

MRL/lpr mice. Complications of human studies are the measurements of complement activation and the multiplicity of potential modes of action. There is also the diversity of immunogenetic backgrounds in lupus and evidence that contributions of different pathways may differ between patients or at different phases of disease.

#### Learning Objectives

- Explain the rationale for complement inhibition in ANCA associated vasculitis
- Discuss the clinical evidence of efficacy of complement inhibition in ANCA associated vasculitis
- Describe lessons can be learned from the ANCA associated vasculitis of relevance to the exploration of complement inhibition in SLE

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## Hot topics: highlighting accomplishments in lupus research

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### TRANSLATIONAL INSIGHTS INTO THE PATHOGENESIS TRANSFORMING SLE TREATMENT

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10.1136/lupus-2021-la.27

Systemic lupus erythematosus (SLE) is a heterogeneous disease characterized by abnormalities in cellular and humoral immunity. Key disturbances comprise abnormal cytokine production (increased type I IFN, IL-6, IL-17, IL-12 and IL-23, BAFF) and B lineage cell abnormalities. In the light of the recent SARS-Cov2 pandemic, the role of type I IFN and humoral immunity became of great interest and a number of similarities, but also subtle differences, to SLE became apparent and will be addressed based on recent data.

Inflammatory cytokines or their corresponding cytokine receptors have been identified as therapeutic targets. Since these cytokines activate various intracellular pathways, such as Jak/Stat signaling, activation of the NfκB or BCR signaling pathways (i.e. spleen tyrosine kinase [Syk]), Bruton's tyrosine kinase (BTK), small molecules inhibiting these pathways are being investigated in various clinical studies permitting a concept of multiple targeting therapy.<sup>1</sup> Recent study experiences blocking Jak1/Jak2 pathways with baricitinib showed clinical improvements over 24 weeks<sup>2</sup> and identified a number of molecules downstream of Stat1, Stat2, and Stat4 correlating

with SLE activity.<sup>3</sup> A Phase Ib/IIa trial using tofacitinib as Jak1/Jak3 selective inhibitor in SLE has also been reported limited to safety but also mechanistic insights.<sup>4</sup>

The recent identification of hyporesponsive but not hyper-responsive B cell functions among SLE and other autoimmune diseases (RA, Sjögren's) require consideration of anergic post-activated (APA) B cells with increased phosphatase activity and responding to CD40 stimulation most pronounced in SLE.<sup>5</sup> As a result, inhibitors of preferred B cell activation pathways (BTK4, Syk etc.) that generated hope based on experiences with anti-CD20 therapy failed in various SLE and rheumatoid arthritis trials, including a Phase 2 study with the BTK inhibitor fenebrutinib (GDC-0853)<sup>4</sup> and evobrutinib (e-ACR 2020). Notably, evobrutinib was very efficacious in RRMS5 which also opens new avenues of the understanding of a differential pathogenesis<sup>6</sup> of the two diseases. Thus, consideration of APA B cells in certain autoimmune diseases responding to CD40 activation may guide the development of successful new therapies in SLE and other diseases.

#### Learning Objectives

- Discuss the translational rationale and distinct mechanisms of action for novel therapeutic targets in SLE within the context of APA B cells
- Explain the significance of certain signaling pathways, especially Jak/Stat and BCR/TLR signaling as potential treatment targets in SLE

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### CLINICAL SCIENCE HIGHLIGHTS THAT ARE TRANSFORMING TREATMENT

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10.1136/lupus-2021-la.28

The recent approvals of treatments that, when added to established background therapies, significantly increase response rates in systemic lupus erythematosus (SLE) is exciting. These approvals include belimumab and voclosporin for lupus nephritis (LN), and the anticipated approval of anifrolumab for cutaneous and musculoskeletal SLE, with several more treatments in the pipeline. And yet, 40–50% of patients in trials do not reach the desired improvement. Achieving lupus low disease activity score (LLDAS) maintained for one year occurs in only 50% of patients. The proportion of LN patients reaching end stage kidney disease (ESKD) has not declined in the last decade. Furthermore, the problems of serious adverse