NUFFIELD DEPARTMENT OF
CLINICAL NEUROSCIENCES
Medical Sciences Division

UKRI Medical Research Council

The B cell biology underlying autoantibody-mediated diseases: Pathogenesis and Therapeutic implications

Sarosh R Irani

Head, Oxford Autoimmune Neurology Group

MRC Senior Clinical Fellow, Honorary Consultant Neurologist

Nuffield Department of Clinical Neurosciences, University of Oxford

Oxford Autoimmune Neurology Group

wellcome

DISCLOSURES

LGI1/CASPR2/Contactin-2/VGKC-complex antibody patent: SI and the University of Oxford receive royalties and payments for Ab assays and is an inventor on patent application WO/2010/046716 entitled ‘‘Neurological Autoimmune Disorders.’’ The patent has been licensed for the development of assays for LGI1 and other VGKC-complex Abs

Travel support: from Lundberg and Grifols to attend conferences / meetings

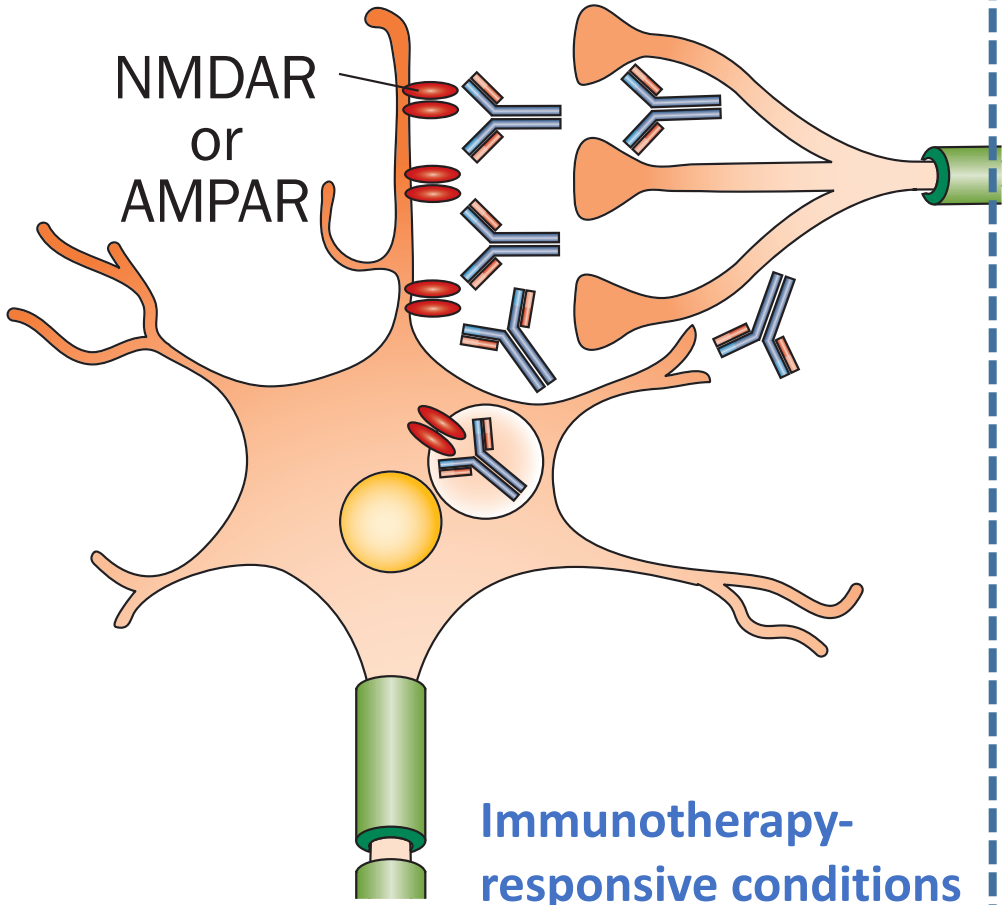
Research support and honoraria: from UCB Pharma, MedImmun, Brain, MedLink Neurology, Immunovant, ONO pharmaceuticals and CSL Behring

Learning objectives

1. In autoantibody-mediated diseases, the antibodies target extracellular epitopes
2. During B cell development, naïve B cells evolve to acquire memory for antigens
3. Autoantibody generation can occur by contrasting mechanisms involving germinal centres and/or long lived plasma cells
4. Autoantibody levels are higher in the periphery than in the CSF
5. The CNS is no longer considered ‘immune privileged’, with clear afferent and efferent limbs

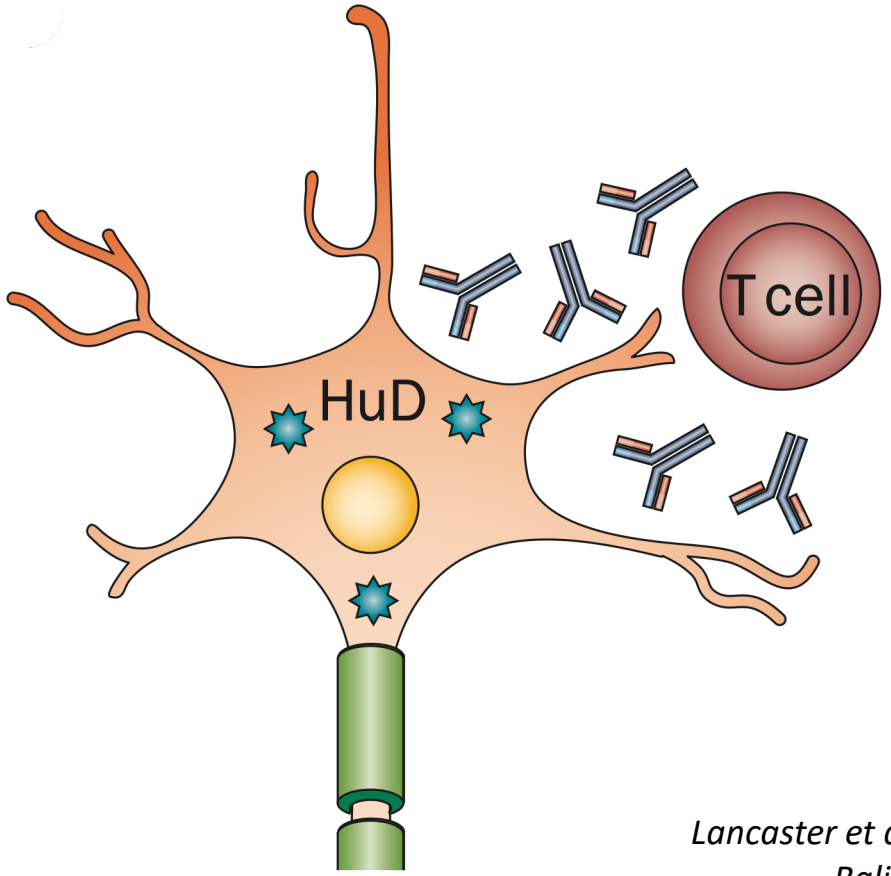
Location location location

EXTRACELLULAR ANTIGEN



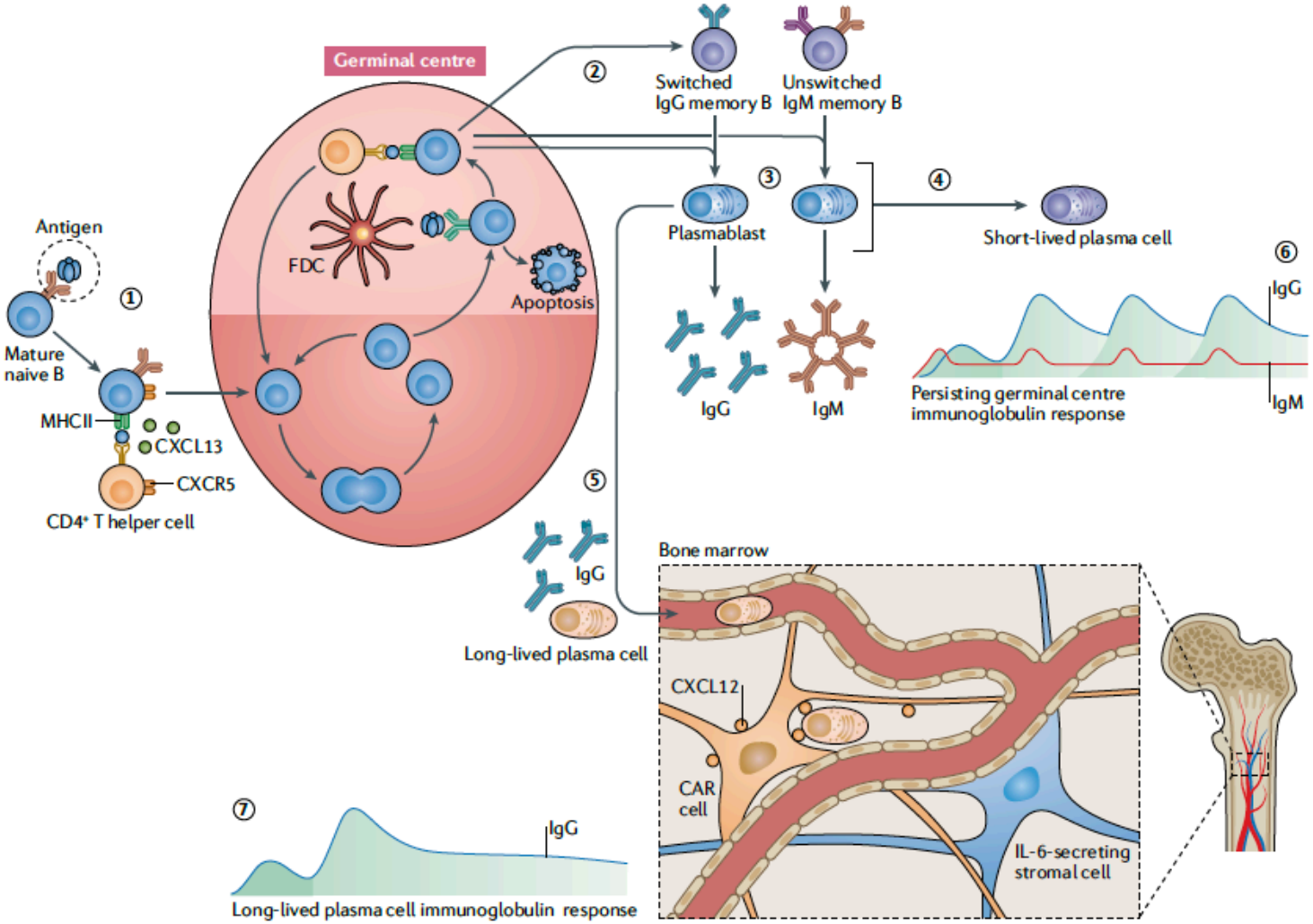
Immunotherapy-responsive conditions

INTRACELLULAR ANTIGEN



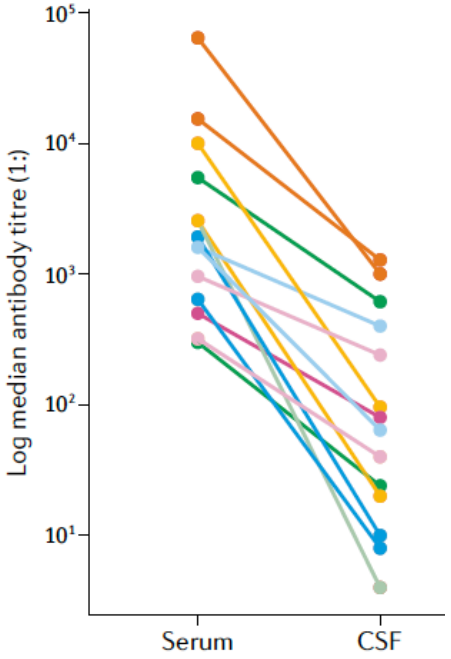
Lancaster et al 2012 Nat Neurol
Balint et al 2018 Brain
Damato et al 2018 MDJ
Ramanathan et al 2020 J Neurol

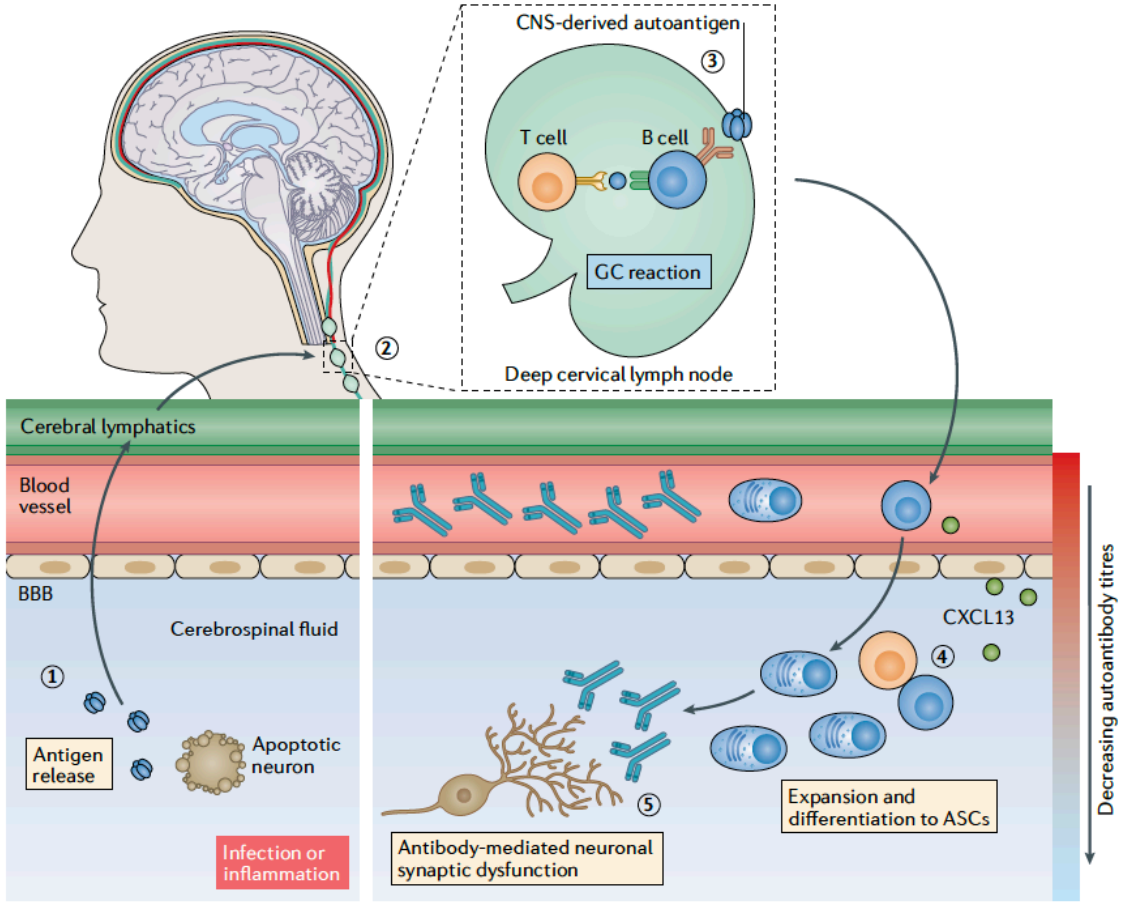
Two contrasting hypotheses of autoantibody production



A hypothesis for disease pathogenesis

Antigen	Serum:CSF ratio
AQP4	104–204
CASPR2	12–64
$GABA_A$ receptor	4–8
$GABA_B$ receptor	4–25
LGI1	80–192
MOG	640
NMDAR	9–13
NMDAR (after HSE)	6





Sun et al 2020 Nature rv Neurol

References

Reviews

Clinical

- Ramanathan, S., Al-Diwani, A., Waters, P. & Irani, S. R. The autoantibody-mediated encephalitides: from clinical observations to molecular pathogenesis. *J. Neurol.* (2019). doi:10.1007/s00415-019-09590-9
- Varley, J., Vincent, A. & Irani, S. R. Clinical and experimental studies of potentially pathogenic brain-directed autoantibodies: current knowledge and future directions. *J. Neurol.* **262**, 1081–1095 (2015).

B cell Biology

- Sun B, Ramberger M, O'Connor KC, Bashford-Rogers RJM, Irani SR. The B cell immunobiology that underlies CNS autoantibody-mediated diseases. *Nat Rev Neurol*. 2020;16(9):481-492. doi:10.1038/s41582-020-0381-z
- Sabatino JJ, Pröbstel A-K, Zamvil SS. B cells in autoimmune and neurodegenerative central nervous system diseases. *Nature Reviews Neuroscience*. Published online November 11, 2019. doi:10.1038/s41583-019-0233-2
- Meffre, E. & O'Connor, K. C. Impaired B-cell tolerance checkpoints promote the development of autoimmune diseases and pathogenic autoantibodies. *Immunol. Rev.* **292**, 90–101 (2019).
- Bennett JL, O'Connor KC, Bar-Or A, et al. B lymphocytes in neuromyelitis optica. *Neurology® neuroimmunology & neuroinflammation*. 2015;2(3):e104. doi:10.1212/nxi.0000000000000104

Original papers

- Bennett JL, Lam C, Kalluri SR, et al. Intrathecal pathogenic anti-aquaporin-4 antibodies in early neuromyelitis optica. *Annals of Neurology*. 2009;66(5):617-629. doi:10.1002/ana.21802
- Kreye, J. *et al.* Human cerebrospinal fluid monoclonal N-methyl-D-aspartate receptor autoantibodies are sufficient for encephalitis pathogenesis. *Brain* **139**, 2641–2652 (2016).
- Ramberger, M. *et al.* Distinctive binding properties of patient-derived monoclonal LGI1-autoantibodies determine pathogenicity. *Brain* **143**:1731-1745. (2020)
- Makuch, M. *et al.* N-methyl-D-aspartate receptor antibody production from germinal center reactions: Therapeutic implications. *Ann. Neurol.* **83**, 553–561 (2018).
- Wilson, R. *et al.* Condition-dependent generation of aquaporin-4 antibodies from circulating B cells in neuromyelitis optica. *Brain* **141**, 1063–1074 (2018).
- van Sonderen, A. *et al.* Anti-LGI1 encephalitis is strongly associated with HLA-DR7 and HLA-DRB4. *Ann. Neurol.* **81**, 193–198 (2017).
- Binks, S. *et al.* Distinct HLA associations of LGI1 and CASPR2-antibody diseases. *Brain* **141**, 2263–2271 (2018).