mote both the production and response to type I IFN. There is also a lack of proper regulation in SLE of cells in the type I IFN system and recently, we observed that autoantibodies to NK cells may contribute to the activation of the type I IFN system. These NK cells autoantibodies block the inhibitory NK cells receptors and were found in an SLE subset with an active and severe disease phenotype.

21 Health professionals

OI21.3

Uncertainties and opportunities for patients with SLE

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The *aim* of this presentation is to describe results from a study in which persons with established systemic lupus erythematosus (SLE) expressed their experiences concerning illness in everyday life and further to discuss implications for healthcare professionals. Nineteen persons with SLE with varying disease activity and low or no organ damage were interviewed in focus groups. Interviews were transcribed and analysed by qualitative content analysis. The study revealed two themes. The theme of Multifaceted uncertainty involved categories such as reliance on medication and healthcare and an unreliable body. The theme of Focus on health and opportunities included categories such as a learning process implying personal strength and limitations and possibilities in activities and work.
Conclusions and implications. Persons with established SLE experienced both uncertainty and focus on health and opportunities. This is in line with theories concerning uncertainty in illness, in which uncertainty could be experienced as a threat or a possibility; and further theories concerning shifting perspectives of illness and wellness in chronic disease; and personal growth following adversity and stressful events. Healthcare professionals could use theories like these when developing patient education, communication, and support. The findings highlight the importance of understanding patients' experiences of uncertainty to support focus on health and opportunities in self-management and lifestyle changes. Patient-reported outcome measures that capture personal factors such as uncertainty and opportunities need to be developed in SLE.

References
M. MATTSSON, *et al*. Uncertainty and opportunities in patients with established systemic lupus erythematosus: A qualitative study. *Musculoskeletal Care* 2012;10:1–12

24 Current state in lupus nephritis

OI24.1

Pathogenesis of LN and differences compared to other organ manifestations in SLE

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Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease with various clinical manifestations. The hallmark of SLE is the presence of antibodies against nuclear constituents, like double-stranded (ds)DNA, histones and nucleosomes. Local deposition of anti-nuclear antibodies in complex with nuclear autoantigens induces serious inflammatory conditions that can affect several tissues and organs, including the kidney.
The levels of anti-nucleosome and anti-dsDNA antibodies seem to correlate with glomerulonephritis. Apoptotic microvesicles are present in the extracellular matrix and circulation of patients with SLE, which is most likely due to an aberrant process of apoptosis and/or insufficient clearance of apoptotic cells and apoptotic debris. In recent years neutrophil extracellular traps (NETs), chromatine-containing web-like structures spit out by dying neutrophils, have been correlated with SLE and lupus nephritis as well. There is evidence for specific chromatin modification patterns within apoptotic microvesicles and NETs, which may lead to activation of both the innate and adaptive immune system.
Lupus nephritis may be classified in different classes based on histological findings in renal biopsies. The chromatin-containing immune complexes deposit in the capillary filter, most likely due to the interaction of chromatin with the polysaccharide heparan sulfate. A decreased renal expression of the endonuclease DNaseI may further contribute to the glomerular persistence of apoptotic chromatin and the development of glomerulonephritis.

28 New therapies and strategies in SLE

OI28.1

Biologicals: evidence, trials, state of the art

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A critical review of recent phase III trials will be presented (*e.g.*, tabalumab, epratuzumab, sifilimumab) in the first part of the talk. The second part will review following innovative ideas and measures are currently under consideration by pharmaceutical companies, biotechnology startups and lupus organizations that underwrite and support drug development:
a. Creating a new paradigm for designing clinical trials: Examples include superiority vs. equivalence trials, being sensitive to international clinical standards of practice, making CROs (clinical research organizations) more user friendly for academic trial sites, improving the quality of reference laboratories and revising requirements for ANA positivity relating to participation.
b. Creating a new and improved clinical trial landscape with more efficient and mission relevant approaches. These include prevention of disease development among those at risk, induction trials limited to patients with early/active disease, initiatives to maintain improvement and prevention of flares, and focusing on organ specific studies.
c. Evaluating the possibility of performing smart, cost-effective, small-scale trials, repurposing agents already on the market for lupus where safety is already documented, withdrawing effective drugs to assess efficacy as short term, highly focused limited interventions.
Improving trial design: Examples include improved composite disease activity measures, data mining from completed studies, evaluating candidate surrogate markers/biomarkers, optimizing trial site and patient recruitment strategies, and educating patients investigators about participation

Submitted Presentations

4 Role of B cell products and B cell function

OS4.4

Epratuzumab, a monoclonal antibody targeting CD22, inhibits BCR/CD40-stimulated B cell proliferation *in vitro*

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Background. Epratuzumab is a humanized monoclonal antibody that targets the B cell-specific protein CD22 and is currently in phase 3 clinical trials in patients with systemic lupus erythematosus (SLE). Epratuzumab inhibits BCR signalling events, but longer-term functional consequences have not been investigated.
Methods. Peripheral blood mononuclear cells (PBMC) from healthy donors were labelled with crystal trace violet (CTV) and cultured with soluble CD40 ligand (sCD40L) (50ng/mL) and/or anti-IgM (12µg/mL) ± epratuzumab in IgG, $F(ab')_2$ or Fab' formats (all at 10µg/mL). Cells were then stained with a panel of surface markers and analyzed by flow cytometry. To assess apoptosis, cells were analyzed for expression of FLICA (caspase 3/7) or for cell membrane integrity (7-aminoactinomycin D, 7-AAD) by flow cytometry.
Results. Proliferation of B cells, assessed by both CTV and cell count, was stimulated in the presence of anti-IgM alone but not by sCD40L alone. However, proliferation was synergistically enhanced in the presence of both stimuli. Epratuzumab in both IgG and $F(ab')_2$ (but not Fab') formats showed statistically significant inhibition of proliferation induced with anti-IgM alone and with anti-IgM+sCD40L (>85% & >70% with epratuzumab IgG in CTV assays, respectively, n=8). There was no evidence that apoptosis was induced irrespective of epratuzumab treatment.
Conclusions. Epratuzumab inhibited the proliferation of B cells in PBMC cultures stimulated through the BCR or through combinatorial BCR and CD40 activation. These data demonstrate that epratuzumab does modulate B cell function, which may have implications for understanding the effects of epratuzumab treatment on B cell function in SLE patients.

OS4.5

Pharmacodynamic changes in gene expression observed in two phase 3 trials of BAFF blockade with tabalumab in SLE

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Purpose. RNA profiling was performed on 1,760 SLE patients from ILLUMINATE 1 & 2 which studied the anti-BAFF, IgG4 monoclonal antibody, tabalumab, for efficacy in SLE. This study characterized baseline and pharmacodynamic (PD)-induced changes in gene expression from these two cohorts of SLE patients.
Methods. Blood was collected at baseline, week (W) 16 and W52. RNA was analyzed using Affymetrix HTA 2.0 microarrays. Serum IgG anti-dsDNA antibodies (abs), C3, C4 and IgG, IgA & IgM were measured and B cells enumerated. Statistical analyses to identify PD-induced gene changes in cohorts receiving 120 mg tabalumab Q2W and Q4W using a mixed effects model.
Results. Significant PD changes were observed in Q2W and Q4W arms vs placebo for serum anti-dsDNA abs, C3 & C4, IgG, IgM & IgA, and B cells (p<0.001). Expression changes in 410 genes were identified in tabalumab-treated patients including plasma cell markers, B cell markers, TNF superfamily members, Fc & Fc-like receptors and complement. Baseline elevation of interferon responsive genes (IRG) was associated with elevated anti-dsDNA abs and decreased levels of C3 & C4. B cell number correlated with expression of B cell-associated gene PD changes in B cell and plasma cell genes were observed in both the treatment doses and associated with changes in anti-dsDNA abs, serum Ig and complement levels.
Conclusions. Pharmacodynamic changes associated with tabalumab treatment included serum anti-dsDNA abs, C3 & C4, IgG, IgA & IgM, and B cells. Significant changes were observed in 410 genes consistent with BAFF blockade.

5 Oral presentations 1: Clinical science

OS5.1

Remission in SLE: consensus findings from a large international panel on Definitions Of Remission in SLE (DORIS)

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Background. Treat-to-target recommendations identified 'remission' as a target in SLE but recognize that there is no generally accepted definition for remission in lupus.
Objective. To achieve consensus, in a large multi-party international panel, on potential definitions for remission in SLE.
Methods. An international expert panel of sixty rheumatologists, nephrologists, dermatologists, clinical immunologists, and patient representatives participated in preparatory exercises, a full-day face-to-face meeting, and follow-up exercises and electronic voting rounds.
Results. Eight key statements regarding remission in SLE achieved >90% agreement. There were different viewpoints on the required duration of remission. In addition, the panel expressed strong support (>90%) for the following principles which will guide the further development of remission definitions:
I. A definition of remission in SLE will be worded as follows: Remission in SLE is a durable state characterized by [a definition of: absence of symptoms, signs, abnormal labs, (serology)]
Ia. Remission-off-therapy requires the patient to be on no other treatment for SLE than maintenance antimalarials.
Ib. Remission-on-therapy allows patients to be treated with maintenance antimalarials, stable, low-dose steroids (prednisone <5 mg/d), maintenance immunosuppressives and/or stable (maintenance) biologics.
II. Assessment of clinical symptoms and signs should be based on a validated index, *e.g.*, clinical-SLEDAI = 0, BILAG D/E only, clinical ECLAM =0; supplemented with PhysGA < 0.5 (0-3), and with labs included.
III. For testing construct validity of each definition the most appropriate outcomes were identified.
Conclusion. The work of this international consensus panel provides a framework for testing individual definitions of remission against longer-term outcomes.

OS5.2

Cardiovascular Events Prior to or Early After Diagnosis of SLE

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Purpose. Previous studies have shown a history of cardiovascular events prior to diagnosis of SLE and RA. This study describes the frequency of myocardial infarction (MI) prior to the diagnosis of SLE and within the first 2 years of follow-up.
Methods. A multinational inception cohort of SLE patients from 31 centres was followed yearly according to a standardized protocol from 2000-2014. MIs were reported and attributed on a specialized vascular event form. Descriptive statistics were used.
Results. 31 of 1848 patients had an MI. Of those, 23 patients had an MI occur prior to diagnosis or within the first 2 years of SLE. Of the 23 patients studied 60.3% were female, 82.6% were Caucasian, 4.3% Black, 8.7% Hispanic and 4.3% other. The mean age at SLE diagnosis was 52.5±15.0 years. Of the 23 MIs that occurred, 16 MIs occurred at a mean of 6.1±7.0 years prior to diagnosis and 7 occurred within the first 2 years.

Table I. Cohort Characteristics and CAD risk Factors at Baseline.

	Early MI Patients	Non-early MI Patients	p
N	23	1825	
Sex (female)	14 (60.9%)	1626 (89.1%)	<0.0001
Age at SLE Diagnosis (years)	52.5 ±15.0	34.5 ± 13.2	<0.0001
SLEDAI-2K	3.65 ± 3.54	5.35 ± 5.39	0.03
Anti-dsDNA	7/22 (31.8%)	650/1661 (39.1%)	0.48
Low C3 and C4	8/22 (36.4%)	617/1666 (37.0%)	0.95
HsCRP	3/12 (25%)	141/742 (19.0%)	0.60
ESR	8/14 (57.1%)	519/927 (55.9%)	0.93
On Steroid	19 (82.6%)	1260 (69.1%)	0.16
On Antimalarials	14 (60.9%)	1234 (67.8%)	0.48
On Immunosuppressives	10 (43.5%)	725 (39.8%)	0.72
Family History of MI	4/9 (44.4%)	127/228 (55.7%)	0.51
Hypercholesterolemia	6 (28.6%)	549 (35.7%)	0.50
Hypertension (≥ 140/90)	7 (30.4%)	213 (11.9%)	0.007
BP Diastolic	74.2 ± 12.2	75.2 ± 11.0	0.67
BP Systolic	125.8 ± 18.5	119.6 ± 16.8	0.08
Diabetes	1 (4.6%)	68 (3.8%)	0.85
Metabolic Syndrome	5/19 (26.3%)	238/1647 (14.5%)	0.15
ACL	1.47 ± 6.06	4.23 ± 13.41	0.09

Risk factors associated with early MI in univariate analysis: male sex, older age at diagnosis, lower SLEDAI-2K and hypertension. In multivariate analysis: age (OR=1.07 95% CI (1.04, 1.10)) and male sex (OR=3.2, 95% CI (0.13, 0.78)) remained significant.
Conclusion. MI prior to or early after SLE diagnosis may indicate earlier low grade disease activity not diagnosed or a concomitant alternative predisposition to AS and SLE.

OS5.3

Use of Antibiotics and Subsequent Risk of Systemic Lupus Erythematosus: A Matched Case-Control Study

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Objective. To examine the association of exposure to cyclines, macrolides, and penicillins antibiotics with the development of subsequent Systemic Lupus Erythematosus (SLE).
Methods. We conducted a nested case-control study using an administrative health database in British Columbia, Canada, from 1997-2010. Cases were defined using a validated algorithm that includes a combination of ICD-9 and ICD-10 codes and SLE drug therapy. Incident cases were age-, sex-, and entry time-matched to 10 controls using density-based sampling. We evaluated cumulative exposure to any cyclines, macrolides, and penicillins prior to SLE diagnosis allowing for removal of cases with any exposure in the year prior to the index date. Adjusted odds ratios were computed using conditional logistic regression.
Results. We identified 3,639 new SLE cases corresponding to 361,032 matched controls. All three classes of antibiotics had a statistically significant association with the development of SLE in the unadjusted models (Table I). However, after adjusting for the Charlson comorbidity index, hormone use, healthcare resource use and socioeconomic status only females exposed to cyclines showed a statistically significant association [OR = 1.6 (95% CI, 1.3-1.9)].
Conclusion. Females exposed to cyclin antibiotics had a 60% increased risk of developing SLE.

Table I. Odds Ratios of SLE in Patients with Prior Exposure to Three Classes of Antibiotics.

Drug Exposure	Unadjusted Odds Ratio	Adjusted Odds Ratio
Cyclines	All 2.5 (2.3-2.8)	All 1.6 (1.3 - 1.9)
	Male 2.0 (1.5-2.7)	Male 1.7 (0.9 -3.1)
	Female 2.6 (2.3-2.9)	Female 1.6 (1.3 - 1.9)
Macrolides	All 2.3 (2.1-2.6)	All 0.9 (0.7 - 1.1)
	Males 2.3 (1.6 - 3.3)	Males 1.4 (0.7 - 2.9)
	Females 2.3 (2.0 - 2.6)	Females 0.8 (0.6 - 1.1)
Penicillins	All 1.9 (1.7-2.1)	All 1.0 (0.8 - 1.2)
	Males 1.9 (1.4 - 2.5)	Males 0.7 (0.3 - 1.3)
	Females 1.9 (1.7 - 2.1)	Females 1.0 (0.8 - 1.3)

OS5.4

Utility of untimed single urine protein/creatinine ratio as a substitute for the 24 hour proteinuria for the assessment of proteinuria in systemic lupus erythematosus

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Objectives. To determine the utility of untimed Sample of Urine Protein/Creatinine (PCR) as a screening test for proteinuria and its ability to accurately measure the level of proteinuria in lupus
Methods. Analysis was performed on data from a single lupus cohort between May 2008-December 2014. Proteinuria was measured concurrently by 24 hour urine sample collection (24H-P) and PCR. Based on 24H-P, samples were divided into groups: I: <0.5, II: 0.5-0.99, III: 1-1.99, and IV: ≥2g/day. Correlation between 24H-P and PCR was measured. Agreement between 24H P/C and PCR was determined by Intraclass Correlation Coefficient (ICC), Concordance Correlation Coefficient (CCC) and Bland-Altman plot. The cut-offs of PCR predicting a 24H-P of 0.5, 1.0 and 2.0 g/day were determined with ROC curve.
Results. Although the correlation of 24H-P and PCR for all samples was high, for groups I, II, III and IV it was low-moderate. The agreement for all samples and groups I, II, III and IV was poor. The Bland-Altman confirmed that PCR overestimated the result of 24H-P (in particular groups III and IV) signifying poor agreement. PCR of 800 mg/g predicted a 24 H-P of 0.5 g/day (91% sensitivity and 80% specificity); PCR of 1590 mg/g and 3540 mg/g predicted 1.0 and 2.0 g/day respectively.
Conclusions. PCR can be used as a screening test for proteinuria and the cut off value to predict a 24H-P 0.5 g/day is 800 mg/g. PCR is not a valid test to quantify proteinuria. The accurate level of proteinuria should be measured by 24H-P.

OS5.5

Comparison of disease characteristics and organ damage in patients with juvenile and adult-onset systemic lupus erythematosus in large cohort from Turkey

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Background. Age at onset has been shown to effect the clinical course and outcome of the SLE. Herein, we aimed to define the differences between patients with juvenile-onset (jo-SLE) and adult-onset (ao-SLE) SLE followed up in two tertiary referral centres.
Methods. Seven hundred nineteen (76.9 %) patients with ao-SLE and 216 (23.1 %) patients with jo-SLE were examined. Demographic characteristics, clinical features, autoantibody profiles and damage data (SLICC damage index) were compared between the groups.
Results. Photosensitivity (71.6 vs 56.5%), malar rash (73.6 vs 45.6%) and oral ulcers (23.1% vs 15.4 %) were significantly more frequent in jo-SLE (p<0.05). Renal involvement was significantly more prevalent in the jo-SLE affecting 53.2 % (vs 38.9 %) (p<0.05). Autoimmune haemolytic anaemia (AIHA) also occured more often in the jo-SLE (33.3 vs 9.5%, p<0.05) whereas reverse was true for pleuritis (11.6 vs 18.4 %, p<0.05). A higher frequency of anti-dsDNA (78,7 vs 69%), anticardiolipin IgG (31.9 vs 21 %) and IgM (36.6 vs 19.3%) were observed in the jo-SLE group. However, there were significantly more patients with anti-Sm positivity in ao-SLE (19.6 vs 10.2%, p<0.05). Renal damage was significantly more frequent in the jo-SLE (43 vs 17.5%) (p<0.05).
Conclusions. jo-SLE was associated with a higher frequency of renal involvement and damage. As renal involvement is a major predictor of prognosis and outcome, this study highlights the importance of awareness of the age of onset of SLE and supports the necessity of vigilant follow-up of this subgroup.

OS5.6

Clinical and serological differences between juvenile-onset and adult-onset systemic lupus erythematosus patients from a national registry of patients (RELESSER)

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Objective. To assess clinical and serological differences between patients with juvenile-onset systemic lupus erythematosus (jSLE) and adult-onset (aSLE) from a National database.
Methods. Data included in the transverse phase of the National Register of lupus of the Spanish Society of Rheumatology (RELESSER –T) were analysed, which includes retrospective data from SLE patients. Inclusion criteria: patients with SLE with > or = 4 ACR criteria for SLE who were divided into 2 groups: disease date onset <18 years and >18. Sociodemographic, clinical, serological, activity, treatment and cumulative damage and chronicity data were collected. Associative descriptive statistical analysis was performed.
Results. we reviewed 3,428 aSLE (89.6% women) and 484 jSLE (89.8% girls), 93.1% Caucasian in both groups; age at diagnosis: 38.1±14 and 16.6±6.3 years, respectively; average delay in diagnosis 24.7±47.4 and 39.9±5 months, respectively; mean age at follow-up: 48.8±14.3, 31.5±30 years, respectively. Table I shows all significant differences (p<0.05). In aSLE 68.7% had positive anti-DNA Ab vs. 82.9% of jSLE (p<0.001).
Conclusions. jSLE have higher percentage of nephritis, hypertension (associated with nephritis), anti-DNA, Creat clearance <5, proteinuria >3.5, recurrent nephritis, chronic renal failure, organic brain syndrome and thrombotic thrombocytopenic purpura and more SLE family background. jSLE also have higher SLEDAI, Katz, but lower Charlson scores. Secondary Sjögren (anti-RO), fibromyalgia and osteoporosis are more common in aSLE. jSLE receive more steroid treatment, synthetic immunosuppressants, IV immunoglobuline, rituximab, splenectomy, dialysis and kidney transplantation.
This study was supported by the FIS (ISCIII) PI11/02857. It has also been partially supported by GSK, UCB , Roche and Novartis. Dr. Pego-Reigosa receives support from Biocaps (grant 316265) of the 7th Framework Programme of the European Union (FP7 / REGPOT - 2012-2013.1).

Table I.

VARIABLE		aSLE	jSLE
Fever (SLEDAI)	No (never)	3261 (96.5%)	455 (94.6%)
	(>10 previous days)	117 (3.4%)	26 (5.4%)
Adenopathy	No	3044 (90.4%)	418 (87.4%)
	Yes	321 (9.5%)	60 (12.5%)
Splenomegalia	No	3242 (97.1%)	445 (93.8%)
	Yes	96 (2.8%)	25 (6.1%)
Myositis	No (never)	3249 (96.6%)	445 (94.4%)
	Yes (hace > 10 días)	102 (3.0%)	25 (5.3%)
Osteoporosis (SLICC)	No	3085 (92.4%)	<455 (96.8%)
	Yes	252 (7.5%)	15(3.1%)
Fibromyalgia	No	3135 (93.3%)	461 (97.6%)
	Yes	224 (6.6%)	11 (2.3%)
Pericarditis	No	2883 (85.5%)	380 (80.1%)
	Yes (hace >10 días)	471 (13.9%)	91 (19.2%)
	Yes (persiste 10 días)	15 (0.4%)	3 (0.6%)
Raynaud	No	2257 (67.8%)	287 (62.5%)
	Yes	1068 (32.1%)	172 (37.4%)
Lupus Nefritis	No	2491 (74.1%)	256 (54.2%)
	Yes	867 (25.8%)	216 (45.7%)
Arterial Hypertension in 1st nefritis flare	No	2966 (90.0%)	385 (84.6%)
	Yes	328 (9.9%)	70 (15.3%)
Hematuria	No	2369 (73.5%)	256 (57.2%)
	Yes (>10 previous days)	770 (23.9%)	172 (38.4%)
	Yes (persisting last 10 days)	83 (2.5%)	19 (4.2%)
Nefritis recurrence	No	1641 (87.3%)	227 (74.9%)
	Yes	237 (12.6%)	76 (25.0%)
Hystologyc Change	No	299 (85.9%)	49 (71.0%)
	Yes	49 (14.0%)	20 (28.9%)
Creatinina clearance<5	No	3184 (95.2%)	430 (97.2%)
	Yes	160 (4.7%)	36 (7.7%)
Proteinuria >3.5g/24hs	No	3226 (96.8%)	437 (94.5%)
	Yes	106 (3.1%)	26 (5.6%)
Terminal Renal Failure	No	3241 (97.8%)	437 (94.1%)
	Yes	72 (2.1%)	27 (5.8%)
Organic Brain Sd	No (never)	3282 (97.5%)	448 (94.7%)
	(>10 previous days)	72 (2.1%)	24 (5.0%)
	(persisting 10 previous days)	11 (0.3%)	1 (0.2%)
Cognitive impairement/psychosis	No	3300 (95.8%)	455 (95.5%)
	Yes	141 (4.1%)	21 (4.4%)
Abdominal Serositis	No	3309 (98.6%)	452 (96.1%)
	Yes	47 (1.4%)	18 (3.8%)
Trombocytic Trombopenic Purpura	No	3286 (97.8%)	452 (96.3%)
	Yes	72 (2.1%)	17 (3.6%)
Low Complement	No (never)	860 (25.5%)	70 (14.8%)
	(> 10 previous days)	1507 (44.8%)	211 (44.6%)
	(Persisting 10 previous days)	996 (29.6%)	192 (40.5%)
Anti-Ro Ab	No	2015 (60.5%)	310 (66.6%)
	Yes	1315 (39.4%)	155 (33.3%)
Secondary Sjögren	No	2850 (84.7%)	447 (93.5%)
	Yes	508 (15.1%)	31 (6.4%)
Malignant Neoplay	No	3171 (93.9%)	462 (96.2%)
	Yes	206 (6.1%)	18 (3.7%)
SLEDAI	Mean-SD	2.4 ± 3.5	3.3 ± [4.1]
	Median-range	2 [0-4]	2 [0-4]
KATZ	Mean-SD	2.4 ± 1.5	3.1 ± 1.9
	Median-range	2 [1-3]	3 [2-4]
CHARLSON	Mean-SD	2.4 ± 1.9	1.6 ± 1.2
	Median-range	2 [1-3]	1 [1-2]
Familiy SLE hystory	No	2128 (84.8%)	286 (78.7%)
	Yes	381 (15.1%)	77 (21.2%)
Diabetes Mellitus	No	3186 (94.2%)	469 (98.3%)
	Yes without impairement	164 (4.8%)	8 (1.6%)
	Yes with impairement	30 (0.8%)	0 (0%)
Dyslipemia	No	2224 (67.3%)	361 (77.6%)
	Yes	1076 (32.6%)	104 (22.3%)
Arterial Hypertension	No	2398 (70.5%)	382 (79.2%)
	Yes	1001 (29.4%)	100 (20.7%)
NSAIDs	No	907 (28.3%)	123 (27.3%)
	Sometime	1806 (56.3%)	281 (62.4%)
	At last evaluation	490 (15.3%)	46 (10.2%)
Steroids	No	450 (13.7%)	33 (7.0%)
	Sometime	1092 (33.4%)	153 (32.8%)
	At last evaluation	1721 (13.7%)	280 (60.0%)
Steroids	No	785 (22.8%)	96 (19.8%)
	Yes	501 (14.5%)	90 (18.6%)
	NS/NC	2149 (62.5%)	298 (61.5%)
Azathioprine	No	2295 (70.9%)	33 (26.8%)
	Sometime	575 (17.7%)	63 (51.2%)
	At last evaluation	364 (11.2%)	27 (21.9%)
Cyclophosphamide	No	2633 (81.3%)	296 (63.9%)
	Sometime	560 (17.3%)	154 (33.2%)
	At last evaluation	44 (1.3%)	13 (2.8%)
Mycofenolate	No	2824 (87.6%)	345 (75.3%)
	Sometime	139 (4.3%)	51 (11.1%)
	At last evaluation	260 (80.0%)	62 (13.5%)
IV IIGG	No	3093 (96.4%)	414 (90.9%)
	Sometime	109 (3.3%)	37 (8.1%)
	At last evaluation	11 (0.3%)	4 (0.8%)
Rituximab	No	3061 (94.4%)	413 (89.7%)
	Sometime	123 (3.8%)	31 (6.7%)
	At last evaluation	56 (1.7%)	16 (3.4%)
Splenectomy	No	3194 (98.6%)	445 (96.9%)
	Yes	45 (1.3%)	14 (3.0%)
Dyalisis	No	3135 (97.3%)	440 (95.0%)
	Sometime	42 (1.3%)	16 (3.4%)
	At last evaluation	42 (1.3%)	7 (1.5%)
Renal Trasplantation	No	3172 (98.6%)	444 (96.7%)
	Yes	42 (1.3%)	15 (3.2%)
Anti-resorptive therapy	No	2379 (75.5%)	360 (80.9%)
	Sometime	250 (7.9%)	37 (8.3%)
	At last evaluation	521 (16.5%)	48 (10.7%)
Statin therapy	No	2315 (74.2%)	354 (80.6%)
	Sometime	155 (4.9%)	19 (4.3%)
	At last evaluation	648 (20.7%)	66 (15.0%)
Hypoglucemiant	No	3035 (95.1%)	441 (98.6%)
	Sometime	20 (0.6%)	3 (0.6%)
	At last evaluation	134 (4.2%)	

OS5.7

Coronary-Artery Atherosclerosis in SLE patients younger than sixty years

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Premature atherosclerosis is a major cause of morbidity and mortality in patients with SLE, but little is known about the frequency, extent, risk-factors, and burden of coronary-artery disease.
Methods. We studied 223 SLE patients (95 males y 128 females) attending our outpatient clinic and 193 healthy controls, matched by age and race. Patients and controls had a standardized assessment of demographic characteristics and traditional cardiovascular risk factors. In addition, patients had an evaluation of lupus characteristics, medications, and laboratory tests including immunological, extended lipid profile, homocystein, and hsCRP. Patients and controls were screened for coronary-artery calcification(CAC) using a 64-slice Multidetector Computed Tomography and the extent of calcification was measured by means of the Agatston score.
Results. Mean (SD) age of lupus patients and controls was 32.9 (9.4) and 33.5 (9.8) years, respectively. Coronary-calcifications were detected in 25 patients (11%) and 7 (4%) controls (OR 3.35, 95% CI 1.36-9.38, p=0.004). Median calcium score in patients was 15.9 (0.2-576.8), and 7.7 (1.1-140.2) in controls. Calcifications in lupus patients and controls were detected since age 23 and 41 years, respectively. Patients had more often hypertension (30% vs 5%, p<0.001) and higher levels of homocysteine (12.3+7.9 vs 9.5+3.6, p<0.001) than controls. Logistic regression analysis showed an independent association of age, male gender and SLE diagnosis with calcifications.
Conclusions. Asymptomatic CAC is more common, extensive and presents at younger age in lupus patients than in the control group. Lupus diagnosis is an independent risk factor for coronary-artery calcification.

7 Genetics and Epigenetics

OS7.4

A genetic variation in HLA-DR region associated with hypomethylation and high expression of HLA-DRB1 and DRB5 genes contribute to enhanced autoantibody production in systemic lupus erythematosus

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Genetic variations within the HLA region have been identified as major risk loci for SLE. However the association between HLA genetic variation and autoantibody production is not well defined. In this study, we measured IgG autoantibodies against 95 self-antigens in a cohort of 212 SLE patients and 320 controls. A SNP in HLA-DR region, rs9268832, previously identified to be associated with SLE, was genotyped on all samples. Whole genome methylation and transcription analysis were perform on a subset of samples. The HLA SNP alleles and their association with DNA methylation, gene expression and autoantibody production was determined.
The SNP rs9268832 is a C/T variation and the TT allele frequency is significantly higher in SLE than controls (p<0.01). Gene expression analysis showed that the SLE patients carrying TT allele exhibited higher DRB1 and DRB5 genes expression compared with CC or CT allele carriers. The TT allele SLE patients also showed a dramatic hypomethylation on DRB1 and DRB5 genes compare

with CC individuals. Autoantibody profiling distinguished 19 highly expressed autoantibodies associated with different clinical manifestations in SLE. Among them, the anti-DNA autoantibodies (anti-dsDNA, anti-ssDNA, anti-Chromatin, anti-nucleosome) were significantly higher in TT allele SLE patients who displayed higher expression of DRB1 and DRB5 gene expression compared with CC or CT allele SLEs.
The HLA-DR risk alleles modulate HLA-DRB1 and DRB5 gene expression through hypomethylation of the CpGs in regulatory regions. The hyper expression of the antigen presenting genes could be associated with initial breach in immune tolerance to self-antigens in the risk population.

8 Oral presentations 2: Basic science

OS8.1

The oxidative burst mediates anti-inflammatory clearance of dead cells in a mouse model of Systemic lupus Erythematosus (SLE) and inflammatory arthritis

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The production of reactive oxygen species (ROS) via the oxidative burst has recently been implicated in regulation of inflammation and protection from arthritis, multiple sclerosis, and psoriasis. The aim of this project was to elucidate the impact of the oxidative burst on lupus-like autoimmunity.
The clinical course of pristane-induced lupus (PIL) was compared between WT and ROS-deficient (Ncf1**) mice by analysis of serological markers and organ involvement. *Ex vivo* phagocytosis assays and flow cytometry were employed to analyze uptake and degradation of cell debris. Formation of neutrophil extracellular traps (NETs) was monitored in blood and peritonea. Involvement of the antioxidative response was investigated by qPCR and ChIP.
Ncf1** mice developed strongly elevated levels of typical lupus-autoantibodies, *e.g.*, anti-dsDNA, anti-histone and anti-Sm/RNP, arthritis, and glomerulonephritis resulting in earlier death. We observed a preferential uptake of dead cell material but not of inert latex beads into inflammatory monocytes and granulocytes, and a dramatically reduced ability to forms NETs in Ncf1** mice. A similar phagocytosis phenotype was observed in patients with SLE. Immunoglobulin G-coating of latex beads significantly enhanced their uptake. Genes related to the antioxidative response dependent on the transcription factor NRF2 were strongly downregulated in Ncf1** mice.
Our results show that autoimmunity occurring in the ROS-deficient Ncf1** mouse gives rise to exacerbated Rupus. Aberrant phagocytosis in ROS-deficient animals caused by spontaneously occurring autoantibodies to surface molecules of dead cells and a defective regulatory antioxidative response contribute to this phenotype.

OS8.2

Aberrant microparticle and micro-RNA profiles in the circulation of SLE patients

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Despite the well-established diagnostic value of specific circulating autoantibodies in SLE there are no laboratory markers for monitoring disease activity. Also, the understanding of mechanisms leading to the sustained autoimmunity, immune complex formation, and the systemic type I interferon response in SLE is incomplete. Clearance defects have been implicated in the development of SLE and there is increasing knowledge about subcellular, circulating vesicles (including their micro-RNA (miRNA) contents) in health and disease. Therefore, in a number of studies, we have characterized circulating miRNAs and microparticles (MPs) in SLE and controls (systemic sclerosis (SSc) and healthy controls).
Altogether, we identify and quantitate more than 1000 MP-associated specific proteins and 30-40 circulating micro-RNAs in plasma samples from a total of 130 SLE patients, 120 SSc patients, and 108 healthy controls. Data show that MPs and circulating miRNAs in SLE patients are distinct from both healthy and disease controls. Specific proteins, such as galectin-3 binding protein are highly upregulated in SLE-MPs, appear to correlate with the degree of type I interferon activation, and are localized in electron-dense deposits in SLE kidneys. Immunoglobulins and complement components are also conspicuously increased in SLE-MPs, and miRNA with common targets in TGF-β signaling pathways are deregulated specifically in SLE. Our findings pave way for new candidate biomarkers, support particle clearance disturbances as a central disease mechanism in SLE, and suggest that miRNAs may hold promise as both disease markers and as the basis of developing disease-modulating medicine.

OS8.3

Modulation of deregulated chaperone-mediated autophagy by a phosphopeptide in Lupus

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The P140 peptide, a 21-mer linear peptide (sequence 131-151) derived from the snRNP U1-70K, holds a lot of promise for treating lupus patients. In a multicenter, randomized, placebo-controlled phase-IIb study, P140/Lupuzor was safe and met its primary efficacy end points in lupus patients (Zimmer *et al*., 2013). These results confirm pre-clinical data generated in MRL/lpr lupus-prone mice. The mechanism of action of P140 was further studied in this mouse model. Previous studies showed that P140 reduces autophagic flux in MRL/lpr B cells (Page *et al*., 2011). We now identify that chaperone-mediated autophagy (CMA) is hyperactivated in MRL/lpr B cells and is down-regulated after treating mice with P140 peptide. The mechanism through which P140 inhibits CMA is likely related to its ability to alter the integrity of the HSPA8/HSP90 heterocomplex of lysosomal chaperones. P140 enters MRL/lpr B-lymphocytes via a clathrin-dependent endo-lysosomal pathway and accumulates at the lysosomal lumen where it could interact with lysosomal HSPA8 and hamper its chaperone function in CMA. This correlates with the observation that P140 decreases the overexpression of LAMP2A (a rate limiting factor in CMA) in MRL/lpr B cells *in vivo*. Loss of HSPA8 chaperoning function and destabilization of LAMP2A induced by P140 may thus interfere with the endogenous (auto)antigen processing and loading to major histocompatibility complex class II molecules, leading to a lower activation of autoreactive T cells and consequently to an improvement of the autoimmune condition observed in lupus individuals. These results shed light on mechanisms by which P140 can modulate lupus disease.

OS8.4

Interferon regulatory factor-5 promotes disease in the MRL/lpr mouse model of lupus

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Interferon regulatory factor 5 (IRF5) polymorphisms are strongly associated with an increased risk of developing systemic lupus erythematosus. In mouse lupus models, IRF5-deficiency reduced disease severity, consistent with an important role for IRF5 in disease pathogenesis. IRF5 is highly expressed in B cells where it is involved in isotype switching to IgG2a and TLR-medicated activation. However, whether IRF5 contributes to lupus pathogenesis by promoting B cell differentiation or plasma cell survival in not fully understood. We generated IRF5-deficient (IRF5-/-) MRL/lpr mouse lupus model, and found that IRF5-/- MRL/lpr mice develop much less severe disease than their IRF5-sufficient (IRF5+/+) littermates. Despite markedly lower serum levels of anti-nuclear autoantibodies and reduced total splenocyte and $CD4^+$ T cell numbers, IRF5-/- MRL/lpr mice have similar numbers of all splenic B cell subsets compared to IRF5+/+ MRL/lpr mice, suggesting that IRF5 is not involved in B cell development up to the mature B cell stage. However, IRF5-/- MRL/lpr mice have greatly reduced numbers of spleen plasmablasts and bone marrow plasma cells. Serum levels of B lymphocyte stimulator (BLyS) were markedly elevated in the MRL/lpr mice but no effect of IRF5 on serum BLyS levels was seen. Overall our data demonstrate that IRF5 contributes to disease pathogenesis in the MRL/lpr lupus model and that this is due, at least in part, to the role of IRF5 in plasma cell formation. Our data also suggest that combined therapy targeting both IRF5 and BLyS might be a particularly effective therapeutic approach in lupus.

OS8.5

Detection of auto-antibodies directed to doublestranded DNA in SLE: comparison of different assays during quiescent and active disease

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Introduction. Auto-antibodies directed to doublestranded DNA (anti-dsDNA) are specific for systemic lupus erythematosus (SLE) and used in diagnosis and follow-up. Multiple assays are used without clear evidence which assay performs best.
Methods. Seven different assays were compared during lupus nephritis (n=58). The two assays with the highest accuracy to detect nephritis were selected and further tested in 152 SLE patients with quiescent disease, 40 SLE patients with active disease and 214 disease controls. Furthermore, longitudinal samples of SLE patients with and without exacerbations were examined to determine the positive predictive value of an increase for an exacerbation.
Results. Of seven assays, Farr (Siemens) and EliA (ThermoFisher Scientific) had the highest diagnostic accuracy in active nephritis (both 95%). Furthermore, sensitivity in active SLE was equal using Farr or EliA (95% vs 93%). In quiescent disease, specificity of EliA was higher (53% vs 91%). In longitudinally analyses, a 25% increase of anti-dsDNA preceded an exacerbation in 75% vs 69%, (Farr vs EliA). In SLE patients without exacerbations a rise was seen in 7% vs 13%. Rises in anti-dsDNA occurred more often prior to nephritis (n=17) compared to non-nephritic flares (n=17), which was not different between both assays (Farr: 82% and 66%, EliA: 93% and 43%).
Conclusions Farr and EliA have the highest diagnostic accuracy in detecting nephritis. However, EliA had higher specificity in quiescent disease. Both assays performed equally in predicting exacerbations. Most importantly, EliA has several advantages compared to Farr, including no use of radioactive materials and less time consumable.

OS8.6

TWEAK Receptor-Fc Suppresses Germinal Center Formation and Pathogenic B Cells in a Lupus Mouse Model via Inhibition of the TWEAK/Fn14 Pathway

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Systemic lupus erythematosus (SLE) is an autoimmune-mediated chronic inflammatory disease. Half of patients with SLE suffer from lupus nephritis, which is major cause of death in SLE. TNF-like weak inducer of apoptosis (TWEAK)/fibroblast growth factor-inducible 14 (Fn14) interactions mediate inflammatory responses that are linked to the pathogenesis of lupus nephritis. Blocking of the TWEAK/Fn14 pathway by TWEAK receptor-Fc was performed in a SLE mouse model and the likely therapeutic mechanisms were investigated.
To investigate the impact of TWEAK on B-cell differentiation in SLE, levels of AID, Blimp-1, and IRF4 messenger RNA were measured in CD19+ B cells extracted from spleen of sanroque mice and cultured with TWEAK. To identify the therapeutic effects of TWEAK receptor-Fc on SLE, sanroque mice were treated with TWEAK receptor-Fc or a control-Fc for 3 weeks. IgG, IgG1, and IgG2a levels were measured in the sera of each group. Spleens from each group were stained with antibodies against CD4, B220, GL-7, CD138, and PD-1. Kidneys were stained with H&E and PAS.
Administration of TWEAK increased the mRNA levels of AID, Blimp-1, and IRF4. Treatment with TWEAK receptor-Fc suppressed levels of IgG, IgG1 and IgG2a in sera and reduced numbers of B-, plasma-, and follicular helper T-cells (Tfh) in spleens of sanroque mice. In addition, renal protective effects of TWEAK receptor-Fc were shown.
TWEAK receptor-Fc had beneficial effects in a SLE mouse model by repressing B cells, plasma cells, Tfh, and renal damage. This suggested that the TWEAK receptor-Fc represents a potential therapeutic agent for SLE.

15 Focus on patient reported outcomes

OS15.5

Hearing the Patient Voice: Clinical Trial Simulation Guides Phase III Study Design in Systemic Lupus Erythematosus (SLE)

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Background. Patients are self-educated about their diseases and are becoming more involved in treatment choices. Rather than serving simply as trial participants, when engaged, patients become partners, contributors, and advocates.
Objectives. We sought patient views and feedback that could be employed in designing protocols and methodology for Phase III studies in SLE.
Methods. At the clinical research center of a large, private, rural rheumatology practice in the United States, AstraZeneca conducted screening and Visit-1 simulations of a mock RCT of a biologic for SLE. Patient volunteers were introduced to the mock trial, informed consent process, and screening/first dosing visit procedures. The visit structure was based on a draft Phase III protocol concept. The simulation was based on four dimensions of patient-centric care: information, communication, and education; responsiveness to needs; quality of care; and continuity/transition.
Results. Twelve female, white patients (ages 32–75 years) with mild to moderate SLE participated. Ten had participated in clinical trials. The simulation resulted in 26 recommendations. Fourteen were implemented, and six are under consideration. The 12 simulation participants indicated a desire for less waiting time/more efficient visits. They deemed PRO and HRQOL tools as easy to complete and meaningful to their experiences. They asked for provision/explanation of lab analyses; easier to understand informed consents forms; subsequent notification of randomization status; and follow up on product status, all of which were incorporated.
Conclusions. Recommendations from this initial simulation included improving and extending study team communications with patients, and decreasing post-infusion wait times.

25 Fc-gamma receptors and complement

OS25.3

Modulating Plasmacytoid Dendritic Cells for the Treatment of SLE

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Type I interferons (IFN-I) are implicated in the pathogenesis of systemic lupus erythematosus (SLE). In SLE, immune complexes bind to the CD32a (FcγRIIa) receptor on the surface of plasmacytoid dendritic cells (pDCs) and stimulate the secretion of IFN-I from pDCs. BDCA2 is a pDC-specific receptor that, when engaged, inhibits the production of IFN-I in human pDCs. BDCA2 engagement, therefore, represents an attractive therapeutic target for inhibiting pDC-derived IFN-I and may be an effective therapy for the treatment of SLE. In this study we show that BIIB059, a humanized monoclonal antibody (mAb) against BDCA2, engages BDCA2 and leads to its internalization and the consequent inhibition of TLR-induced IFN-I by pDCs in vitro using blood from both healthy and SLE donors. These effects were confirmed in vivo using a single injection of BIIB059 in cynomolgus monkeys. BIIB059 also inhibited pDC activation by SLE-associated immune complexes (IC). In addition to the inhibitory effect of BIIB059 through engagement of BDCA2, the Fc region of BIIB059 was critical for potent inhibition of IC-induced IFN-I production through internalization of CD32a.This study highlights the novel therapeutic potential of an effector competent anti-BDCA2 mAb that demonstrates a dual mechanism to dampen pDC responses for enhanced clinical efficacy in SLE. Additional data on the relevance of this dual pathway in humans will be presented.