How can our understanding of the pathogenesis of MS drive therapy choice in relapsing MS?

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MS, multiple sclerosis.

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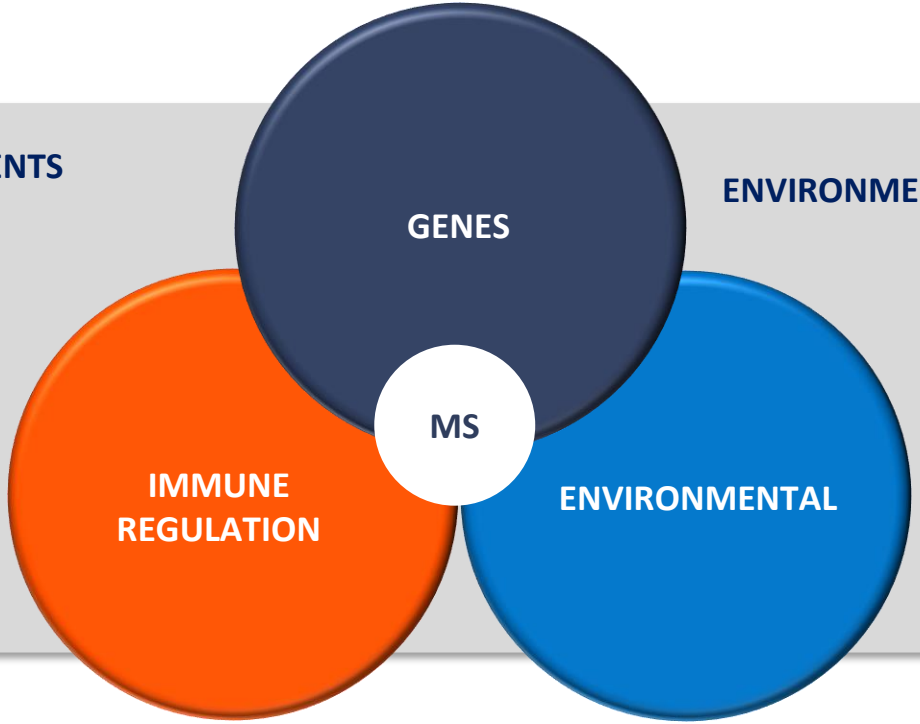
Genetic and environmental risk factors in MS



MAIN GENETIC COMPONENTS

Susceptibility:
HLA DRB15:01

- **25–30%** of the population in northern Europe and the USA[1]
- IL-7 receptor α chain locus polymorphisms[2]

Protective: *HLA A02*[1]

ENVIRONMENTAL RISK FACTORS[1]

Strong evidence:
Prior EBV infection and cigarette smoking

Moderate evidence:
Low sun exposure, childhood/adolescent obesity, low vitamin D, high fish intake

EBV, Epstein-Barr virus; HLA, human leukocyte antigen; IL, interleukin; MS multiple sclerosis.

1. Waubant E, et al. *Ann Clin Transl Neurol.* 2019;**6**:1905–22; 2. Liu H, et al. *Sci Rep.* 2017;**7**:1207.

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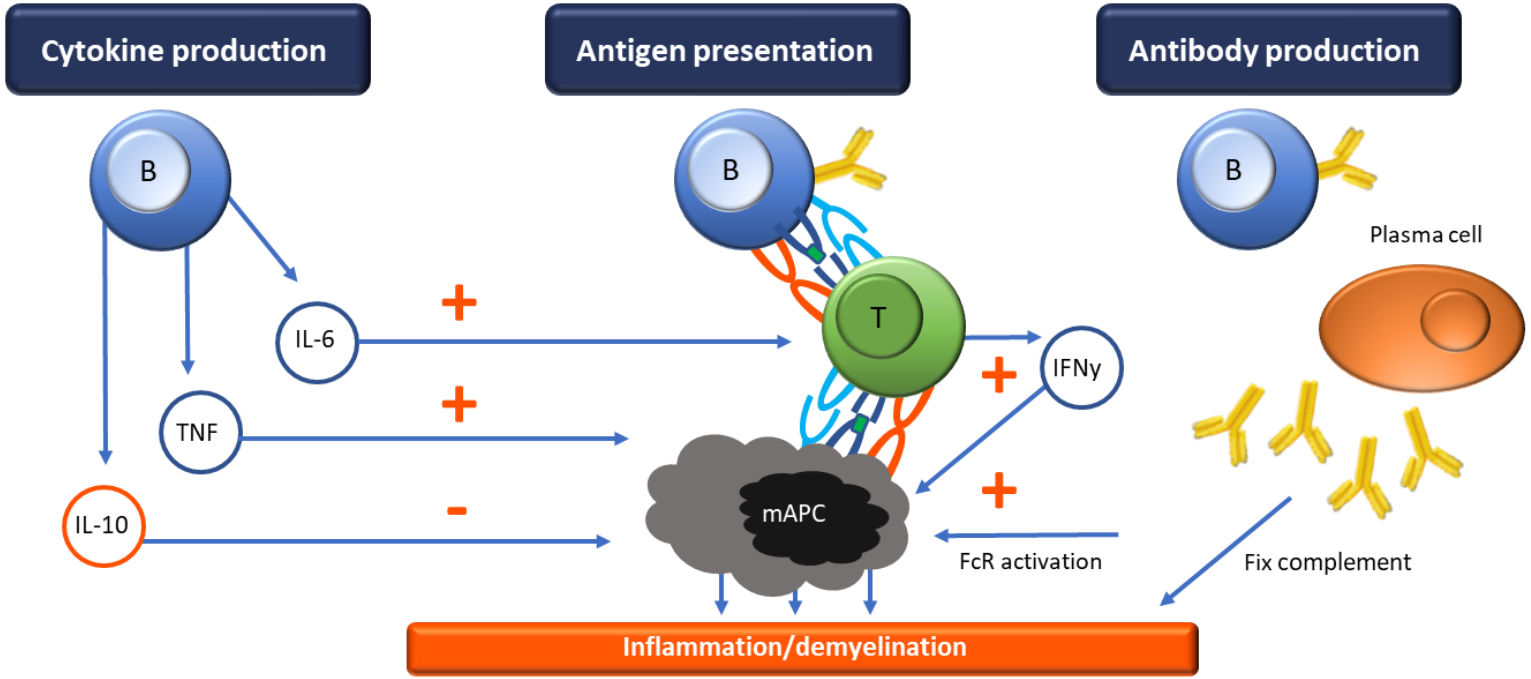
The role of B cells in MS



B, B cell; FcR, Fc receptor; IFNγ, interferon gamma; IL-6/10, interleukin 6/10; mAPC, myeloid antigen-presenting cells; T, T cell; TNF, tumour necrosis factor.

Lehmann-Horn K, et al. *Ther Adv Neurol Disord.* 2013;**6**:161–173.

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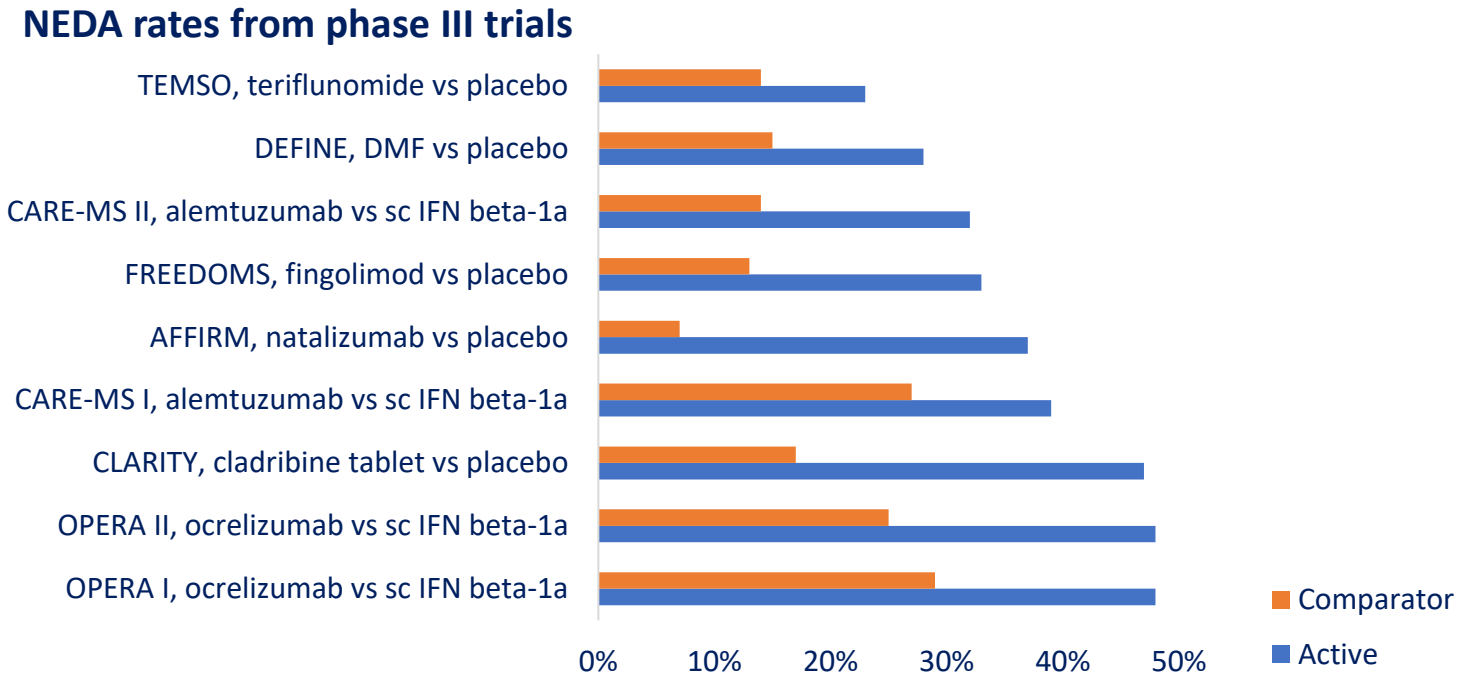
Efficacy of B-cell targeted therapy in relapsing forms of MS



DMF, dimethyl fumarate; NEDA, no evident disease activity

Giovannoni G. *Curr Opin Neurol.* 2018;**31**:233–243.

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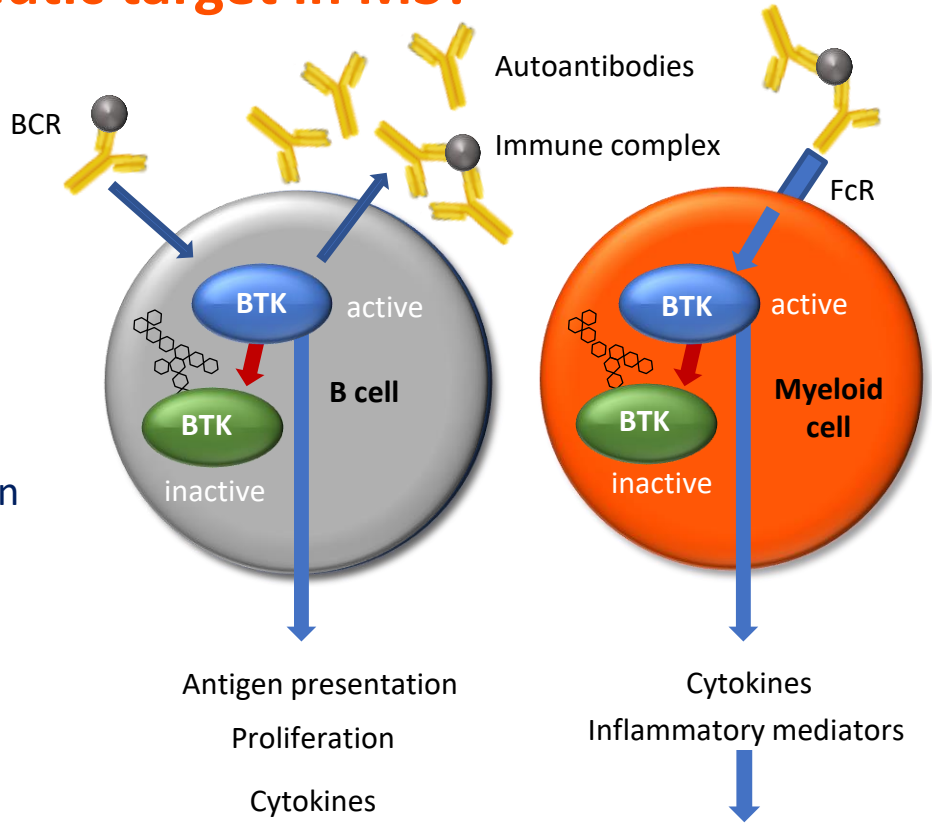
BTK: A potential therapeutic target in MS?

- A promising target for the treatment of autoimmune disease due to its role in mediating both BCR- and FcR-signalling
- BTK inhibitors block BCR- and FcR-mediated signalling and subsequent activation and function of human B cells and innate immune cells



BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; FcR, Fc receptor.
Haselmeyer P, et al. *J Immunol.* 2019;**202**:2888–2906.

Brain imaging advances have informed understanding of MS pathophysiology

New or enlarging T2 lesions and T1 Gd+ lesions	Classical phase II trial outcome measures[1]
Atrophy including white and grey matter and cortical thickness	Correlates with disability progression and cognitive dysfunction[2]
Paramagnetic rims	Associated with smouldering MS lesions, which correlate with increased disability[3]
Leptomeningeal contrast enhancement	Correlates with focal cortical thinning; plausible target for B-cell targeting therapies[4]

Gd, gadolinium; MS, multiple sclerosis.

1. Moccia M, et al. *Mult Scler*. 2017;**23**:1614–1626; 2. Rocca MA, et al. *Neurology*. 2017;**88**:403–413. 3. Absinta M, et al. *JAMA Neurol.* 2019;**76**:1474–1483;
4. Bergsland N, et al. *Am J Neuroradiol*. 2019;**40**:620–625.