Systemic lupus erythematosus (SLE) is a heterogeneous disease characterised by abnormalities in cellular and humoral immunity. Here disturbances in cytokine production and B lineage cell disturbances became very evident in recent years. Identification of increased interleukin (IL)-6, IL-17, IL-12 and IL-23, BAFF, and especially type I interferon (IFN) production by different cell types, provided the rationale for targeting these cytokines or their corresponding cytokine receptors using biologics. Since these cytokines activate various intracellular pathways, such as Jak/Stat signaling, activation of the NFκB or using spleen tyrosine kinase (Syk), Bruton’s tyrosine kinase (BTK), small molecules inhibiting these pathways are being investigated in various clinical studies.

It should be emphasised that most of the above-mentioned intracellular pathways may vary between different immune cells and tissues and can have interactions which have not been fully described. However, certain strategies target multiple key pathways along with inhibiting various cytokines (multiple targeting therapy),\textsuperscript{1} which holds the promise to cover broadly heterogeneous SLE, a therapeutic principle that has already been introduced in other disciplines, such as antihypertensive and anti-infectious treatment algorithms.

As a first example in patients with SLE, treatment with the Jak1/Jak2 blocking agent (jakinib) baricitinib showed improved symptoms of skin and joint manifestations among patients with a daily dose of 4 mg/d but less pronounced under 2 mg/d in a Phase II trial over 24 weeks.\textsuperscript{2} Another Phase Ib/IIa trial using tofacitinib as Jak1/Jak3 selective inhibitor in SLE has been reported without substantial safety concerns and early signs of efficacy.\textsuperscript{3} In addition to jakinib in studies with SLE, there are also trials of inhibitors of other pathways (BTK\textsuperscript{4}, Syk etc.) that hold promise for a new era of more efficacious and well-tolerated therapies, which may address the current and substantial need for the effective treatment of SLE. Of note, recent Phase 2 data of the BTK inhibitor fenebrutinib (GDC-0853) targeting B cells, monocytes and mast cells did not demonstrate differentiating efficacy in general SLE\textsuperscript{5}. While this is an unexpected but interesting finding, targeting BTK in SLE needs to be further explored based on convincing efficacy of the BTK inhibitor evobrutinib in relapse-remitting multiple sclerosis.\textsuperscript{5}

Learning Objectives
- Discuss the potential for novel therapeutic targets in SLE
- Explain the significance of certain signaling pathways with a particular focus on Jak/Stat system and current treatment developments in SLE

REFERENCES