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:**