Dear Reader,

We are happy to present the third issue of the ‘Press Review and Journal Club’ newsletter that is part of a EULAR School of Rheumatology educational initiative, the EULAR-EMEUNET Journal Club. This newsletter includes an overview of relevant articles published both in top rheumatology journals and in major general medicine journals during the previous 4 months. The article selection includes translational and clinical research papers as well as systematic literature reviews and meta-analyses and you will find a hyperlink that will redirect you to the journal page to read the article in full. Among these, one article has been selected by the School of Rheumatology faculty to be discussed in a few weeks in an online Twitter Journal Club. Another article, the ‘EMEUNET Paper of the Month’ has been selected by popular vote through a survey circulated among the rheumatology community. For the latter, a video interview with the first author explaining the main findings of the paper is available on our YouTube channel.

The Journal Club aims to bring together rheumatologists, clinical researchers, basic scientists, and anyone else who might be interested in the topic, to participate in an online, lively discussion. These 'meetings' take place on Twitter at pre-specified times and dates, the next is planned on the 21st February 2018 at 8:30 PM GMT (9:30PM CET). ‘Save the date’ reminders will be sent in advance. Where possible, key authors involved in selected articles will be invited to participate. The selected article will be freely accessible for a limited period of time on the journal website. Details of the article selected and of the Journal Club are included on page 3 of this issue.

We hope that you will enjoy reading this newsletter and look forward to 'seeing' you soon at our Twitter JC meeting!

Alessia Alunno, Elena Nikiphorou, Richard Conway, Mary Canavan, Santiago Rodrigues Manica, Sarah Wade, and Casper Webers,
on behalf of the EMEUNET Newsletter and Social Media Subgroups

DIRECTORY

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Serum anti-citrullinated peptide antibodies (ACPAs) are present in many patients with rheumatoid arthritis (RA) and may predict more severe, erosive disease. The authors aimed to assess synovial tissue immunophenotype according to ACPA status and whether this predicted erosive disease or treatment response. Synovial biopsy samples from consecutive RA patients were analysed. 123 subjects were included. ACPA+ patients has higher synovial levels of CD19+ B cells as well as CD3+ and CD8+ T cells. Lymphoid aggregates of CD19+ B cells were significantly higher in ACPA+ patients and this was associated with serum levels of the B cell chemoattractant CXCL13. CD19+ B cells and CD4+ T cells were increased in those with erosive disease. The level of CD3+ T cell infiltrates at baseline predicted EULAR response while CD68+ macrophage and CD8+ T cell levels predicted response to TNF inhibitors. In summary, the authors have demonstrated important differences in synovial tissue cellularity according to ACPA status, which predict treatment response.

The online Journal Club will take place on:
Wednesday 21st February 2018 at 8:30PM GMT (9:30PM CET)
-duration 1 hour-

Follow the accounts @EULAR_JC, @eular_org and @EMEUNET

Use the hashtag #EULARJC to follow and join the discussion

Tadej Avčin
Ljubljana University
Slovenia

Xenofon Baraliakos
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Save the Date!
Impact of Obesity and Adiposity on Inflammatory Markers in Patients With Rheumatoid Arthritis.

*Arthritis Care Res (Hoboken)*. 2017;69:1789-1798 (full text here)

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are important biomarkers used to measure disease activity in rheumatoid arthritis (RA). This study aimed to assess the influence of obesity on ESR and CRP. Body mass index (BMI) and DXA-measured fat mass index associations with ESR and CRP were assessed using the Body Composition cohort (n=451), and the Veteran Affairs Rheumatoid Arthritis (VARA) registry (n=1652). Obesity was found to be associated with CRP, and to a lesser extent ESR, levels in women with RA and in the general population. This effect was particularly marked in those with severe obesity (BMI ≥35). This association was related to fat mass index and not to RA disease activity. In contrast, in men with RA lower BMI was associated with higher CRP and ESR.

Explore this paper in greater detail through an exclusive interview with study first author Dr Michael George.

Interview available [here](#)

The EMEUNET Paper of the Month is selected by an online vote of selected articles from each of the rheumatology journal contributions.

**Watch out for our next poll!**
Mary is a postdoctoral researcher in molecular rheumatology in Trinity College Dublin. She completed her PhD in Immunology in Dublin City University and is now completing her second postdoctoral research fellowship. Her research interests include examining immune infiltration, in particular dendritic cells and T cells in inflammatory arthritis, and the effects of the joint microenvironment on immune cell activation. Mary is co-leader of the EMEUNET Social Media Subgroup and leader of the ARD-EMEUNET social media collaboration.

Santiago is a rheumatology fellow at the Hospital Egas Moniz, CHLO and a researcher at CEDOC (from NOVA University) in Lisbon, Portugal. His main scientific interests are outcomes research and epidemiology in RMDs. He enjoys taking new challenges, travelling, and learning new languages. Santiago is co-leader of the EMEUNET Social Media Subgroup and a member of the Peer Mentoring Subgroup.

Kerschbaumer et al studied the effect of structural damage on functional disability in psoriatic arthritis (PsA). Their key message is, that when targeting functional scores in PsA patients, one cannot be over-ambitious in patients who already have some extent of structural damage (pp 2038-2045). It is well appreciated that both PsA and psoriasis harbour a large genetic component which influences disease susceptibility. Understanding genetic factors that may differentiate PsA from psoriasis is important not only for screening purposes but also for our understanding of the unique disease mechanisms involved. A study by Bowes et al aimed to address this by identifying genetic variants within the major histocompatibility complex (MHC) that could differentiate patients with PsA from patients with cutaneous psoriasis. The authors show, for the first time, that HLA-C*06:02 is not associated with PsA and that amino acid position 97 of HLA-B differentiates PsA from cutaneous psoriasis (pp 1774-1779). In systemic lupus erythematosus (SLE) Md Yusof et al used B-cell biomarkers to predict and manage primary and secondary non-response to rituximab, using the BILAG score as primary outcome. The results appeared promising in 125 patients treated with rituximab over 12 years (pp 1829-1836). New European recommendations for the diagnosis and treatment of childhood-onset lupus nephritis were also published by the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative (pp 1965-1973). Lundberg et al presented the new 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. The new criteria have been partially validated and performed better than pre-existing criteria, but still require full validation (pp 1955-1964). Reginster et al presented the results of the CONCEPT RCT of pain control in symptomatic knee osteoarthritis (OA). The authors showed that after 6 months chondroitin sulphate is superior to placebo and similar to the NSAID celecoxib, reducing pain, and improving function. Given the superior safer profile of chondroitin sulphate to NSAIDs, this may have implications on their recommendation as first line agents in the future (pp 1537-1543).
Ez-Zatoumi et al studied the performance of MRI of the spine in classifying axial spondyloarthritis (axSpA) patients from two cohorts of patients with chronic back pain (SPACE and DESIR) with a maximum symptom duration of 3 years. A positive spine MRI was rare in patients without sacroiliitis on sacroiliac joint (SIJ) MRI and SIJ radiography, providing evidence that addition of MRI of the spine as an imaging criterion to the ASAS axSpA criteria has a low yield of newly classified patients and is therefore not recommended (pp 1731-1736). Breban et al evaluated a possible role of the gut microbiota in the pathogenesis of spondyloarthritis. In both rheumatoid arthritis and SpA the authors noted altered microbiota composition or dysbiosis compared with healthy controls. The microbiota biodiversity was significantly restricted in both disease groups while an increased abundance of ruminococcus gnavus was identified in SpA. This study provides evidence for commensal involvement in autoimmune diseases such as SpA (pp 1614-1622). Mercer et al published a paper on the safety of tumour necrosis factor inhibitors (TNFi) in rheumatoid arthritis (RA) regarding the risk of lymphoma. The authors analysed data from 12 European registers. Evidence is growing that the risk of lymphoma is more dependent on RA itself, especially on disease activity, than on RA treatment. The spectrum of lymphoma subtypes does not seem to be altered by TNFi (pp 2025-2030). Arts et al showed that disease activity control (DAS28 ≤3.2) in RA can reduce cardiovascular risk, strengthening the rationale for the use of tight control strategies in daily clinical practice to achieve low stable disease activity or remission in these patients as soon as possible (pp 1693-1699). Interestingly, a new study by Filer et al identified a transitional fibroblast early in RA disease. Fibroblasts in RA are known to have a proliferative and pro-inflammatory phenotype which contributes to disease. These fibroblasts appear to be intrinsically programmed as they remain active in the absence of pro-inflammatory stimuli. The authors of this study however show for the first time that these synovial fibroblasts undergo two distinct functional changes. Firstly and early in disease, they lose their immunosuppressive capabilities and subsequently as disease progresses they acquire a more stimulatory and pro-inflammatory phenotype (pp 2105-2112). Finally, a recent report by Tak et al (pp 1924-1930) examined B cell clones in the peripheral blood in individuals at risk of developing RA. In a prospective cohort study involving 21 individuals at risk for RA based on the presence of autoantibodies, the BCR repertoire of paired peripheral blood and synovial tissue samples was analysed. They identified dominant BCR clones which were present in the peripheral blood and found these clones to predict the onset of clinical signs and symptoms of RA.
Kurosawa et al (pp 2193-2202) identified the CXCR4/CXCL12 pathway as an important regulator of T cell infiltration in allograft (aly/aly) mice, a model of Sjögren's syndrome (SS). Effector memory T cells from aly/aly mice displayed enhanced migratory capacity ex-vivo in response to the potent chemokine CXCL12, expression of which was elevated in SS targeted tissues. Blockade of the CXCL12 receptor, CXCR4, significantly decreased T cell infiltration, therefore warranting further investigation. Asquith et al (pp 1984-1995) examined the effects of HLA-B27 expression on the intestinal metabolome, as HLA-B27-associated spondyloarthritides are associated with an increased risk of bowel inflammation. Metabolomic profiling of caecal content from HLA-B27/β2 m-transgenic rats was examined by mass spectrometry, wherein 254 metabolites were differentially expressed. Interestingly, propionate-treated HLA-B27/β2 m-transgenic rats showed reduced inflammation, indicating short-chain fatty acid therapy as an alternative therapeutic mechanism for B27-dependent inflammation. Huang et al (pp 1762-1771) tested the effect of FLICE-like inhibitory protein (FLIP) on tissue resident macrophage phenotype in the K/BxN serum model of arthritis. While FLIP deletion in myeloid cells resulted in an initial exacerbation of disease severity, ultimately disease resolution was improved. The authors report that reduction of FLIP promotes synovial enrichment of anti-inflammatory F4/80 high macrophages, thereby suppressing inflammation and promoting resolution. In osteoarthritis (OA) van den Bosch et al (pp 1978-1983) investigated the pathogenic mechanisms of Wnt signalling. Using both human samples and mouse knee joints, the authors reported elevated Wnt expression in the knee joint which they found to promote the expression of matrix degrading enzymes (MMPs), an effect which was attenuated by inhibition of Wnt signalling. In rheumatoid arthritis (RA), targeting both TNF and IL-17 could control disease activity in those who do not respond adequately to a TNF inhibitor alone. Fleischmann et al (pp 2283-2291) demonstrated that the safety and tolerability of ABT-122, an immunoglobulin targeting TNF and IL-17A, was similar to placebo in two phase I studies. The efficacy of ABT-122 in RA is currently under investigation. Weinblatt et al (pp 1937-1948) compared the efficacy and safety of full-dose continuation, tapering, or withdrawal of certolizumab in early RA patients who had previously received full-dose certolizumab for 52 weeks and experienced sustained low disease activity (LDA). The proportion of patients that maintained LDA (DAS28-ESR ≤ 3.2) during weeks 52-104 did not differ significantly between those who continued certolizumab (48.8%) and those who stopped (39.2%). The results suggest that tapering certolizumab provides similar control of disease compared to full-dose continuation.
In clinical practice, managing biological DMARDs in patients undergoing elective surgery can be challenging. George et al (pp 1845-1854) demonstrated in a retrospective, propensity-adjusted analysis that receiving infliximab within 4 weeks prior to elective hip or knee arthroplasty, compared to 8-12 weeks prior to surgery, was not associated with an increased risk of hospitalised infection within 30 days or prosthetic joint infection within 1 year. Among other variables explored, glucocorticoid use was an important risk factor for post-operative infection. Carpenter et al (pp 1809-1817) investigated 5-year radiographic progression in early rheumatoid arthritis (RA) in two cohorts. As expected with advances in treatment, radiographic progression was significantly less in the recent cohort (2002-2013) compared to the older cohort (1986-2001). Interestingly, rheumatoid factor was no longer a predictor of clinically meaningful radiographic change in the recent cohort. In an observational study, George et al (pp 1789-1798) observed that increased BMI was associated with higher CRP levels in women with RA and in the general population. This association was related to fat mass and not to disease activity. An unexpected (and partially unexplained) finding was that in men with RA, but not in the general population, low BMI was associated with higher CRP levels. In psoriatic arthritis (PsA), Mease et al (pp 1692-1699) identified enthesitis and dactylitis, found in 26% and 15% of PsA patients respectively, as key contributing risk factors for greater disease activity and inflammatory burden. Consistent with this, higher rates of patient reported pain, fatigue, and impaired activity were also reported, thus highlighting the importance of characterising and effectively managing these manifestations. Until now, data on adult outcomes of juvenile-onset systemic lupus erythematosus (SLE) has been lacking. Lim et al (pp 1627-1635) showed in a longitudinal study that damage (assessed by the SDI, a measure of irreversible damage in SLE) continued to accumulate over the entire disease course into adulthood (no “plateau effect”). Both prior clinical characteristics and therapeutic exposures predicted change in damage trajectories. Rogers et al (pp 1909-1914) examined the clinical phenotype of dermatomyositis patients positive for anti-nuclear matrix protein 2 (anti-NXP-2) antibodies. Data was analysed from 178 patients of which 11% were NXP-2 positive. Upon initial analysis NXP-2 positive patients experienced milder skin disease. In contrast, greater systemic phenotypes including dysphagia, myalgia, peripheral oedema, and calcinosis were associated with NXP-2 positivity.
Van der Zee Neuen et al used data from the COMORA study to explore whether country of residence or specific country characteristics are associated with work outcomes in rheumatoid arthritis (RA). They observed substantial between country differences. Lower economic wealth and human development countries were associated with worse employment and higher absenteeism, but lower presenteeism (19:216). McQueen et al compared changes in MRI detected inflammation on treatment escalation in a real-world RA cohort escalating to conventional and biologic DMARDs. The association was significant but relatively weak (Spearman’s 0.36, p = 0.003), suggesting that MRI targets cannot yet be advocated as outcomes for treat-to-target escalation (19:241). Sato et al (19:263) examined the pathogenic role of adipokines in RA. Resistin, an adipokine, is known to be increased in the serum and synovial fluid in RA. The authors found that the expression of resistin was increased in synovial tissue, and that stimulation with resistin increased the production of chemokines by synovial fibroblasts via CAP1. These results suggest that resistin may contribute to cell infiltration into synovial tissue through chemokine production. Le Goff et al compared the 2002 AECG and 2016 ACR/EULAR classification criteria in a patient cohort with suspected primary Sjögren’s syndrome (pSS). Agreement between both criteria sets was excellent with the ACR/EULAR criteria having slightly better sensitivity and classifying some patients without sicca symptoms as having pSS. The inclusion of salivary gland ultrasound in the ACR/EULAR criteria further improved their sensitivity (19:269). Previous studies have demonstrated that synovitis contributes to the development of inflammatory osteoarthritis (OA) and specifically that alarmins such as S100A8/A9 can contribute to this synovial inflammation. A recent study by Cremers et al (19:217) explored the involvement of S100A8/A9 in the recruitment of monocyte subpopulations into the synovium in inflammatory OA and report that prolonged S100A8/A9 production during induction of inflammatory OA locally leads to the recruitment of predominantly Ly6Chigh monocytes into the joint. Finally, Ceeraz et al (19:270) examined the role of the immune checkpoint inhibitor V domain-containing Ig suppressor of T-cell activation (VISTA) in a collagen antibody-induced arthritis model (CAIA). Immune checkpoint inhibitors are considered of high importance in maintaining tolerance and therefore preventing excessive immune responses. This study concluded that VISTA expression supports immune complex inflammation in animal induced arthritis and that VISTA supports optimal responses to C5a and modulates macrophage responses to immune complexes.
Using the **collagen induced arthritis model** (CIA) Tao et al (pp 1804-1813) reported increased expression of miR-106b, which positively associated with bone loss and immune cell infiltration. Intra-orbital injections of a lentiviral-mediated miR-106b inhibitor significantly decreased disease scores, joint destruction, macrophage differentiation, inflammatory cytokine expression, and systemic inflammation, thus indicating a new treatment approach. Baldwin et al (pp 1607-1617) examined the expression of atypical chemokine receptor 2 (ACKR2) in a variety of arthropathies including early **rheumatoid arthritis** (RA), established RA, and **psoriatic arthritis** (PsA). The authors reported elevated expression of ACKR2 in the peripheral blood and synovium, particularly in T cells and macrophages, of inflammatory arthritis patients. Whilst the exact mechanism contributing to elevated ACKR2 remains to be elucidated, cytokines present in a pro-inflammatory micro-environment, including IL-6, IL-1β, and TNF-α appear to play a role. Further work aims to characterise the pathological function of the ACKR family in inflammatory arthritis. Patients with RA are at increased risk of cardiovascular (CV) disease. In an observational study by Van den Oever et al (pp 1472-1478), 53% of patients had high CV risk. Preventive CV treatment was indicated in 69% of patients, but of these 42% received inadequate treatment and 40% received no preventive treatment at all. The authors call for better awareness and management of CV risk in RA. A systematic review of epidemiological studies of **systemic lupus erythematosus** (SLE) by Rees et al (pp 1945-1961) showed that the prevalence of SLE might be increasing over time. Despite substantial variation in the reported incidence and prevalence of SLE worldwide, there remained a female predominance across all nationalities. The authors emphasize the lack of, and need for, epidemiological SLE studies in Africa. In practice, discriminating between SLE-related and SLE-unrelated neuropsychiatric (NP) events is a challenge. Magro-Checa et al (pp 1676-1683) investigated reassessment of NP events in SLE to provide insight in misclassification of events. In their prospective study, reassessment of NP events revealed that 14% were initially misattributed to SLE. The authors propose multidisciplinary reassessment as the reference standard in NPSLE diagnosis. Gan et al (pp 2229-2236) investigated whether high levels of omega-3 fatty acid (n-3 FAs) reduced the risk of anti-CCP positive healthy control subjects transitioning to **inflammatory arthritis** (IA). Subjects with higher baseline levels of n-3 FAs, including docosapentaenoic acid and docosahexaenoic acid, showed lower odds of transitioning to IA, therefore warranting further investigation of n-3 FAs for the prevention of IA in at risk individuals.
Harvard et al (pp 1436-1444) evaluated a recently developed system to classify adherence to recommendations for TNFi use in axial spondyloarthritis (axSpA). They compared outcomes in patients grouped by adherence to TNFi recommendations (based on timing of TNFi use in relation to disease activity). The effect of adherence was very sensitive to the definition of adherence used, and the classification system had substantial limitations. Ultimately, there remains an urgent need to improve methods to measure adherence to axSpA TNFi recommendations. Vodnizza et al (pp 1355-1361) investigated how body composition affects TNFi response in biologic-naive patients with ankylosing spondylitis. Higher fat mass at baseline was associated with a lower probability of TNFi response (defined as ASDAS-CRP and BASDAI change). These findings support the hypothesis that adipose tissue has an influence on inflammatory processes. In addition, as women had higher fat mass, this might explain why their TNFi response rates are generally lower. Tillet et al (pp 1445-1452) investigated the efficacy of existing composite measures in representing treatment outcomes important to patients with psoriatic arthritis (PsA). By evaluating 31 PsA patients across 4 hospital sites, the authors identified pain and fatigue as the most highly ranked desired targeted outcomes for PsA patients receiving treatment but these are poorly identified in existing composite measures. As temporal artery biopsy, the gold standard for diagnosis of giant cell arteritis (GCA), can give false-negative results, further diagnostic tests such as PET/CT imaging are potentially of value. Clifford et al (pp 1859-1866) investigated PET/CT in GCA patients with positive and negative biopsies, and in controls. Despite higher PET/CT scores in GCA patients, sensitivity and specificity were low (71% and 64%). Notably, GCA patients received glucocorticoids prior to PET/CT. Using the Skåne Healthcare Registry, Mohammad et al (pp 1468-1475) reported increased rates of severe infection following the onset of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Higher rate ratios for upper respiratory tract infections, clostridium difficile, and skin infections were reported for AAV patients within the first 6-24 months following diagnosis. Serum creatinine levels and age were identified as potential risk factors for severe infection among vasculitis patients. In juvenile idiopathic arthritis (JIA), Fotis et al (pp 1624-1631) demonstrated that several subtypes of patients had increased intestinal permeability and reactivity to lipopolysaccharide (a gut bacterial product) compared to controls. These findings support the concept of a link between JIA and gut microbes.
In osteoporosis, Marques et al studied the performance of FRAX®, with and without bone mineral densitometry (BMD), in predicting the occurrence of fragility fractures over 10 years. They showed that, when assessing osteoporotic fracture risk in the general population in individuals aged ≥40 years, adding BMD to FRAX® did not improve the performance of the tool (e000509). In spondyloarthritis (SpA), Navarro-Compán et al performed a systematic literature review that showed that switching to a second bDMARD after TNFi failure is a reasonable practice supported by scientific evidence; even though the clinical response after the second bDMARD is lower than that observed in bDMARD naive patients (e000524). In rheumatoid arthritis (RA), Wee et al performed a cost-utility analysis comparing COBRA-light vs COBRA strategies. The two strategies produced similar QALY’s. However, the COBRA-light strategy would have been more costly if the protocol had been followed, due to additional etanercept costs, for a limited health gain (e000502). Sigaux et al studied the sustainability of TNFi tapering in RA over 3 years in the STRASS study, showing that, for patients in stable remission, TNFi de-escalation or withdrawal is achievable in 41% (e000474). Rákóczi et al published a nice review on the indications for and management of pneumococcal vaccination in inflammatory rheumatic diseases (e000484). Damage-associated molecular patterns (DAMPs) released from damaged or dying cells are thought to contribute to inflammation if they are not appropriately cleared. Akbar et al (e000456) recently examined the contribution of the danger molecule high-mobility group protein B1 (HMGB1) in human tendinopathy. They discovered that tendinopathic tissues contained significantly increased levels of the danger molecule HMGB1 compared with control tissues. The addition of recombinant human HMGB1 to tenocytes resulted in a pro-inflammatory phenotype as assessed by significant increases in the expression of IL-1β, IL-6, IL-33, CCL2, CXCL12, and genes involved in matrix remodelling. This study provides evidence that danger molecules propagate inflammation in human tendon disorders. Finally, a study by Guns et al (e000604) examined the potential role of suramin as a protective drug against joint damage. They hypothesised that suramin may interact with tissue inhibitor of metalloproteinase-3 (TIMP3) thus contributing to its protective capacity. The authors demonstrated that suramin prevented loss of articular cartilage in a mouse model of cartilage damage and that this effect was mediated by a functional increase of TIMP3 and a subsequent decrease in the activity of catabolic enzymes.
Two trials were published in the New England Journal of Medicine regarding the use of tofacitinib in psoriatic arthritis (PsA). They showed tofacitinib to be superior to placebo, in patients with previous exposure to csDMARDs but naïve to TNFi (N Engl J Med 2017;377:1537-1550) and also in patients with an inadequate response to TNFi (N Engl J Med 2017;377:1525-1536). A limitation of the first trial mentioned is that even though adalimumab was used as an active control, the trial was not powered to assess superiority or non-inferiority. Ryu et al published the first study on factors predicting pericarditis and pleurisy in 2390 SLE patients from the Hopkins Lupus Cohort using multivariate regression. In this population pericarditis was predicted by haemolytic anemia, proteinuria, lymphadenopathy, and anti-Sm antibodies. Pleurisy was predicted by pulmonary fibrosis and GI infarction, and both conditions were predicted by fever, Raynaud’s syndrome, and presence of anti-DNA antibodies (Lupus Sci Med. 2017;4:e000221). Schett et al published a comprehensive review on the pathophysiology and therapeutic implications of enthesitis with a particular focus on the differences between synovitis and enthesitis and the role of innate immunity though prostaglandins (PGE2) and the IL-17/23 axis. One of the most striking ideas of this review is that no study has been specifically designed to evaluate the treatment of enthesitis (Nat Rev Rheumatol. 2017;13:731-741). Even though the role of epigenetics is well-known in oncology and several epigenetic biomarkers and treatments are currently in use, these have still almost no practical application in rheumatology. Ballestar et al published a review that summarises the most relevant findings in epigenetics in inflammatory rheumatic diseases that emerged during the last 5 years and their potential practical applications (Nat Rev Rheumatol. 2017;13:593-605). Arora et al published a review on how clinical judgement is sufficient to diagnose fibromyalgia, and specific serology (such as ANA and ANCA) is unnecessary the majority of the time (JAMA Intern Med. 2017 Sep 1;177(9):1369-1370).
A recent article in the Journal of Immunology explored the potential role for the limb bud and heart development (LBH) gene in **rheumatoid arthritis (RA)**. Matsuda et al identified LBH as a dysregulated gene in RA and anticipated its function may be related to the cell cycle (J. Immunol. 2017;199:2316-2322). The authors examined this possible role in fibroblast like synoviocytes (FLS) which are known to be the key invasive cell in inflammatory arthritis. They demonstrated that LBH deficiency in FLS leads to S-phase arrest and failure to progress through the cell cycle. LBH-deficient FLS had increased DNA damage and reduced expression of the catalytic subunit of DNA polymerase α. Because DNA fragments can increase arthritis severity in preclinical models, they then explored the effect of LBH deficiency in the K/BxN serum transfer model. Here they demonstrated that LBH knockout exacerbated disease severity, which was associated with elevated levels of IL-1β. They conclude that LBH deficiency induces S-phase arrest that, in turn, exacerbates inflammation. Another article from the Journal of Immunology also examined fibroblast like synoviocytes (FLS) and their proinflammatory properties. Emori et al explored the role of integrin α9 and its ligand, tenasin-C (Tn-C), on the proliferative and inflammatory response of FLSs from RA patients (J. Immunol. 2017;199:3427-3436). These cells were grown in three-dimensional (3D)–micromass cultures to recapitulate the in-vivo microenvironment. The cells showed autonomous production of proinflammatory mediators and the expression of α9 and Tn-C was confirmed in the condensed lining, and knockdown of these molecules abrogated the abnormal lining-like structure formation and suppressed the spontaneous expression of matrix metalloproteinases, IL-6, TNFSF11/RANKL, and cadherin-11. Disruption of α9 also inhibited expression of Tn-C, suggesting the existence of a positive feedback loop in which the engagement of α9 with Tn-C self-amplifies its own signaling and promotes progression of synovial hyperplasia. While a link between RA and antibodies to citrullinated proteins is well established, it remains unproven if other post-translational modifications elicit an antibody response that can contribute to disease. A recent study in the Journal of Autoimmunity, explored a possible pathogenic role for oxidation-associated malondialdehyde (MDA) modification of proteins. Interestingly the authors reported that MDA post-translational modification occurs within the RA joint in self-proteins. Additionally, synovial B cells that produced specific anti–MDA antibodies have also been identified in RA patients. Finally, the authors also show that anti-MDA reactivity is elevated in RA and this in turn is associated with disease activity (J Autoimmun. 2017;84:29-45).
EDUCATIONAL EVENTS
FEBRUARY-MARCH 2018

FEBRUARY 2018

Innovative Insights into Arthritis and its Treatment
- When and Where: 2 – 3 Feb 2018, Turin, Italy
- Website: http://www.arthritisturin.com/

11th Annual Rheumatology Winter Clinical Symposium
- When and Where: 7 – 10 Feb 2018, Maui, Hawaii, USA
- Website: https://r-w-c-s.com/2018/

5th Systemic Sclerosis World Congress
- When and Where: 15 – 17 Feb 2018, Bordeaux, France
- Website: http://web.aimgroupinternational.com/2018/sclerosiscongress/

Canadian Rheumatology Association 2018
- When and Where: 21 – 24 Feb 2018, Vancouver, BC, Canada
- Website: https://rheum.ca/en/events/upcoming_events/2018_cra_annual_scientific_meeting_ahpa_annual_meeting

38th European Workshop on Rheumatology Research
- When and Where: 22 – 24 Feb 2018, Geneva, Switzerland
- Website: http://www.ewrr.org

International Society For Clinical Densitometry Annual Meeting 2018
- When and Where: 28 Feb – 3 Mar 2018, Boston, MA, USA
- Website: https://www.iscd.org/education/annual-meeting/

MARCH 2018

PReS Advanced Educational Course on Autoinflammatory Syndromes
- When and Where: 4 – 7 Mar 2018, Jerusalem, Israel
- Website: https://pres.instyle-forms.co.il/menu_links/12

Intensive Course in Applied Epidemiology
- When and Where: 5 – 9 Mar 2018, Aberdeen, UK
- Website: https://www.abdn.ac.uk/iahs/research/epidemiology/icae-aberdeen-course-158.php

International Cartilage Repair Society World Congress 2018
- When and Where: 9 – 12 Mar 2018, Macau, China
- Website: https://cartilage.org/icrs2018-world-congress-macau/
EDUCATIONAL EVENTS

FEBRUARY-MARCH 2017

MARCH 2018 continued

BSR Rare Disease Fellowship
o When and Where: 12 – 15 Mar 2018, London/Sheffield/Manchester, UK
o Website: https://www.rheumatology.org.uk/Professional-Development/Education-Events/Rare-Disease-Fellowship

9th Global Basic to Intermediate Hands-On Musculoskeletal MRI & Ultrasound Conference and Workshop for Radiologists
o When and Where: 14 – 17 Mar 2018, Penang, Malaysia
o Website: http://www.penangmskrad.com

Musculoskeletal Ultrasound in Rheumatology - Basic Course
o When and Where: 15 – 17 Mar 2018, Rome, Italy
o Website: https://www.eular.org/myUploadData/files/Programme_Musculoskeletal_Ultrasound_in_Rheumatology_Scientific.pdf

9th Global Musculoskeletal Ultrasound Course with Basic MRI Correlation for Orthopaedic/Sports Medicine, Rheumatology and Rehabilitation Physicians
o When and Where: 18 – 19 Mar 2018, Penang, Malaysia
o Website: http://www.penangmskrad.com

11th European Lupus Meeting
o When and Where: 21 – 24 Mar 2018, Düsseldorf, Germany
o Website: http://www.lupus2018.com/

Bulgarian Association for Musculoskeletal Ultrasound Intermediate Level and Focused Course
o When and Where: 29 – 31 Mar 2018, Plovdiv, Bulgaria
**25TH EULAR ULTRASOUND COURSES**

The aim of this annual multi-level course is to cover the whole spectrum of conditions in which musculoskeletal ultrasound (MSUS) could be used in rheumatology practice and research.

The advanced course (for up to 50 participants with considerable experience in MSUS) focuses on difficult issues within MSUS and emerging research fields in MSUS (contrast enhanced, 3D, quantification of inflammation). This includes time for discussion with expert rheumatologists and radiologists in MSUS.

The intermediate course (for up to 50 participants with some experience in MSUS) aims at consolidating standardised MSUS scanning methods according to EULAR guidelines, as well as describing and identifying musculoskeletal lesions/abnormalities by US and knowing the role of MSUS in different musculoskeletal pathologies (inflammatory, degenerative and/or traumatic). The standardised approach in the study of the various anatomic regions as well as the future development of US technique and its role as a research tool is discussed.

For colleagues interested in taking the basic level ultrasound course, please note that it is a EULAR recommendation to first complete the EULAR Online Introductory Ultrasound Course which provides the basic knowledge in form of a 7 module online course including video clips and a final exam. A new online course starts each September.

**The EULAR Ultrasound Course**

**will take place on**

**10-13 June 2018 in Amsterdam, The Netherlands, prior to EULAR**

**REGISTRATION OPEN**

**COURSE BURSARIES ALSO AVAILABLE**

For information and to register visit:  
[https://www.eular.org/edu_course_ultrasound.cfm](https://www.eular.org/edu_course_ultrasound.cfm)
8TH EULAR COURSE ON CAPILLAROSCOPY

The aim of this intensive and interactive course is to provide all participants with an update on the power of the safe and non-invasive nailfold videocapillaroscopy (NVC) technique in the field of rheumatic diseases, in particular for the early diagnosis of scleroderma spectrum diseases, its predictability and prognostic value, as well as its role as a tool for therapeutic follow up.

The EULAR course on NVC first ran in 2004 and has been successfully tested for both beginners and already trained operators in microcirculation investigations, by over 740 total participants from almost 52 different countries. Participants will be fully involved in interactive theoretical and practical capillaroscopic sessions. Updated clinical sessions concerning the diagnostic/prognostic value of NVC in diseases such as systemic sclerosis will be presented. Links between capillaroscopic patterns and biomarkers such as autoantibodies will also be discussed. In particular, reading and scoring (manual and automated systems) of videocapillaroscopic images of living patients will be discussed and their predictive value to identify possible clinical complications (i.e. digital ulcers in systemic sclerosis, lung involvement etc.) will be analyzed.

New sessions on practical evaluation of peripheral blood flow by laser doppler and LASCA imaging have been introduced. Lessons and practical sessions on skin ultrasound (US) evaluation will be also available and will be combined with the severity of the videocapillaroscopic images (patterns) in living patients.

At the end of this excellent course that is delivered by a faculty formed by many of the world experts in this area, the participants will be able to use capillaroscopy for their day-to-day assessment and follow-up, in particular of patients affected by scleroderma spectrum diseases.

The next EULAR Capillaroscopy Course

will take place on

13-15 September 2018 in Genova, Italy

REGISTRATION OPEN

COURSE BURSARIES ALSO AVAILABLE

For information and to register visit:
https://www.eular.org/edu_course_capillaroscopy.cfm
SHARE YOUR IDEAS!

Over the years EMEUNET has developed several projects covering different topics and areas of interest. However, we appreciate any suggestions and welcome new ideas to expand on what we currently offer to EMEUNET members. Make your voice heard and share your ideas with us!

It is easy, just write down some lines to summarize your proposal and send it either via email at emeunet@eular.ch or through our website (http://emeunet.eular.org/contact_us.cfm). Don’t forget to provide your contacts so we can come back to you for additional details!

We look forward to hearing from you!!!

More information about EMEUNET can be found at http://emeunet.eular.org
You can also reach us through the following email emeunet@eular.ch

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