Oral Presentations

Invited Presentations

1 History of SLE

OI1.1

A History of SLE -New insights into possible etio-pathogenesis pathways

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A standout feature of SLE is the profusion of autoantibodies and a classical example is the LE cell which is associated with antibodies to chromatin and is a highly specific diagnostic marker. The diagnostic specificity of autoantibodies is not due to high sensitivity of a single autoantibody but to a profile of several antibodies which collectively is more specific for one disease over another. The basis of autoantibody multiplicity and profile specificity had always been an enigma until the same pattern emerged in studies of autoantibodies to Tumor-Associated-Antigens (TAAs) in malignancy. In most tumors, the number of autoantibodies to TAAs range from two to six and among the targets are oncogene products and tumor suppressor proteins, where the genes are mutated and likely to be driving the autoimmune response. The requirement for multiple hits is related to an observation called 'synthetic lethality', where more than a single gene abnormality is needed for morbidity. At this time, whether gene mutations or epigenetic alterations are the drivers of the autoantibody responses in SLE is unknown.
Recent findings of autoantibodies to citrullinated proteins in RA has confirmed the studies of the late Henry Kunkel and his associates in the 1950's when they showed that rheumatoid factors had the properties of antibodies to altered IgG. It is highly convincing that RF is autoantibody to citrullinated proteins complexed to IgG, giving us the answer to the identity of the hypothetical antigen-antibody complex that drives the RF response. Thus, RA might be a two-tiered immune complex disorder, the first between citrullinated proteins and antibody and the second between RF and the first immune complex. If these considerations are correct, there should be new treatment targets as options for RA to supplement those already in practice. These insights into etiopathogenesis of SLE and RA have been provided by the immune system which is often a reflection of cellular pathways gone awry.

6 Therapy of SLE: conventional drugs

OI6.2

HCQ and adherence to therapy

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Hydroxychloroquine (HCQ) has an excellent benefit/risk ratio, and increasing evidence shows that this drug is an important medication for systemic lupus erythematosus (SLE). Its efficacy in preventing SLE flares is well demonstrated, and its other benefits, along with being inexpensive, include protection against the occurrence of diabetes, thrombotic events, dyslipidemia, and overall damage accrual in SLE patients. As a consequence, HCQ appears to have a protective effect on survival in people with SLE.
Another benefit of HCQ is due to its long half-life and to the availability of its blood assay (meaning that blood HCQ concentration can be measured). Indeed, some studies have shown that undetectable blood HCQ concentration may be a simple, objective and reliable marker of non-adherence in SLE patients. This is very important since one of the main causes of persistent SLE activity (or flares) despite treatment is the lack of adherence to the treatment since "drugs don't work in patients who don't take them". The accurate diagnosis of non-adherence may prevent to incorrectly interpret it, as a lack of response. It may then avoid an unnecessary or even dangerous treatment escalation.

7 Genetics and Epigenetics

OI7.2

From Gene discovery to Disease Mechanisms

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BANK1 is a B cell scaffold protein with ankyrin repeats involved in signaling pathways that remain unclear. Our group discovered the genetic association of *BANK1* with systemic lupus erythematosus (SLE). The risk contribution of BANK1 associated with increased expression of a full-length isoform and pinpointed a conformational protein domain coded by the second exon of the gene. This domain, a Toll-like receptor/IL-1 (TIR) is found in Toll-like receptors and TLR signaling adaptors. BANK1 deficiency reduces signaling induced by CpG *in vitro*, leading to reduction in activation of the MAPK p38 and reduced activation of MNK1/2-eIF4E translation initiation pathway. This effect leads to a decrease in the secretion of the pro-inflammatory cytokine IL-6.
Based on our *in vitro* data on CpG induced signaling, we investigated if BANK1 had effects in TLR7 signaling *in vivo*. TLR7, a nucleic acid sensing molecule is key in development of SLE. We produced crosses of Bank1-/- and the lupus B6.*Sle1.yaa*, a model with a duplicated genomic region containing TLR7/8, translocated to the Y chromosome with disease in males. Our results show that BANK1 deficiency reduces total IgG antibodies in serum, IgG2c anti-dsDNA antibodies, kidney disease and mortality. The levels of IL-6 in serum are also partially reduced. Lack of BANK1 restores mature and recirculating B cell numbers in spleen and bone marrow and modifies the presence of activity markers of B cells but not T cells.
Our results show that BANK1 disrupts TLR7-mediated signaling and supports its role as a susceptibility gene for SLE.

9 Evaluating and assessing lupus: Better tools for a better future

OI9.2

Outcome measures and trial design: pitfalls and potentials - Is the SRI of any value?

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Despite unprecedented activity and enthusiasm in the search for new, targeted therapies for systemic lupus erythematosus (SLE), only belimumab has succeeded in phase III trials and attained regulatory approval. In contrast, several large trials have not met their primary efficacy endpoints, in some cases resulting in the discontinuation of further development of potentially beneficial agents. Although many factors have likely contributed to these disappointing results, the complexity of clinical trial design continues to be a key issue. Choice of outcome measures is particularly challenging. Several disease activity measures have demonstrated validity and reliability, but there is no gold standard, uniformly accepted measure. Each has strengths and limitations. Global indices such as the SLEDAI and the BILAG have been most commonly used, and newer composite indices such as the SRI and the BICLA are being used more frequently. The SRI is a composite index in which disease improvement is measured by the SELENA SLEDAI, and worsening is measured by BILAG and physician global assessment. The success of the belimumab drug development program has spurred the use of SRI in several ongoing, large trials. These trials have enrolled hundreds of patients with heterogeneous manifestations of SLE, but at best they have achieved only modest effect sizes using variations of the SRI approach. Although statistical significance may be achieved, clinical significance remains unclear. Given our limited resource of eligible patients, we should consider other designs such as smaller trials with homogenous subgroups (*e.g.*, arthritis or rash) that would constitute a different paradigm for drug development that might enhance the likelihood of finding effective and safe therapies for SLE.

13 Regulatory T cells in SLE

OI13.1

Adaptation of proinflammatory Th lymphocytes to chronic inflammation

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Immunological memory has evolved to protect us and adapt our immune system to recurrent pathogens of the environment. However, in inflammatory rheumatic diseases, an immunological memory for persistent and autoantigens probably can drive chronic inflammation. We previously have demonstrated that memory $CD4^+$ T cells generated in protective and finite immune responses, *e.g.* against a vaccine, migrate to the bone marrow and persist there as resting cells in dedicated survival niches. In contrast, effector/memory $CD4^+$ T cells of chronic inflammation apparently reside mainly in the inflamed tissue itself. The molecular mechanisms underlying the transition of a protective, self-limiting T helper (Th) cell response to chronification of inflammatory processes are not well understood. We could show that proinflammatory Th1 cells adapt to chronic immune reactions by upregulating expression of the transcription factors Twist1 and Hopx. Twist1 downregulates the proinflammatory effector functions of Th1 cells, but Twist1 also promotes the persistence of Th1 cells in the inflamed tissue, allowing them to perpetuate inflammation. Twist1 does so by promoting expression of the microRNA miR-148a. Mir-148a inhibits expression of the proapoptotic factor Bim and thus enhances the survival of the Th1 cells. Hopx promotes the survival of Th1 cells as well. shRNA-mediated knock-down of Hopx in Th1 cells drastically reduces their ability to persist and consequently their ability to induce inflammation *in vivo*. The molecular adaptation of proinflammatory Th1 lymphocytes to repeated/chronic restimulation explains why these cells are refractory to conventional immunosuppressive therapies based on an understanding of protective immune responses. Targeting these molecular adaptations may be a way to eliminate pathogenic memory Th cells selectively, sparing protective memory Th cells.

14 Pediatric lupus

OI14.3

Outcome measures in juvenile systemic lupus erythematosus

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In the recent years there has been an important improvement of the survival of patients with juvenile systemic lupus erythematosus (SLE), which now is close to 90% at 10 years, as well as the appearance of new biologic drugs for the treatment of the disease. Parallel to this improvement there has been an increase in morbidity related to the occurrence of adverse events of medications currently used, the long term damage associated to the disease and observed in 50-60% of the patients, which include the effects on growth and on the physical and psychosocial well-being.
The improvement in survival and health related quality of life and the accompanying disease damage demand the use of validated tools to appropriately measures the short and long term outcome of juvenile SLE as well as the efficacy of treatments. This is essential in order to prevent or at least limit the accrual of irreversible damage.
This presentation will review the current evidence for the survival, the evaluation of response to therapy, the presence of damage and the effect on the physical and psychosocial well-being of children with juvenile SLE.

16 B cells as therapeutic target

OI16.1

Targeting B-cells in experimental lupus

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"How Autoimmunity Gets Started"
Activation and generation of effector T cells is a lynchpin in various autoimmune syndromes including SLE. It has long been thought that (presumably self-reactive) T cells are important for helping autoreactive B cells to expand, mature and differentiate. However, it has become increasingly clear that autoreactive T cells are involved also in direct tissue damage in organs such as skin and kidney. We have been interested in how such T cells are activated and expanded *in vivo* during lupus in a murine model. Two major cell types, DCs and B cells, could in principal be important APCs for autoreactive T cells. Their relative roles in initial self-reactive T cell activation, most likely in secondary lymphoid tissues, as well as in expansion and differentiation of such T cells in target tissues are not well defined. Moreover, self-Ags in lupus typically contain endogenous ligands for nucleic acid-specific TLRs. Such TLRs can be expressed by APCs and may govern their activation, which in turn enables them to break self-tolerance in the T cell compartment. We have been taking genetic approaches to try to shed light on these processes in vivo. I will discuss our results from studies in which we have knocked out either B cells, DCs, or key molecules in B cells or DCs in the MRL.Fas^{lpr} murine lupus model.

17 Antiphospholipid Syndrome (APS)

OI17.2

Therapy of APS. Value and evidence of anticoagulation

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Currently, there is consensus in treating patients with antiphospholipid syndrome (APS) with thrombosis with long-term oral anticoagulation and to prevent obstetric manifestations with the use of aspirin and heparin. These recommendations are based on randomized controlled trials and observational studies. Despite of this body of knowledgement, there are grey areas where evidence is scarce or it does not exist. In other words, there is a set of patients with difficult management. Some examples are patients with "seronegative" APS, those who do not display formal (clinical or laboratory) classification criteria for APS, those with recurrent thrombotic events despite optimal anticoagulation, and the treatment of clinical manifestations not included in the classification criteria such as hematologic manifestations (thrombocytopenia and hemolytic anemia), neurologic manifestations (chorea, myelitis or multiple sclerosis-like lesions), nephropathy and heart valve disease associated with antiphospholipid antibodies, and the possibility to withdrawn anticoagulant treatment in selected cases of thrombotic APS whose antiphospholipid antibodies become persistently negative.

20 Cytokines and interferons - the role of the innate immune response in SLE

OI20.2

Immune complex mediated activation of plasmacytoid dendritic cells in SLE

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A majority of patients with SLE display a dominant pattern of type I interferon (IFN) - inducible gene expression, an IFN signature. One reason for the IFN signature is the occurrence of endogenous IFN inducers consisting of immune complexes (IC) containing nucleic acid. These interferogenic ICs activate the plasmacytoid dendritic cell (pDC), which is the most potent IFN-α producing cell. Because type I IFN is an immune adjuvant and stimulate cells in both the innate and adaptive immune system, produced IFN will contribute to the disease process. There are several reasons behind the continuous activation of the type I IFN system in SLE, besides the presence of self-derived type I IFN inducers. Thus, SLE susceptibility genes within the type I IFN signaling pathway can pro-

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.