

WEDNESDAY, 13 JUNE 2018

**Shaping the future in systemic sclerosis**

SP0010 FIBROBLAST-MATRIX-VESSEL: THE UNHAPPY TRIAD

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Systemic sclerosis (SSc) is a complex multisystem disease that links autoimmunity, inflammation, vascular damage to development of fibrosis or scarring in target organs. The pathogenesis of the disease involves reciprocal interaction between the immunological, vascular and mesenchymal compartments and involves processes that are central to connective tissue growth and repair. However in the context of SSc this process is dysfunctional in that the amount of tissue damage is excessive or the repair process is dysregulated. Thus it seems likely that perturbation of the cross talk between cells and pathways that regulate the cell types involved are important in pathogenesis and represent appropriate targets for therapeutic intervention. It is likely that some emerging therapies can attenuate the pathogenesis of SSc by acting on multiple cell type and this is perhaps especially relevant to an approach such as autologous haematopoietic stem cell transplant. However it is likely that individual pathways or mediators can be modified in a less extreme manner and have benefit as potential disease modifying therapy. A number of key mediators and pathways are emerging including IL6, TGFbeta and intracellular pathways linked to nuclear hormone receptors. These are being targeted experimentally. Another strategy for treatment would be targeting the initiating cells such as monocytes, especially those with a profibrotic phenotype, or the effector cells in fibrosis such as myofibroblasts. Evidence supporting these strategies is emerging and it is likely that restoration of a more balanced interaction between vessels, extracellular matrix and fibroblasts would underpin effective therapies for the fibrotic and vascular components of SSc.

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SP0011 IS THERE AN UNIVERSAL TRANSLATOR? WHICH (ANIMAL) MODELS TELL US MOST?

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We will review the key features of currently available preclinical models of SSc, highlight their strengths and limitations and analyse, which subsets of SSc patients individual models mimic. We will also discuss how to employ models to evaluate drug candidates with different modes of actions and how to combine different models for an optimal preclinical portfolio.

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SP0012 NOVEL THERAPIES THAT MAY MAKE IT INTO THE CLINIC IN SYSTEMIC SCLEROSIS

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**Introduction:** Many therapies have been tested in systemic sclerosis (SSc), often failing but new approaches to measuring effect may improve the probability of success. The Combined Response Index for Systemic Sclerosis (CRI SS) combines measurement of the skin, lungs, activities of daily living and global assessments of disease activity into a single number. Like the DAS 28, this measure may be more powerful than any single outcome measure such as modified Rodnan skin score (mRSS) or forced vital capacity (FVC).

Novel approaches:

Multiple therapies are being tested which modify the immune system and the vascular pathogenetic node underlying the pathogenesis of SSc. Among these are tocilizumab (an IL-6 inhibitor), abatacept (affecting CD8 receptors) and rituximab (a CD20 inhibitor), all of whom are being tested in late phase studies and for whom results can be expected soon.

A more novel approach involves inhibition of tyrosine kinases which, in turn, affect TGF-beta, PDGF, FGF beta and VEGF. Among these are nintedanib and a

nanoparticle preparation delivering imatinib selectively. Encouraging animal studies and early human studies are resulting in larger studies in SSC patients. Other drugs affecting fibrosis and inflammation are also being tested, including a cannabinoid which has shown encouraging early results.

While hematopoietic stem cell therapy will soon become a standard of care, other cellular therapies such as adipose derived mesenchymal cells and mesenchymal products such as exosomes and microparticles are being tested in systemic sclerosis.

There may or may not be enough time to discuss even more novel approaches to treating systemic sclerosis, with good rationale and some early results, which may reach the clinic.

Overall, this is an encouraging time for novel therapies to treat systemic sclerosis.

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**Basic mechanisms of inflammation**

SP0013 S100-ALARMIN: POTENTIAL THERAPEUTIC TARGETS FOR ARTHRITIS

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Innate immunity is a pivotal factor in the pathogenesis of rheumatic diseases. During the last years there is growing evidence that pro-inflammatory alarmins of the family of calcium-binding S100-proteins promote inflammation in rheumatic, auto-inflammatory and auto-immune diseases. Serum concentrations of S100A8/S100A9 correlate with disease activity in several rheumatic diseases and are useful surrogate markers for monitoring disease activity predicting response to treatment, systemic organ involvement, or relapses in several autoimmune diseases. We have now identified a novel mechanism of auto-inhibition in mice and man restricting S100-alarmin activity to local sites of inflammation. We identified specific peptide sequences within the second calcium-binding EF-hands of S100A8 and S100A9 binding to TLR4/MD2 and triggering inflammation. However, biological activity of S100A8/S100A9 is locally restricted by calcium-induced (S100A8/S100A9)<sub>2</sub>-tetramer formation hiding the TLR4/MD2-binding site within the tetramer interphase. This auto-inhibitory mechanism is essential to prevent fatal inflammation in mice *in vivo*. Since S100A8/S100A9 complexes are the most abundant alarmins in arthritis, blocking of active S100A8/S100A9-dimers may represent an innovative approach for local inhibition of inflammatory processes in rheumatic diseases.

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**Health professionals welcome session**

SP0014 HEALTH PROFESSIONALS IN RHEUMATOLOGY WELCOME

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An increasing amount of people are diagnosed with Rheumatic and Musculoskeletal Diseases (RMDs). EULAR Health Professionals in Rheumatology (HPR) can through substantial knowledge and clinical expertise contribute significantly to better lives with RMDs. Examples of important HPR core competencies are education, evidence-based treatment, prevention, team-based rehabilitation, and the support of individuals to participate in work, or education. The presentation will address some of the important multidisciplinary contributions to reduce the individual and societal burden of RMDs in the future.

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SP0015 WHAT'S NEW? PRESENTATION OF THE HPR NEWSLETTER

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The presentation will aim to showcase HPR News – the newsletter for EULAR's Health Professionals in Rheumatology. HPR News is available twice a year and is published to support EULAR's commitment to enable networking and learning

amongst HPRs across Europe. It also shares information about the work of the HPR Standing Committee, Study Groups as well as showcasing projects being carried out by HPR country member associations. The new design for the newsletter will be highlighted, alongside the content structure and HPRs will be encouraged to contribute to ensure the newsletter stays relevant to its audience.

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## Statistics made simple: a practical approach to complex concepts

SP0016 STEPWISE OR NOT TO STEPWISE? THE DO'S AND DON'T'S OF MULTIVARIABLE MODELLING

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**Introduction:** Different types of regression analyses, including linear, logistic, and Cox regression, are commonly used methods in medical research. Usually, these analyses include more than one covariate as independent variables. This is particularly the case in observational studies: When investigating the possible association between an exposure and an outcome, there can be a large number of potential confounders. Examples are age, sex, body mass index, and lifestyle factors. How should we choose which variables to include in the model? Here I shall focus on two issues:

- Attempting to include too many covariates in the analyses
- Use of stepwise selection of covariates

These are among the most frequently encountered issues in statistical review of manuscripts submitted for the Annals of the Rheumatic Diseases Lydersen 2015 Limit the number of covariates

With a limited number of observations, how many covariates can you include? Traditional rules of thumb state that the ratio of observations per variable ought to be in the size of order 10. Some authors recommend 15, some 20, others state that 5 is sufficient. See Lydersen, 2015 and references therein.

Do not use stepwise selection

Stepwise selection of covariates basically means that only covariates that are statistically significant, typically with a p-value less than 0.05 or 0.10, are included in the model. A fundamental problem is the following: As always is the case in estimation, regression coefficients are estimated with some uncertainty. Hence, some are underestimated, and some are overestimated, that is, too far away from the null hypothesis. Including only covariates with small p-values causes overestimated coefficients to be more likely to be selected. This introduces bias away from the null hypothesis. Stepwise procedures used to be very popular, but today an increasing number of analyst criticise such methods. For example, Rothman et al. 2008 page 419 state: "There are several systematic, mechanical, and traditional algorithms for finding models (such as stepwise and best-subset regression) that lack logical and statistical justification and that perform poorly in theory, simulations and case studies ... One serious problem is that the P-values and standard errors ... will be downwardly biased, usually to a large degree".

**Recommendation:** Selection of covariates should be based on the research question at hand and on substantial knowledge such as what is biologically plausible. Chapter 10 'Predictor selection' in the book Vittinghoff et al. 2012 gives good guidance. Check that the number of covariates is small enough compared to the number of observations. Do not use stepwise selection.

### REFERENCES:

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## E-health for better care

SP0017 BITS AND BYTES: FITTING MEDICAL INFORMATION – PICASO THE PLATFORM FOR IMPROVED PERSONAL, COORDINATED CARE

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Coordination of care plans between healthcare sectors and efficient management of patients with co-morbidities is of large demand. Rheumatoid arthritis (RA) patients are at increased risk of cardiovascular diseases. Different stakeholders are potentially involved in the EULAR recommended management processes. Optimised orchestration of accumulated information is of major importance to ensure data quality, meaningful management processes and cost effectiveness. A newly developed information and communications technology platform within the Horizon2020-funded PICASO-project ([www.picaso-project.eu](http://www.picaso-project.eu)) will support a continuum of care from hospitals and outpatient clinics to the home. The PICASO platform will be developed and trialled with patients and clinicians. First experiences will be reported. The platform will become available for RA-patients in routine care but also for wider applicability in Rheumatology and other chronic diseases.

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SP0018 SMART WEARABLES AND HEALTH APPS – THE RIGHT TOOL FOR HEALTH MONITORING AND IMPROVING QUALITY OF HEALTH?

M. Silva, on behalf of E-health for better care. *ReumNet, Brussels, Belgium*

What role can technology play in enabling a shift from a traditional paternalistic model of care to a model based on empowered patient sharing ownership? In the traditional model, patients are fully reliant on the healthcare professional for information, diagnosis and treatment, with complexity to navigate through the ecosystem and where physicians are empowered rather than patients. Patient empowerment is enhanced thanks to technology enabled care, in which patients have access to their medical files, can use tools that allow them to be proactive and focus on prevention and where self-management is supported across the treatment pathway. Smart wearables and health apps are becoming more widespread and a commodity, while more and more research is being performed on the effectiveness of such devices on the quality of life of patients. The design of wearables and health apps itself can be approached in a patient-centric way, to maximise the benefits for patients and the uptake by patients. This presentation will discuss some evidences of the impact of technology on improvement of quality of life and how patients should be included in the design process.

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## EULAR projects in paediatric rheumatology and UCAN

SP0019 UCAN AND PRINTO ALIGNED TO LINK BED AND BEDSIDE: PERSPECTIVE FROM THE BENCHSIDE

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In the past 2 decades we have gained important insights on the mechanisms of disease and therapy in children with Juvenile Idiopathic Arthritis (JIA). These insights have resulted in several game-changing therapeutic modalities in several