Systemic lupus erythematosus (SLE) is a heterogeneous disease characterised by abnormalities in cellular and humoral immunity with clear hints that abnormalities of B lineage cells (B and plasma cells) are key drivers.

Clinical experiences with belimumab as a first approved targeted SLE treatment provide robust evidence that blocking BLyS/BAFF selectively interfering with B cell survival can change the course of the disease, including prevention of damage accrual. Recent failures of first generation anti-CD20 (rituximab, ocrelizumab) and BTK inhibitors (fenebrutinib/GDC-0853) together with the occurrence of agric B cells in SLE provide the rational for various innovative strategies. These include more profound targeting by second generation anti-CD20 modalities (obinutuzumab) and plasma cells) are key drivers.

In addition, enhancing regulatory B-cell functions may hold attractive opportunities. Such strategies have potential to reinstall the balance of pathogenic and protective B cells with the potential of more specific therapies. Moreover, these treatment targets should have the potential to overcome the status of anergic B cells holding promise to escape the detrimental chronic autoimmune process. In this context, targeting checkpoint molecules that downmodulate intracellular phosphatases, such as CD40 or other targets of this family on B cells, and enhancing Treg cells, may provide increased control of B-cell activation. Another potential innovative treatment modality could be the use of non-depleting bispecific antibodies may open more selective B cell subsets targeting of enhancing the potency of depletion in the future.

REFERENCES

**Learning Objectives**
- Discuss the translational concept of anergic (APA, immunosenescent) B cells in SLE
- Explain the impact of indirect targeting of B cells by anti-BLyS/BAFF treatment
- Discuss depleting versus non-depleting strategies of B cells in SLE
- Explain the concept of overcoming APA (immunosenescent) B cells and the rational of anti-CD40 treatment as a checkpoint modulatory concept