associated changes in antibody glycosylation that promote engagement of the complement system. In contrast, clinical trials in patients with classified RA utilizing inhibitors of complement C5 have demonstrated minimal improvement. Nevertheless, recent translational research studies of patients during the natural history of RA have opened up new avenues for therapeutic intervention. Specifically, there exists in seropositive RA a prolonged asymptomatic preclinical stage wherein mucosal autoantibody production in the lung is associated with NETosis, elevated cytokines and evidence of activated innate immunity, with the capacity of each to interact and promote localized inflammation. Beyond this, murine studies have strongly suggested that complement C3d generation promotes autoimmunity and therapeutic pathway inhibitory strategies should encompass all of the effector mechanisms and not just those at C5 and beyond.

Objectives: The presentation objective is to explore the evidence for involvement of the complement system in the preclinical development of RA, and what mechanisms may be involved to promote autoimmunity and ultimate joint damage.

Methods: The presentation will review studies of the natural history of human RA, with an emphasis on the potential roles for complement in multiple stages of disease. In addition, the results of informative murine studies which have explored the mechanisms by which the complement system can modulate the development of experimental autoimmune arthritis will be summarized.

Results: Studies of preclinical RA in subjects have suggested the potential for complement and NETs to interact and promote localized mucosal inflammation in the lung. In addition, murine studies of the roles of complement have supported that all components of the pathway, including C3d linked to antigens, the anaphylatoxins C5a and C3a, as well as the MAC, are centrally involved in promoting arthritis.

Conclusion: Complement likely plays a role in multiple phases of RA development, including: 1) mucosal inflammation and the break in systemic tolerance to citrullinated antigens, 2) initial inflammation following targeting of ACPA to the synovium in early RA, and 3) regulation of RA-related autoantibody production. In addition, it is likely that inhibition of C3 and C5 convertases in tandem will be necessary to see major clinical effects in patients with active synovitis. Finally, the use of a complement inhibitor or modulator in the pre-clinical, transitioning and/or early RA populations are all intriguing approaches.

REFERENCE:

- [1] Holers, V.M., et al. 2018. Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. *Nature Reviews Rheumatology* 14:542-557. 2. Holers, V.M., and Banda, N.K. 2018. Complement in the initiation and evolution of rheumatoid arthritis. *Front. Immunol.* 9:1057.

Disclosure of Interests: V. Michael Holers Grant/research support from: Janssen, Consultant for: Janssen

DOI: 10.1136/annrheumdis-2019-eular.8502

SP0171

THE NEW COMPLEMENT THERAPEUTICS

Claire Harris. Newcastle University, School of Medicine, Newcastle-upon-Tyne, United Kingdom

Despite a wealth of knowledge in the complexities of the complement cascade, and many decades of endeavour, very few drugs have progressed to the clinic. Recently, strong genetic associations of complement with common diseases have emerged and fuelled the fire of complement drug discovery leading to an explosion in complement therapies in development; while many of these agents and others before them have failed to progress, their legacy is key to future success. Obstacles to successful drug development include target concentration and turnover rates, and ability to target to the appropriate site. The drug development landscape is littered with agents that have failed at the preclinical or early clinical stage; their modes of action and modalities are wide-ranging. It is becoming increasingly clear that an understanding of disease mechanism and matching of drug modality and mode of action to the right disease and patient population (or stratified sub-population) is critical to success. A number of drugs are now in phase 3 clinical development for a number of different diseases. In this talk, innovative approaches that are emerging to overcome obstacles blocking success will be explored, highlighting drugs in development which employ new state-of-the-art strategies. These include 'homing' drugs and a new generation of orally bioavailable molecules.

Complement biomarkers that can decipher disease mechanism and be applied for patient stratification will be discussed. It is clear that a range of different drugs, or combination of drugs, will be needed for effective management of the many and diverse complement-mediated diseases.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.8492

SATURDAY, 15 JUNE 2019

09:00:00 – 10:30:00

Lights at both ends of the tunnel? Advances in GI Involvement in SSC

SP0172

CASE 2 PRESENTER: ALWAYS AT THE EDGE: SEVERE GI COMPLICATIONS

Kristina Clark. University College London, Centre for Rheumatology and Connective Tissue Diseases, London, United Kingdom

The clinical impact of lower gastrointestinal tract involvement in systemic sclerosis will be illustrated through a case presentation. This will describe the challenges of managing patients with systemic sclerosis presenting with pseudo-obstruction, severe malnutrition, and electrolyte imbalance and how these were managed to optimise patient care.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.8447

SP0173

CASE 2 DISCUSSANT: IMMUNOSUPPRESSION OR ANTIBIOTICS – WHEN TO CHOOSE WHAT?

Christopher Denton. Royal Free Campus, x, x, United Kingdom

Gastrointestinal tract involvement is almost universal in systemic sclerosis but in most patients is relatively mild with symptoms of gastro-oesophageal dysmotility and reflux or lower bowel symptoms of constipation. A minority of cases have severe involvement, and this can be life-threatening. The key issues related to severe disease are attacks of pseudo-obstruction with complications such as pneumatosis coli and perforation of infection. Additional issues include malnutrition and intestinal failure that may require long term home parenteral supplementation. Finally, the most severe lower tract involvement can result in intractable diarrhoea, persistent anorectal incompetence and complications of severe chronic constipation such as sigmoid volvulus. Management is challenging and requires interaction with gastroenterology and nutritional expert colleagues. Some newer approaches that have been beneficial include long term intravenous immunoglobulin therapy although in general response to immunosuppression are relatively modest. This discussion will focus on treatment with immunomodulation and use of antibiotic therapy to treat small intestinal bacterial overgrowth and also to manage other infective problems and the potential impact on intestinal dysbiosis.

Disclosure of Interests: Christopher Denton Grant/research support from: GlaxoSmithKline, Inventiva, CSF Behring, Consultant for: Roche-Genentech, Actelion, GlaxoSmithKline, Sanofi Aventis, Inventiva, CSL Behring, Boehringer Ingelheim, Bayer

DOI: 10.1136/annrheumdis-2019-eular.8459

SATURDAY, 15 JUNE 2019

09:00:00 – 10:30:00

Novel autoantibodies in RMD: a neverending quest?

SP0174

ADVANCES IN THE DETECTION OF PATHOGENIC AUTOANTIBODIES IN SLE

Luis Munoz. Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Internal Medicine 3, Erlangen, Germany

Background: The accumulation of late apoptotic or so-called Secondary Necrotic Cells (SNEC) in germinal centers challenges B and T cell tolerance and leads to the development of autoimmunity and the production of autoantibodies.

Objectives: Determine the test performance of immobilized SNEC autoantigens for the diagnosis of Systemic Lupus Erythematosus.

Methods: SNEC ELISA of sera from patients with SLE and test performance statistics were deployed to evaluate the diagnostic potential SNEC-derived autoantigens. Functional assays confirmed its pathophysiological relevance.

Results: SNEC contains nuclear autoantigens bearing apoptosis-associated modifications such as histone H3 K27me3, histone H2A/H4AcK8,12,16, and histone H2B-AcK12. The SNEC ELISA clearly discriminated patients with SLE from patients with Rheumatoid Arthritis (RA), Primary Anti-Phospholipid Syndrome (PAPS), Spondyloarthritis (SpA), Psoriatic Arthritis (PsA), and Systemic Sclerosis (SSc). A positive test result in SNEC ELISA significantly correlated with

serological variables and reflected the uptake of opsonized SNEC by neutrophils in the blood.

Conclusion: SNEC ELISA allows for the sensitive detection of pathologically relevant autoantibodies in the serum of patients with SLE. The clearance of nuclear remnants by neutrophils enhances inflammatory responses supporting the role of clearance deficiency in the etiopathogenesis of SLE.

REFERENCE:

- [1] Biermann MHC, Boeltz S, Pieterse E, Knopf J, Rech J, Bilyy R, van der Vlag J, Tincani A, Distler JHW, Krönke G, Schett GA, Herrmann M and Muñoz LE (2018) Autoantibodies Recognizing Secondary Necrotic Cells Promote Neutrophilic Phagocytosis and Identify Patients With Systemic Lupus Erythematosus. *Front. Immunol.* 9:989. doi: 10.3389/fimmu.2018.00989

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.8544

SP0175 POST-TRANSLATIONAL MODIFICATIONS OF ANTIBODIES: WHERE THERE'S SMOKE THERE'S FIRE

Rene Toes. *Leiden University Medical Center, Rheumatology, Leiden, Netherlands*

Rheumatoid arthritis (RA) is a prototype autoimmune disease, with the hallmark signs of synovial inflammation and the presence of autoantibodies. One of the most prominent examples of such autoantibodies are anti-citrullinated protein antibodies (ACPA), which are directed against a wide-array of citrullinated proteins. The immune response to citrullinated antigens is a dynamic response that expands before the onset of disease and generates antibodies that are extensively glycosylated in the variable domain. This feature of ACPAs is remarkable and might be involved in the breach of tolerance to citrullinated proteins as well as function as an additional biomarker to predict disease onset in subjects at risk.

Next to ACPA, it has become clear that the autoantibody response in RA extends towards several other modified proteins, such as proteins modified by carbamylation or acetylation. Carbamylation leads to the formation of homocitrulline. Structurally, homocitrulline greatly resembles citrulline but is one methylene group longer. In contrast, acetylation is mediated by intracellular acetyltransferases and is structurally less related to citrulline or homo-citrulline. Although the presence of autoantibodies against these post-translationally modified proteins (Anti-Modified Protein Antibodies; AMPA) hallmark RA, at present, there is no conceptual framework explaining the concordant presence of different AMPA-responses in RA. In the context of this presentation, the latest insights into the development of humoral response against citrullinated-, carbamylated and acetylated proteins in relation to their role as biomarkers to predict the development of RA will be discussed.

Disclosure of Interests: Rene Toes Grant/research support from: Sanofi

DOI: 10.1136/annrheumdis-2019-eular.8603

SP0176 PATHOGENIC ANTIBODIES IN PHOSPHOLIPID SYNDROM

Sasa Cucnik. *University Medical Center Ljubljana, Department of Rheumatology, Immunology Laboratory, Ljubljana, Slovenia*

Antiphospholipid syndrome (APS) is prothrombotic systemic autoimmune disorder characterized with multisystem manifestation, most commonly venous and arterial thromboembolism and/or recurrent pregnancy loss. The varying clinical phenotype is associated with heterogeneity in the pathogenic antiphospholipid antibodies (aPL) that are central to the diagnosis of APS. According to the international consensus statement on classification criteria, APS is classified when persistently elevated levels of specific aPL, such as lupus anticoagulant (LA), anticardiolipin (aCL) and anti- β 2 glycoprotein I (anti- β 2GPI) antibodies, are confirmed in addition to clinical manifestations (1, 2). The exact pathogenesis of APS is unknown, but aPL have been described to activate monocytes, neutrophils, dendritic cells and placental tissue (3). Despite the fact that many different proteins have been identified as being involved in the pathogenesis of APS, accumulating evidence from in vitro experiments as well as animal studies has revealed that β 2GPI is the main target for aPL. It was also shown that triple aPL positivity, defined by detection LA, high titres of aCL and anti- β 2GPI antibodies, correlates better with both thrombosis and pregnancy morbidity than any other aPL profile (4).

Several autoantibodies outside those included in APS classification criteria could be also relevant to APS pathogenesis (5) and therefore, antibodies against other antigen targets have been investigated. Current evidence shows that some of these antibodies, particularly antibodies against domain I of β 2GPI (anti-DI- β 2GPI) and phosphatidylserine dependent anti-prothrombin antibodies (aPS/PT)

might be relevant in the better recognition of APS patients. These antibodies are commonly referred as non-criteria aPL (6) because they have not been yet accepted as laboratory criterion for the diagnosis of APS. The DI of β 2GPI has been identified as the most relevant antigenic target involved in β 2GPI/anti- β 2GPI antibody binding. Anti-DI- β 2GPI antibodies were found to be strongly related to thrombosis and pregnancy complication and are more frequently detected in patients with APS than in asymptomatic aPL carriers (7). High titres of anti-DI- β 2GPI are also frequently present in triple aPL positive patients. Nevertheless, it is far too soon to recommend replacement of anti- β 2GPI testing with an anti-DI- β 2GPI antibody assay because it was shown that about 30% of patients with anti- β 2GPI antibodies are negative for anti-DI- β 2GPI antibodies (8). The clinical significance of autoantibodies reacting with epitopes other than DI was also investigated in multicenter study (9). The results showed a diverse clinical association with reactivity to different epitopes on β 2GPI, suggesting all domains were relevant. Therefore, more detailed profiling of domain specificity and avidity of anti- β 2GPI antibodies may be useful as risk stratification for clinical events.

aPS/PT antibodies also represent strong risk factor for thrombosis. Results of multicenter study demonstrated that IgG aPS/PT detection might contribute to a better and more reliable identification of APS patients (10).

Due to the heterogeneity of aPL (criteria and non-criteria) the interpretation of aPL results is huge challenge in daily routine practice and should always be related to clinical symptoms and therefore, interaction between the laboratory and clinician is essential.

REFERENCES:

- [1] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4(2):295-306.
- [2] Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum.* 1999;42(7):1309-11.
- [3] Yin D, de Laat B, Devreese KM, Kelchtermans. The clinical value of assays detecting antibodies against domain I of β 2-glycoprotein I in the antiphospholipid syndrome. *Autoimmunity Reviews* 2018;17:1210-1218.
- [4] Pengo V, Ruffatti A, Legnani C, Gesele P, Barcellona D, Erba N, Testa S, Marongiu F, Bison E, Denas G, Banzato A, Padayattil JS, Iliceto S. Clinical course of high-riskpatients diagnosed with antiphospholipid syndrome. *J Thromb Haemost* 2010;8:237-242.
- [5] Sciascia S, Amigo MC, Roccatello D, Khamashta M. Diagnosing antiphospholipid syndrome: 'extra-criteria' manifestations and technical advances. *Natural reviews* 2017;13:548-560.
- [6] Amengual O, Atsumi T. Antiphospholipid syndrome: "the best prophet of the future". *Modern Rheumatology* 2018; 409-416.
- [7] Chighizola CB, Gerosa M, Meroni PL. New Tests to Detect Antiphospholipid Antibodies: Anti-Domain I Beta-2-Glycoprotein-I Antibodies. *Curr Rheumatol Rep* 2014;16:402-410.
- [8] Pengo V, Ruffatti A, Tonello M, Cuffaro S, Banzato A, Bison E, Denas G, Padayattil JS. Antiphospholipid syndrome: antibodies to Domain 1 of beta2-glycoprotein 1 correctly classify patients at risk. *J Thromb Haemost* 2015;13:782-787.
- [9] . Artenjak A, Locatelli I, Brelih H, Simoncic DM, Ulcova-Gallova Z, Swadzba J, et al. Immunoreactivity and avidity of IgG anti-beta2-glycoprotein I antibodies from patients with autoimmune diseases to different peptide clusters of beta2-glycoprotein I. *Immunologic Research* 2015;61:35-44.
- [10] Amengual O, Forastiero R, Sugiura-Ogasawara M, Otomo K, Oku K, Favas C, et al. Evaluation of phosphatidylserine-dependent antiprothrombin antibody testing for the diagnosis of antiphospholipid syndrome: results of an international multicentre study. *Lupus* 2017;26:266-76.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.8453

SATURDAY, 15 JUNE 2019

09:00:00 – 10:30:00

Lessons learned from checkpoint inhibitors

SP0177 IMPACT OF CHECKPOINT INHIBITORS ON B CELLS

David Pisetsky. *Duke University Medical Center, Medicine/Immunology, Durham, North Carolina, United States of America*

Immune checkpoint inhibitors (ICI) are a new class of biological agents that has revolutionized the treatment of cancer. Unlike conventional cytotoxic agents that