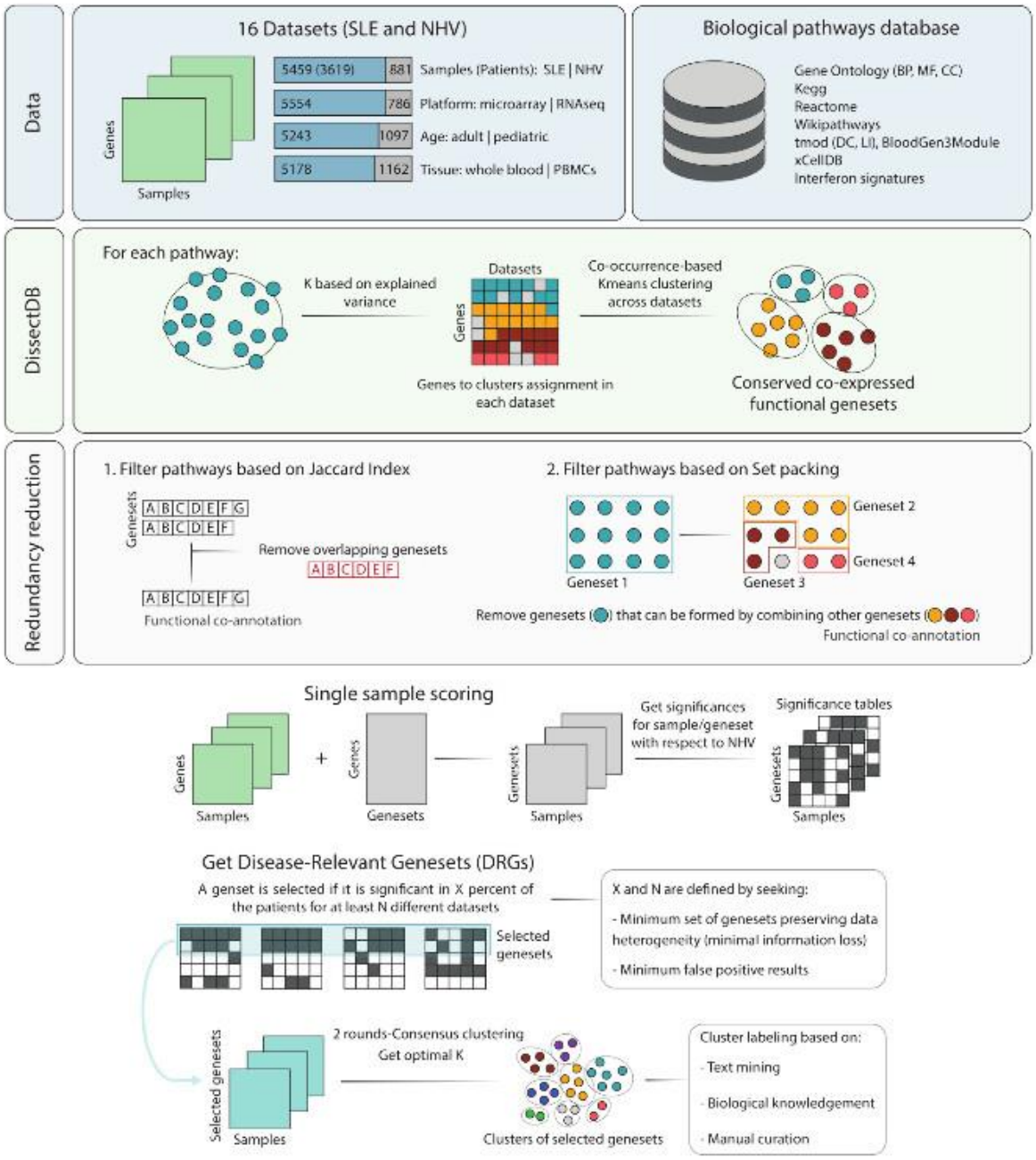



Figure 1: SLE Diseasome database development workflow.

**Results:** We obtained a total of 4400 SLE-relevant and robust functional pathways integrating 16 SLE datasets and 11 different pathway databases. By obtaining clusters of pathways from different initial sources, we can go one step further when interpreting results, establishing connections between different functions and annotations. The applicability of the SLE-diseasome was tested in different scenarios, for patient stratification analysis and for the generation and cross-cohort validation of machine learning models to predict clinical manifestations and drug response.

**Conclusions:** The SLE-diseasome offers a new SLE-specific database connecting multiple layers of database-derived biological knowledge. It is defined using a robust

multi-cohort approach, bringing us one step closer to the effective use of molecular information in clinical practice through single-sample molecular scoring.

**References:**

1. Toro-Dominguez D. Brief Bioinform. 2022;23(5):bbac332.

(https://pubmed.ncbi.nlm.nih.gov/35947992/)

2. Foroutan M. BMC Bioinformatics 2018;19:404.

(https://pubmed.ncbi.nlm.nih.gov/30400809/)

**PT018 / #183**

**Topic:** ***AS12 - Genetics, Epigenetics, Transcriptomics***

**POSTER TOUR 04: SLE PATHOGENESIS**
**24-05-2025 10:00 AM - 10:40 AM**

## SINGLE-CELL RNA SEQUENCING UNVEILS PROGRESSIVE IMMUNE DYSREGULATION FROM GENERAL POPULATION, PRECLINICAL SLE TO SLE PATIENTS

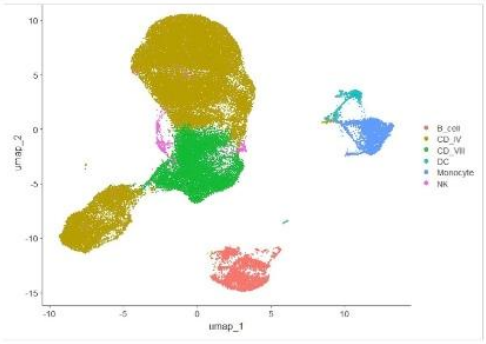
Wei-Ting Hung[1], Ting-Shuan Wu[2], Yi-Ming Chen[1]
[1]Taichung Veterans General Hospital, Taichung, Taiwan, [2]Chung Shan Medical University, Taichung, Taiwan

**Background/Purpose:** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by complex immunological disturbances. Early detection is challenging due to heterogeneous clinical manifestations. Understanding cellular and molecular changes from preclinical (pre-SLE) to clinical stages is essential for early intervention. Polygenic risk score (PRS) has been widely used to identify subjects at risk. However, the immune dysregulation of subjects with high SLE-PRS has never been demonstrated. This study aims to delineate the cellular transcriptomic landscapes of healthy controls, pre-SLE, and SLE patients using single-cell RNA sequencing (scRNA-seq) to identify molecular signatures associated with disease progression.

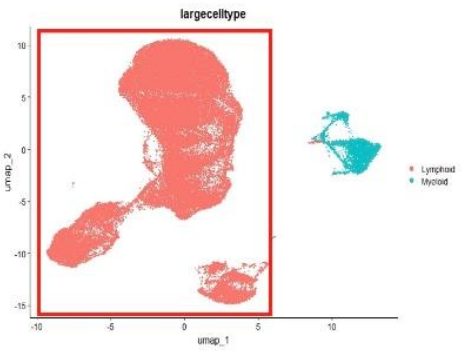
**Methods:** Peripheral blood mononuclear cells (PBMCs) were collected from 10 healthy controls, 23 pre-SLE patients with top 5 percent SLE-PRS without previous diagnosis of SLE, and 12 SLE patients. scRNA-seq was performed using the BD Rhapsody. Data was processed and analyzed with Seurat and other bioinformatics tools to identify differentially expressed genes and pathway enrichments across cell types and patient groups.

**Results:** The analysis revealed distinct transcriptional profiles among the three groups. PBMCs (peripheral blood mononuclear cells) were clustered and annotated into five major cell types: B cells, CD4+ T cells, CD8+ T cells, monocytes, and NK cells, as shown by UMAP (Uniform Manifold Approximation and Projection). Additionally, the cells were further categorized into myeloid and lymphoid lineages. The myeloid-to-lymphoid (M/L) ratio progressively increased in the healthy controls to pre-SLE and SLE patients, indicating an elevated myeloid cell presence as the disease progresses. To identify key immune cell types within the lymphoid subsets, further clustering and analysis of immune cell were performed to resolve immune subpopulations. Differential gene expression between pre-SLE patients and healthy controls was visualized using volcano plots across key immune cell populations. Notably, pre-SLE patients exhibited significant upregulation of genes associated with early immune activation and

dysregulation, such as IFI44L and IGKC, suggesting that these genes may act as potential molecular drivers in the pathogenesis of SLE.




| | PT(N) | Lymphoid | Myeloid | M/L % |
|---|---|---|---|---|
| Healthy | 10 | 11581 | 533 | 0.046024 |
| Pre_SLE | 23 | 26536 | 2417 | 0.091084 |
| SLE | 12 | 14901 | 1366 | 0.091672 |



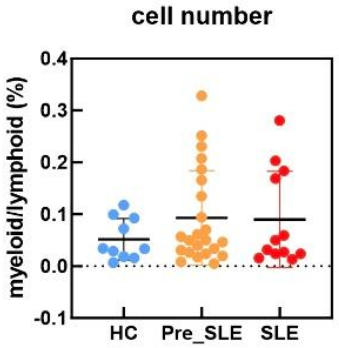




Figure 1. UMAP clustering of immune cells from healthy controls, pre-SLE, and SLE patients with distinct color-coded cell types. The accompanying table and scatter plot demonstrate an elevated myeloid-to-lymphoid ratio in pre-SLE and SLE, highlighting immune composition
shifts.

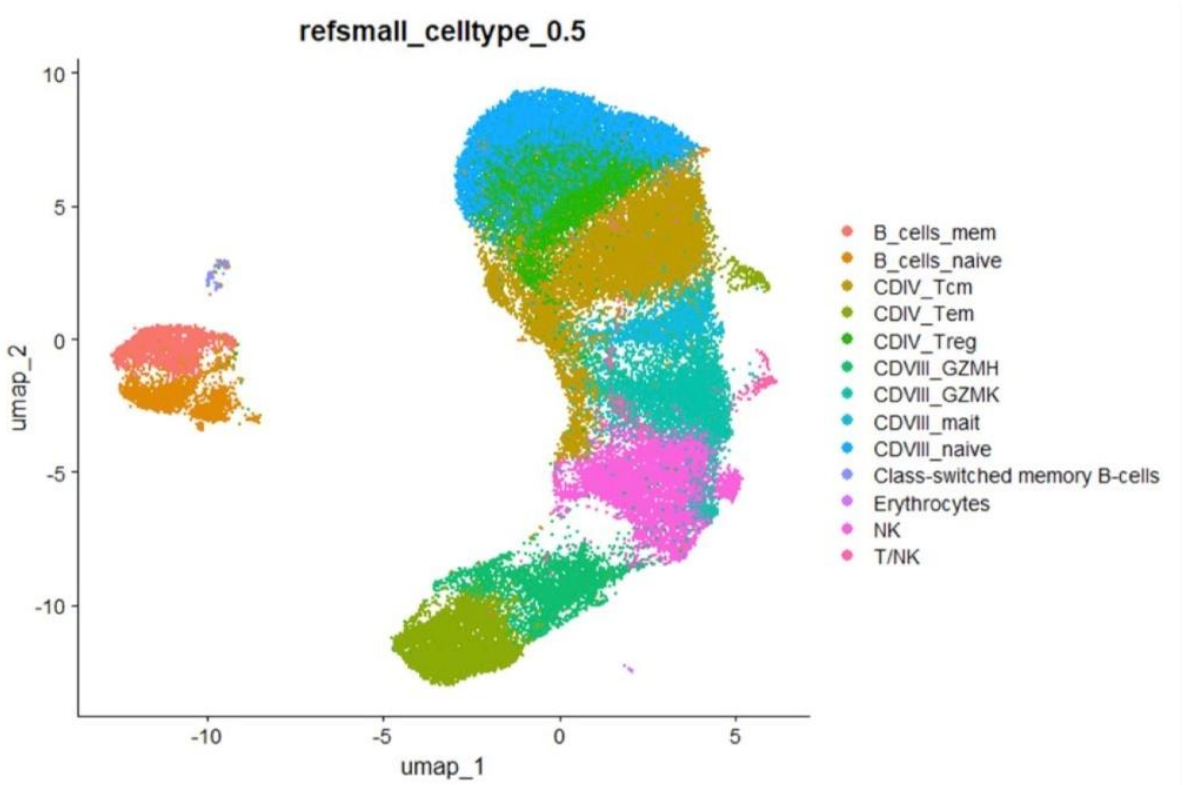



Figure 2. UMAP with subcluster analysis of immune cell types, displaying specific populations such as memory B cells and T cell subsets.

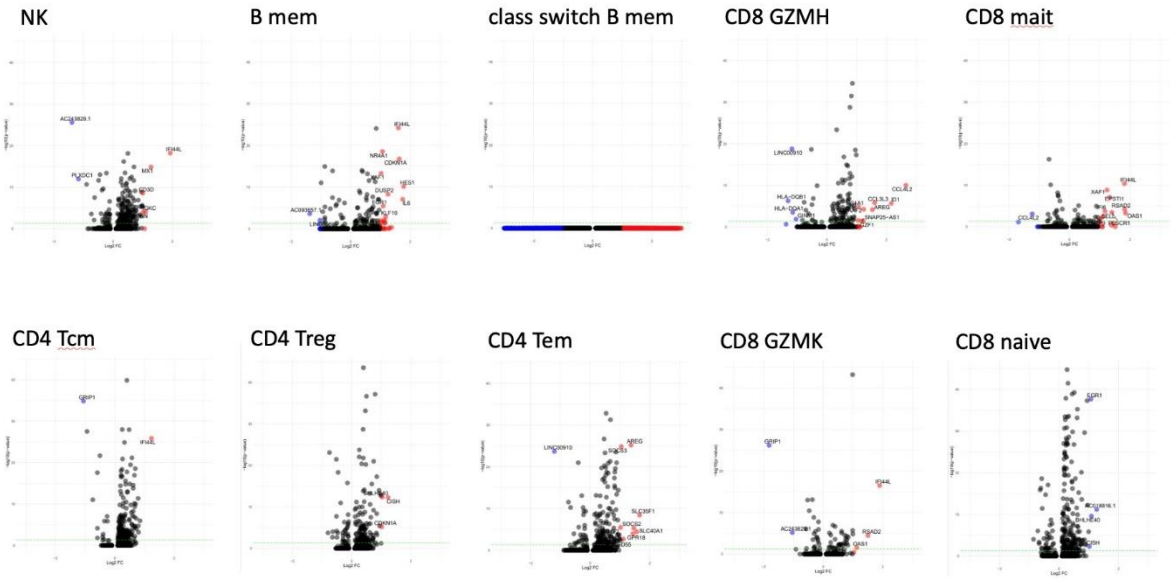



Figure 3. Volcano plots show differentially expressed genes in various immune cell populations between pre-SLE and healthy controls

**Conclusions:** Our findings demonstrate progressive immune dysregulation at the single-cell level from pre-SLE to SLE patients. The identified molecular signatures, altered cell subsets, and immune composition shifts provide insights into SLE

pathogenesis and suggest potential biomarkers for early diagnosis and therapeutic targets.

**PT019 / #196**

**Topic:** ***AS16 - Lupus Nephritis-Pathogenesis***

**POSTER TOUR 04: SLE PATHOGENESIS**
**24-05-2025 10:00 AM - 10:40 AM**

# FERROPTOSIS AND PYROPTOSIS IN KIDNEY MACROPHAGES AND EPITHELIAL KIDNEY CELLS IS MEDIATED BY A METABOLIC SWITCH TOWARDS GLYCOLYSIS IN LUPUS NEPHRITIS

Soraya Játiva[1,2], Selene Torrico[1,2], Ángeles Muñoz[1], Georgina Hotter[1,3]
[1]IIBB-CSIC, Barcelona, Spain, [2]M2RLAB, Barcelona, Spain, [3]CIBER-BBN, Zaragoza, Spain

**Background/Purpose:** Lupus nephritis (LN) is a type of immune-complex nephritis caused by systemic lupus erythematosus, a chronic autoimmune inflammatory disease frequently identified with a poor prognosis. Macrophages and renal tubular cells play an important role in the pathogenesis of LN. Understanding the mechanisms that lead both types of cells to sustained renal inflammation and development of LN is not well defined and is crucial for developing novel therapeutic strategies.

**Methods:** We used rat NRK-52E tubular cells and mice Raw 264.7 macrophages treated with ovalbumin immunocomplexes (OVA-IC) to mimic lupus nephritis injury model in vitro. Experimental groups were: the control group, OVA-IC group, the 2DG (2-desoxi-D-glucose) group, and DFO (deferroxamine) group. Human HK-2 tubular cells and THP-1 monocytes were treated with healthy serum or lupus nephritis serum. After 24 hours of culture, glycolysis and ferroptosis activity assay was analyzed and expression levels related to pyroptosis, ferroptosis, glycolisis, fatty acid oxidation and fibrosis genes were detected by q-PCRS. An in vivo murine model of LN was conducted in CD-1 mice subjected to intraperitoneal administration of pristane. Experimental groups were: sham group and pristane-induced group. 6 weeks after, cell sorting was used to isolate renal epithelial and macrophages cells to be analyzed.

**Results:** Our results demonstrate that OVA-IC administration promotes glycolysis upregulation and enhances ferroptosis and piroptosis, which were reverted by 2DG and DFO treatment in NRK and RAW cells. In the in vivo mice pristane-induced model, the isolated renal epithelial cells and macrophages from kidneys, showed an increase in the expression of glycolytic, pyroptotic and ferroptotic related genes related genes, while fatty acid oxidation were downregulated. Notably, treatment of HK-2 tubular human cells and THP-1 human monocytes with lupus nephritis serum provoked upregulated glycolysis and enhancement of pyroptosis and ferroptosis.

**Conclusions:** Collectively, our findings identify that pharmacological induction of lupus in vitro and in vivo provokes a metabolic switch towards glycolysis that provokes

enhancement of ferroptosis and inflammatory/pyroptotic markers in both tubular epithelial cells and monocytes/macrophages since 2DG treatment reduces the ferroptosis and inflammatory marker upregulation. Indeed, this study provides a novel anti-LN treatment strategy targeting glycolysis activation in renal macrophages and renal tubular epithelial cells that prevents pyroptosis and ferroptosis cell death to reduced sustained LN tissue inflammation.

**PT020 / #451**

**Topic:** ***AS16 - Lupus Nephritis-Pathogenesis***

**POSTER TOUR 04: SLE PATHOGENESIS**
**24-05-2025 10:00 AM - 10:40 AM**

# REDUCED FREQUENCY OF CIRCULATING INTERLEUKIN-16 EXPRESSING CD4+AND CD8+T CELLS ASSOCIATE WITH INCREASED URINARY IL16 LEVELS AND PROMOTE TH1 AND CD8+T CELL MIGRATION IN LUPUS PATIENTS

Kittikorn Wangriatisak, Francesca Faustini, Vivianne Malmström, Iva Gunnarsson, Vilija Oke
Division of Rheumatology, Department Of Medicine, Karolinska Institutet, Stockholm, Sweden

**Background/Purpose: Background/Purpose:** Cytokine dysregulation is recognized as key factor in the development of several autoimmune diseases. Data suggests interleukin-16 (IL16) is involved in the pathogenesis of systemic lupus erythematosus (SLE) and especially in lupus nephritis (LN). Yet, information on the cellular source of IL16 as well as its pathogenic relevance is scarce. Elucidating IL16- producing and secreting cells and their association with SLE manifestations may provide more precise disease biomarker and guide in developing new therapeutic interventions.

**Methods: Methods:** Thirty-four SLE patients and fifteen healthy controls (HCs) were included. Among lupus patients, sixteen had LN (48%). In patient cohort, thirty-two plasma (LN, n = 13 and non-LN, n = 19) and twenty-one urine (LN, n = 10 and non-LN, n = 11) samples were collected for IL16 measurement by ELISA. Data is represented as median and interquartile range (IQR). *Ex vivo* IL16-expressing cells were analyzed by spectral flow cytometry. Correlation analysis between IL16-expressing cells and plasma/urine IL16 levels and clinical parameters was performed. The capacity of IL16 to induce T-cell migration was evaluated in SLE patients (n = 2) and HCs (n = 2) using a chemotaxis assay.

**Results: Results:** Patients were mainly females (95%), of median age 41 (31-49) years. We first proceeded to detect IL16 at cellular level without any stimulation, finding IL16 at intracellular level while no surface expression was detected. Compared with HCs, a decreased frequency of IL16-expressing cells within CD4+T, CD8+T, B and NK cells was observed in SLE patients. Through multiparameter flow cytometric analysis, we observed a reduction of IL16-expressing cells from several B cell subsets which included plasmablasts (CD19+CD27$^{high}$CD38$^{high}$), double negative (CD19+CD27-IgD-) and naive (CD19+CD27-IgD+) in patients. Similarly, fewer IL16-expressing T helper1 cells (Th1: CXCR3+CCR6-) were detected in patients. LN patients showed decreased IL16-expression in total CD4+T cells as well as in their subsets including Th1 and

regulatory T (Treg: CD25+CD127-), compared to non-LN. Concerning plasma (p-) and urine (u-) IL16, we found elevated p-IL16 levels in patients *vs* HCs, while increased u-IL16 was only detected in LN subgroup. Additionally, a significant negative correlation between circulating IL16-expressing CD4+ ($r$ = -0.52, $p$=0.03) and CD8+ ($r$ = -0.46, $p$=0.04) T cells with u-IL16 was observed, suggesting their IL16-secreting roles. The u-IL16 levels of LN patients showed positive correlation with SLEDAI-2K index ($r$ = 0.85, $p$=0.003) and negative with C4 levels ($r$ = -0.66, $p$=0.04). We further explored the migratory role of IL16 by in vitro assays which showed that IL16 could preferentially induce T cell migration in both patients and HCs. Intriguingly, an increased proportion of transmigrated CD8+T cells was observed in patients, while HCs showed increased transmigrating CD4+T cells. Among transmigrated CD4+T cell subsets, Th1 cells were enriched after IL16 stimulation. The addition of IL16 blocking antibody resulted in a diminished frequency of transmigrated T cells with significantly decreased proportion of CD8+T cells which was observed in SLE patients.

**Conclusions: Conclusions:** Both B and T cell compartments in SLE patients show reduced positivity for IL16 expression. Reduced numbers of circulating IL16-expressing CD4+ and IL16-expressing CD8+T cells in patients appear associated with u-IL16 levels, suggesting their IL16 secreting abilities. The biological effect of IL16 in inducing migratory responses in Th1 and CD8+T cells in SLE may suggest pivotal role in the recruitment of pathogenic T cells. Therefore, targeting the IL16 might be an alternative strategy for targeted therapy.

**PT021 / #495**

**Topic:** ***AS01 - Adaptive Immunity***

**POSTER TOUR 04: SLE PATHOGENESIS**
**24-05-2025 10:00 AM - 10:40 AM**

# B CELL RECEPTOR SEQUENCING REVEALS DISTINCT SELECTION OF AUTOREACTIVE AGE/AUTOIMMUNITY-ASSOCIATED B CELLS IN PATIENTS WITH SLE

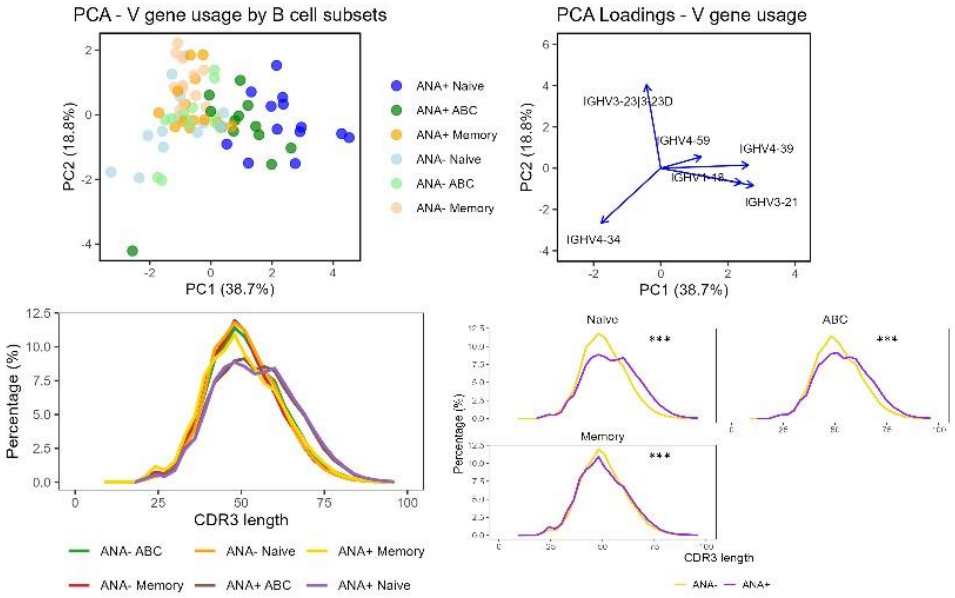
Yemil Atisha-Fregoso[1], Wenzhao Meng[2], Aaron Rosenfeld[2], Fang Liu[2], Scott Feltman[3], Matthew Scharff[4], Eline Luning Prak[2], Betty Diamond[1]
[1]Feinstein Institutes for Medical Research, Institute Of Molecular Medicine, Manhasset, United States of America, [2]University of Pennsylvania, Philadelphia, United States of America, [3]Stony Brook University, Stony Brook, United States of America, [4]Albert Einstein College of Medicine, New York, United States of America

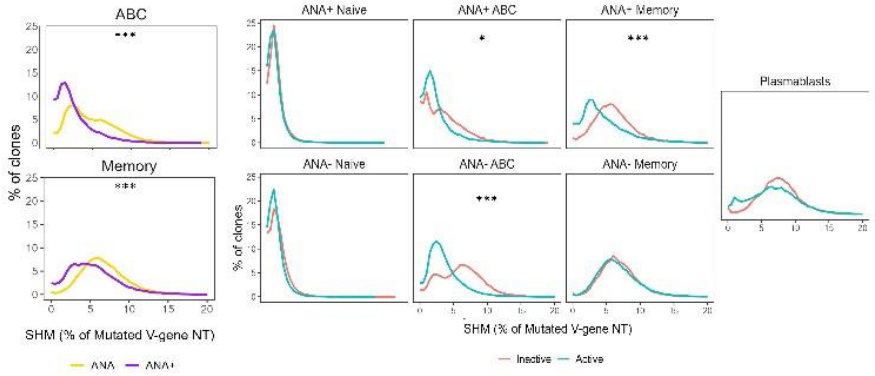
**Background/Purpose:** Autoreactive B cells that recognize nuclear antigens are normally present in healthy individuals and patients with systemic lupus erythematosus (SLE). Age/autoimmunity associated B cells (ABCs) are a recently characterized subset of B cells that are reported to be enriched in autoreactivity and differentiate into plasmablasts or plasma cells. The selection process and regulation of autoreactive B cells and ABCs in patients with SLE has not been completely understood. To gain insights into tolerance checkpoints and the developmental trajectories of autoreactive clones, we studied the BCR sequences from thousands of anti-nuclear antigens (ANA) positive and ANA-negative B cells from patients with SLE.

**Methods:** We included 13 patients with SLE. From peripheral blood samples, we identified and sorted ANA+ and ANA- cells from three different B-cell subsets: naïve, memory, and ABCs, as well as from total plasmablasts. ANA+ cells were identified by flow cytometry using a novel method based on their binding to nuclear extract. We performed bulk B-cell receptor sequencing from genomic DNA. We mapped and sequenced B-cell receptor (BCR) regions and investigated the features of the immunoglobulin heavy chain (IgH) repertoire of the sorted subsets. ***Statistical analysis:*** To compare CDR3 length and SHM at clone level, we used a generalized mixed-effects model design in which patient of origin was included as a random effect and B cell subsets or patient disease activity status as fixed effects. To analyze the patterns of V gene usage of the most prevalent genes across different B cell subsets, we performed Principal Component Analysis (PCA) with scaled and centered data.

**Results:** Ten (77%) patients were female. Mean ± SD age of 38.3 ± 11.5 years. According to the PGA score, 8 patients had at least mild activity (PGA ≥ 0.5), and 5 were inactive. ANA reactivity was similar in ABCs (median 8.3%, IQR 4.8-11.9%) and naive B cells (8.3%; 6-9.8%) and higher in both than in memory B cells (4.1%; 3.3-6.3; $p<0.05$ both

comparisons). We observed preferential usage of some VH (IGHV1-18, IGHV3-21, IGHV3-23|3-23D, IGHV4-34, IGHV4-39 and IGHV4-59) and VJ genes (IGHJ4 and IGHJ6) in our cohort. ANA+ naïve and ANA+ ABCs used different gene segments (Figure 1 top panel) and have longer CDR3 regions (Figure 1, lower panel) than ANA+ memory B cells and ANA- subsets, which suggests a close relationship between these two subsets. ANA+ ABCs and memory B cells have lower frequency of somatic hypermutation (SHM) compared with their ANA- counterparts (Figure 2, left panel). This suggests extrafollicular (EF) generation of ANA+ antigen experienced B cells. Patients with active disease have a lower frequency of SHM in ANA+ ABCs and memory B cells and ANA- ABCs (Figure 2, right panel), suggesting increased EF activation in patients with active SLE.




**Conclusions:** Compared to memory B cells, ABCs are enriched in autoreactivity. ANA+ ABCs have evidence of a different selection process than memory B cells, and are probably directly derived from ANA+ naïve B cells. Our data support that ANA+ B cells, and particularly ANA+ ABCs can contribute to the generation of autoantibodies in patients with SLE through an EF pathway, and that in patients with active SLE there is more EF activation.

**PT022 / #742**

**Topic: *AS12 - Genetics, Epigenetics, Transcriptomics***
**Late-Breaking Abstract**

**POSTER TOUR 04: SLE PATHOGENESIS**
**24-05-2025 10:00 AM - 10:40 AM**

# XIST EXPRESSION IN MALES WITH SYSTEMIC LUPUS ERYTHEMATOSUS: BIMODAL DISTRIBUTION AND PARTIAL X-CHROMOSOME INACTIVATION

Helen Masson, Jonathan Crawford, David Gemperline, James Scherschel, Guilherme Rocha, Christoph Preuss, Matthew Linnik, Richard Higgs, Ernst Dow
Eli Lilly, Indianapolis, United States of America

**Background/Purpose:** Systemic lupus erythematosus (SLE) exhibits a pronounced female-biased imbalance in disease prevalence, with a female-to-male ratio of 9:1. Although the exact mechanisms remain unclear, the significant role of X chromosome dosage is supported by karyotypic risks associated with SLE. This study utilizes paired transcriptomic (RNAseq), proteomic (Olink), and epigenomic (EMSeq) data from large phase 3 trials to gain mechanistic insights into the drivers behind the sexual bias in SLE.

**Methods:** Baseline RNAseq, Olink, and EMseq data were collected from the whole blood of 722 SLE patients (680 female, 42 male) and 84 healthy controls (77 female, 7 male) from two phase 3 clinical trials (NCT03616964, NCT03616912). Differential expression analysis was performed using a factorial design to calculate the following comparisons for each modality: i) SLE vs healthy controls in females, ii) SLE vs healthy controls in males, and iii) interaction between sex and disease. Gene set enrichment analysis (GSEA) of patient subsets was conducted using Gene Ontology (GO) biological process terms. To ensure our cohort did not contain erroneous results due to Klinefelter's males, we inferred X-chromosome heterozygosity by calculating the read depth of the X-chromosome from the EMseq bam files. To validate our results, we performed similar differential expression analysis on EMseq data from an independent cohort of SLE patients (241 females, 13 males) from two additional phase 3 clinical trials (NCT01205438, NCT01196091).

**Results:** The strongest changes differentiating how sexes respond to disease were observed in the expression of lncRNA XIST (X-inactive specific transcript) and epigenetics. Specifically, we noted an increased expression of XIST in males with SLE compared to healthy controls (Fig. 1A), with this expression exhibiting a bimodal distribution (Fig. 1B). GSEA indicated that males with high XIST expression exhibit enrichment in biological processes (GO) related to metabolism and immunoglobulin production, such as oxidative phosphorylation, B-cell mediated immunity, and immunoglobulin production compared to XIST low males. Consistent with XIST's known

role in X-chromosome inactivation, we observed corresponding hypermethylation of the X-chromosome and downregulation of X-linked genes in males with SLE (Fig. 1C). Lastly, we observed similar patterns of X-chromosome hypermethylation using EMseq data from an independent cohort of SLE patients.

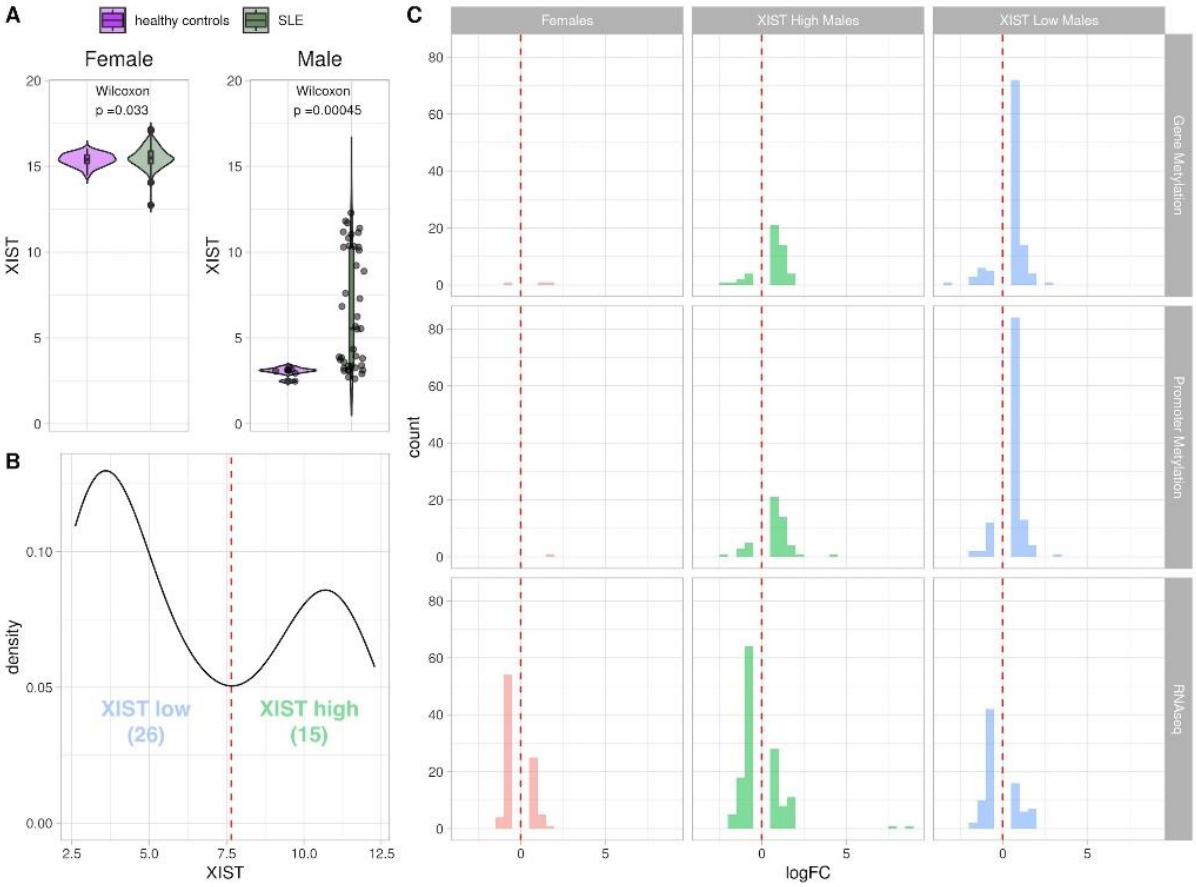



**Figure 1. Partial X-chromosome inactivation in males with SLE**. **A)** Violin plots of XIST expression (RNAseq) in women (left) and men (right). **B)** Density plot of the bimodal expression of XIST in men with SLE. Dashed red line indicates the separation between XIST high and XIST low groups. **C)** Distribution plots of significant changes (|FC| > 1.5; FDR < 0.1) in gene methylation (top), promoter methylation (middle), and gene expression (bottom) on the X chromosome in females (pink), XIST high males (green), and XIST low males (blue) compared to healthy controls.

**Conclusions:** This study, which includes the most comprehensive and largest dataset of male SLE patients to date, shows that males with SLE express significantly higher levels of XIST, accompanied by hypermethylation of the X-chromosome and downregulation of X-linked genes compared to healthy controls, suggesting partial X-chromosome inactivation in males with SLE. Importantly, we have confirmed that these changes are not artifacts of Klinefelter's patients within the cohort. We hypothesize that this X-chromosome inactivation may be driving SLE via several mechanisms, including: i) inactivation of immunoregulatory molecules, ii) inducing development of SLE autoantibodies, and/or iii) driving interferon production via TLR7.