RP and for prevention of DUs onset and treatment of PAH, both intravenous prostanoid iloprost (ILO), and the dual endothelin-1 receptor antagonist (ERA) BOSE are used, respectively [10]. Bosentan seems to block pathogenic activities of Endothelin-1, the endothelial derived mediator determining both vasoconstriction and also the fibrosis genes induction [11–14].
Previous long-term follow up studies, showed that treatment with BOSE in combination with ILO interferes with progression of nailfold microvascular damage, evaluated through both capillary number semi-quantitative scoring at NVC and fingertip blood perfusion (FBP) at LDF [15,16].
In particular, an open label, prospective study of 4 follow up years showed that long-term treatment with BOSE added to ILO infusions administered quarterly in SSc patients, exerts a remodelling effect on structural and functional microvascular alterations and on stabilization of lung function, compared to ILO mono-therapy [17].

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SP0177 NEW APPROACHES BY TARGETING SOLUBLE MEDIATORS

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Although the aetiopathogenesis of systemic sclerosis (SSc) remains incompletely understood there is now sufficient knowledge about the pathobiology of the disease and mechanisms underlying development of fibrosis, autoimmunity and vasculopathy to permit informed selection of candidate soluble mediators that may be important drivers of the disease. This has permitted testing of potential targeting approaches in preclinical models and in vitro tissue culture systems. The data from these studies has informed understanding of the disease and has started to be translated into clinical trials that test hypotheses in vivo in patients. This approach has in turn fueled the concepts of reverse translation that are being applied to further understand SSc mechanisms in model systems and observational cohort studies. Soluble mediators that have emerged as strong targets for therapeutic intervention include TGFbeta superfamily members, connective tissue growth factor, IL13, IL4 and IL6. Studies of agents that target these proteins have been proposed or undertaken. Targeting TGF-beta appears to have benefit for skin thickening and attenuate some of the characteristic TGF-beta regulated genes and proteins in skin. However, the most encouraging data have emerged from targeting the IL6 axis using anti-IL6R neutralizing antibodies. This approach was promising in a Phase II study and further trials are ongoing. Interestingly this approach appears to attenuate macrophage gene expression signatures in the skin, may prevent worsening of lung fibrosis and showed significant benefit in the skin by biomarker analysis and a strong trend of benefit over 48 weeks for skin sclerosis score. Other small clinical trials testing TNF-alpha blockade have been more disappointing. Finally, it is possible that soluble mediators may be identified that directly attenuate the fibroproliferative mechanism of SSc. Experimental studies have suggested that increasing alpha-MSH may have benefit for skin fibrosis in a small controlled clinical trial. Clinical trial design is critical to the success and interpretation of studies targeting soluble mediators to define target engagement, mechanism of action, and possible clinical benefit. Advances in trial design are facilitating progress and it seems likely that, as in other rheumatic diseases, targeting key soluble mediators will become a therapeutic reality of the next few years. Defining the place of such approaches compared to other emerging treatment strategies will remain challenging.

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SATURDAY, 17 JUNE 2017

How diet influences musculoskeletal diseases

SP0178 GUT DYSBIOSIS AND OTHER CHALLENGES PRECIPITATE ARTHRITIS

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Environmental factors contribute to development of autoimmune diseases. For instance, human autoimmune arthritis can associate with intestinal inflammation, cigarette smoking, periodontal disease, and various infections. The cellular and molecular pathways whereby such remote challenges might precipitate arthritis or flares remain unclear. We have defined many of the pathways in the gut that contribute to homeostasis, particularly GPCRs such as GPR43 and their ligands the short chain fatty acids. Such receptors and their ligands are anti-inflammatory. To probe peripheral inflammation connections to arthritis, we used a transfer model of self-reactive arthritis-inducing CD4 cells from KRNtg mice that, upon transfer, induce a very mild form of auto-inflammatory arthritis in recipient animals. This model enabled us to identify external factors that greatly aggravated disease, such as microbiota effects or disruption of gut homeostasis. We show that several distinct challenges precipitated full-blown arthritis, including intestinal inflammation through DSS-induced colitis, and bronchial stress through Influenza infection. Both triggers induced strong IL-17 expression primarily in self-reactive CD4 cells in lymph nodes draining the site of inflammation. Moreover, treatment of mice with IL-1b greatly exacerbated arthritis, while transfer of KRNtg CD4 cells lacking IL-1R significantly reduced disease and IL-17 expression. Thus, IL-1b enhances the autoaggressive potential of self-reactive CD4 cells, through increased Th17 differentiation, and this influences inflammatory events in the joints. We propose that diverse challenges that cause remote inflammation (lung infection, colitis, gut dysbiosis) result in IL-1b -driven Th17 differentiation, and this precipitates arthritis in genetically susceptible individuals. Thus the etiology of autoimmune inflammatory arthritis likely relates to diverse triggers that converge to a common pathway involving IL-1b production and Th17 cell distribution.

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SATURDAY, 17 JUNE 2017

Can targeting disease activity in hand osteoarthritis improve our treatment in the 21st century

SP0179 WHAT IS DISEASE ACTIVITY IN FINGER OA?

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Osteoarthritis of the interphalangeal finger joints constitutes one of the most prevalent musculoskeletal diseases with variable clinical impact ranging from nearly asymptomatic to severe inflammatory pain in and around affected joints, presence of soft tissue and bony swelling, stiffness and gradual loss of function. Current therapeutic options are limited to analgesic treatment but research on targeted therapies is increasing.
In order to improve the current treatments, a critical appraisal of the needs for improvement in finger OA is needed and how disease activity is best defined.
Assessing disease activity or joint activity in finger OA is challenging: disease activity can comprise pain, inflammatory activity and structural damage.
In clinical practice, a combination of patient-reported (e.g. visual analogue scale or Likert scale pain), more objective and performance-based measures (e.g. grip strength) are used to assess and follow disease activity. In clinical research, pharmacological trials and epidemiological studies, a standardized approach to assess the disease activity is necessary to estimate the burden of disease and to evaluate the efficacy of potential new treatments. The instruments being used, depend mostly on the aim of the study or research question. In case structural disease progression is being studied, imaging-based outcome measures are mostly used. Structural changes can be assessed on joint level or on patient level, both by conventional radiographs, ultrasound and magnetic resonance imaging. Several imaging based outcome measures and scoring systems are being suggested but true consensus about the instruments of preference is still lacking. Therefore, further validation of these instruments is warranted.
This lecture will give an overview of the current instruments to measure activity in finger OA in several domains and discuss its strengths and limitations.

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SP0180 BIOLOGICS AND OTHER INFLAMMATORY THERAPIES IN FINGER OA. WHAT HAVE WE LEARNED?

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Hand osteoarthritis (HOA) is the most frequent form of osteoarthritis. A subset of digital hand OA is marked by an “inflammatory” like presentation with painful interphalangeal joints, refractory to NSAIDS and analgesics.

This clinical form of OA may be associated with a so called "erosive" radiographic aspect marked by subchondral erosions of the finger joints and ankylosis. Many mediators of inflammation have been involved in the pathogenesis of osteoarthritis such as prostaglandin E2, free radicals and main cytokines (IL1B, IL6, and TNFa). Using Doppler power ultrasonography and magnetic resonance imaging, it has been shown that synovitis is frequently associated with HOA and correlates with pain and with disease progression.
Taking all those considerations together, it appears logical to target synovitis in HOA, especially with an erosive form.
Because erosive hand OA is a polyarticular disease, the treatment is more systemic than local.
Local or oral NSAIDS are out of scope because this presentation focuses on patients with HOA non responders to analgesics and NSAIDS. So far, none of the disease modifying drugs such as methotrexate has proved its efficacy.
Regarding biologics, several strategies have been approached. The first biotherapy used in HOA was IL2 receptor plus hydroxychloroquine in a very limited number of patients. Then and more recently, anti-TNFa strategy has been tested in well done RCT, in painful hand OA: one with adalimumab over a year, one with adalimumab 40 mg with 2 sub-cutaneous injections, one using Etanercept (50 mg/week 24 weeks and then 25 mg/week the next 24 weeks). None of those anti-TNFa blockers demonstrated a structural or an analgesic effect. However in the long term trial published by Verbruggen G, the incidence of new erosive lesions was decreased in Adalimumab group compared to placebo, only in a subgroup of patient with clinically inflamed IP joints.
Using anti-IL1B strategy, a decrease in pain has been observed in 3 patients using daily subcutaneous injection of Anakinra (100mg) over 3 months ( ).
In this Eular meeting a double inhibition of IL-1 Beta and IL-1 Alpha (using a monoclonal antibody directed against both cytokine) failed to demonstrate any benefit compared to placebo injection over 26 weeks.
Finally anti-IL6 strategy has been presented in this 2017 Eular meeting in a limited number of patients (n=18) with erosive HOA. Using monthly IV perfusion, the authors showed an improvement in pain level and functional status.
Conclusion: though anti-inflammatory strategy in painful HOA is logical, no treatment so far has been able to demonstrate a beneficial effect. Further studies should contemplate either news targets, or new modalities of repeated injections and should be adapted according to the phenotype of pain.
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Why we do develop autoimmunity

SP0181 FAILURE OF NATURAL REGULATORY AUTOANTIBODY NETWORK AS CAUSE OF AUTOIMUNITY

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The role of autoantibodies in normal physiology is under debate. In investigating autoantibody (aab) concentrations against G protein-coupled receptors (GPCR) in different autoimmune diseases, we found both increased and decreased aab concentrations, which suggests physiological anti-GPCR aab levels may be dysregulated in autoimmune diseases. During our analysis of healthy donor antibodies to 16 GPCR and 15 growth factors and related signaling molecules, we discovered several clusters of correlations in these antibody concentrations. Possible functional interactions of these 31 autoantibody target molecules were studied by STRING, DAVID, and enriched Gene Ontology analyses. Through these analyses, a network of GPCR, growth factors, and signaling molecules with endothelin receptor type A (ETAR) in the center was revealed. Migration and locomotion were suggested to be the most significant functions regulated by the antibody network. Accordingly, IgG from healthy donors induced both IL-8 expression by peripheral blood mononuclear cells (PBMCs) as well as migration of neutrophils and tumor cells, which was specifically diminished by the ETAR inhibition. These data supports a change of paradigm from the notion that autoantibodies are an exclusive autoimmune phenomenon to the concept that they are part of the normal human physiology, which become dysregulated under the influence of different factors and subsequently cause autoimmune diseases.
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SP0182 ALTERATIONS IN THE ANTIBODY REPERTOIRE AND SUGAR MODULATION AS CAUSE FOR AUTOIMMUNITY

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Many auto-immune diseases are hallmarked by the presence of auto-reactive B cells that can develop into autoantibody-secreting plasma cells. In most cases, the secreted autoantibodies have extensively been studied in their role as disease-associated biomarkers, and for some, specific pathogenic effector functions have been demonstrated supporting the use of interventions that target the plasma cell compartment. In other cases such as rheumatoid arthritis (RA), however, the pathogenicity of specific autoantibodies is less clear, and the therapeutic efficacy of B cell depleting therapy that spares the plasma cell compartment indicates that auto-reactive B cells themselves can have pathogenic effector functions that contribute to disease. In this context, it is of great interest to understand the mechanisms that allow auto-reactive B cells to emerge from the naïve repertoire, a process that marks the onset of systemic autoimmunity and frequently precedes the clinical onset of disease.
RA is characterized by a remarkable appearance of autoantibodies that target post-translational modifications of proteins, of which anti-citrullinated protein antibodies (ACPA) display the highest specificity for disease. In addition, ACPA associate with active destructive RA and pose individuals with arthralgia at-risk for progression towards arthritis. We recently found that ACPA display significant alterations with regard to the glycosylation of both the Fc-tail as well as the F(ab)-domain. While the ACPA-IgG Fc-tail loses galactose and sialic acid residues prior to the onset of arthritis, a process associated with enhanced inflammatory antibody activity that occurs potentially under the influence of IL-17 producing T cells, ACPA also carry abundant glycans in the antigen-binding region of the F(ab) domain. These latter glycans are reminiscent of F(ab)-glycans found in follicular lymphoma B cells, and were here identified as N-linked, biantennary glycans composed of a remarkably high frequency of sialic acid residues. Notably, N-glycosylation requires the presence of glycosylation consensus sequences in the protein. As such sequences are normally scarce in the germline encoded variable regions of B cell receptors (BCR), the acquisition of F(ab)-glycans requires mutations of the amino-acid sequence to generate N-glycosylation sites. This process is mediated by somatic hypermutation, which is mainly induced by T cells that provide help to B cells. As >90% of all ACPA-IgG molecules carry such F(ab)-linked N-glycans, and as protective antibodies in the same individuals and many autoantibodies in other diseases do not show this feature, it is conceivable that the acquisition of F(ab)-glycans by ACPA-IgG is a T cell –mediated process that provides a selective advantage to ACPA-expressing B cells. This notion is supported by the observation that additional F(ab)-glycans are not found on ACPA-IgM. How F(ab)-glycans facilitate the emergence and/or expansion of auto-reactive B cells in this context, however, remains unclear. Using recently developed technology to identify and isolate citrullinated antigen-specific B cells from patients, we can now address this question by studying the frequency and localisation of N-glycosylation sites in the antibody repertoire and by studying the phenotype and functional characteristics of ACPA-expressing B cells. Together with our investigations on the modulation of ACPA Fc-glycans, these studies provide a deeper understanding of mechanisms that allow the development of autoimmunity as such, and of the mechanisms that underlie the progression from systemic autoimmunity towards overt autoimmune disease.
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SP0183 FAILURE OF TREG CONTROL TO UNDERSTAND AUTOIMMUNITY

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Regulatory T cells (Treg) expressing the transcription factor FoxP3 are crucial for the maintenance of immunological tolerance to self and thus for the control of autoimmunity. There is strong evidence that numeric or functional defects in Treg cell biology are involved in the pathogenesis of particular autoimmune diseases. Here we will focus on the fundamental role of Treg cells in diverse autoimmune and rheumatic diseases and will explain how a failure of the Treg cell system can evolve and contribute to the development of such diseases. Furthermore, therapeutic approaches aiming to overcome these Treg cell defects and to restore Treg cell activity in the patients will be discussed.
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SP0184 ROLE OF MICROENVIRONMENT AND ENDOGENOUS PATHWAYS TO BREAK TOLERANCE

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Break of tolerance driving autoimmune disease is initiated by a combination of predisposing genetic and environmental factors resulting in self-perpetuating chronic inflammation and tissue damage. Effector molecules and cells targeting tissues housing the inciting autoantigen(s) maintain tissue damage and the autoimmune response. Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) is a prototypical autoimmune disease characterized by extravascular necrotizing granulomatous inflammation and a systemic autoimmune vasculitis associated with anti-neutrophil cytoplasmic autoantibodies specific for the neutrophil- and monocyte-derived serine-protease proteinase 3 (PR3-ANCA). GPA is strongly associated with *HLA-DPB1*0401* polymorphisms. Its association with the *R620W* variant of the *PTPN22* gene has been linked to reduced immune-regulatory interleukin (IL)-10 transcription. Epidemiological studies and molecular analysis of immune cells suggests a multifactorial pathogenesis of GPA, in which a potentially metachronous and individually varying sequence of infectious agents contributes to the break of tolerance and chronic inflammation sustaining autoimmunity in GPA.