Anti B cell or non-specific anti B+T cell therapy

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Multiple sclerosis (MS) is a multifactorial disease, with complex aetiology driven by genetics and the environment. Pathogenesis is clearly immune-mediated, as had been suspected for a long time. In this respect, findings from genome-wide association studies (GWAS; Sawcer et al. 2011; *Nature* 476:214), the pathology of MS brain lesions (Kutzelnigg and Lassmann 2014; *Handb Clin Neurol* 122:15), animal model studies (Constantinescu et al., 2011; *Br J Pharmacol* 164:1079), and the response to immunotherapies (Nylander and Hafler 2012; *J Clin Invest* 122:1180) have confirmed that the immune system is the effector of central nervous system (CNS) tissue damage. In progressive disease, it is likely that neurodegenerative mechanisms are also important.

I will argue that MS is driven by potent T-cell and B-cell cooperative mechanisms.

Activated T cells are thought to be essential. They enter the CNS through its microvasculature, forming characteristic perivascular cuffs, and are re-activated by CNS-resident antigen-presenting cells to trigger an inflammatory and autoreactive cascade (Hohlfeld et al 2016; *Lancet Neurol* 15: 198). Such mechanisms have been interfered with, most specifically and successfully, by designing natalizumab as an effective anti-integrin Mab that blocks T-cell entry into the CNS (Yednock et al 1992; *Nature* 356:6; Polman et al 2006; *N Engl J Med* 354:899). $CD4^+$ T cells, crucial coordinators of the adaptive immune response, can activate or inhibit other immune cells as they respond to foreign or self antigens in physiological or pathological responses. $CD8^+$ T cells are also well represented in MS lesions and could potentially target oligodendrocytes and neurons directly, through HLA class I-restricted antigen recognition (Friese et al 2008; *Nat Med* 14:1227).

B cells are involved in an immune signature of MS in >90% of patients, namely cerebrospinal fluid oligoclonal IgG bands (OCB; Housley et al 2015; *Clin Immunol* 161:51). Although the specificity of such oligoclonal response remains unclear, we know from its molecular features that it is antigen-driven, quite possibly by one of more viruses, such as Epstein-Barr virus (EBV, HHV-4). The importance of B cells is also emphasised by their targeting for infection by EBV, a virtually essential factor in susceptibility to MS (Pakpoor et al 2013; *Mult Scler* 19:162). Production of antibodies by B-cell derived plasma cells is also known to promote more efficient myelin damage by monocyte-derived CNS-infiltrating macrophages, chemo-attracted by activated T cells (Hohlfeld et al 2016; *Lancet Neurol* 15:317).

In addition to their productive interactions in peripheral lymphoid organs and the "classic" perivascular cuffs that characterise MS lesions (immune pathogenesis "from the inside"), T and B cells also interact in the subarachnoid spaces adjacent to the pial surface of the cerebral cortex, most likely leading to different types of cortical lesions "from the outside" (Calabrese et al 2015; *Nat Rev Neurosci* 16:147). This is most evident, but not necessarily limited to, the

tertiary lymphoid follicles observed in advanced progressive cases (Pikor et al 2016; *Front Immunol* 6:657). Crucially, not only GWAS, but also epigenetic studies indicate unequivocally that MS susceptibility genes are most highly expressed in both T cells and B cells (Farh et al., 2015; *Nature* 518:337).

The excitement for the success of B-cell targeting therapies that started with rituximab (Hauser et al 2008; *N Engl J Med* 358:676) and led to ocrelizumab (Sorensen and Blinkenberg 2016; *Ther Adv Neurol Disord* 9:44) and other potential Mabs, should not hinder our efforts to control disease by thoughtful, pathogenesis-driven approaches. We know that the effects of anti-B cell treatments are too fast to be mediated by antibody production and that plasma cells are not even depleted by such antibodies. It is likely that antigen presentation by B cells to T cells is inhibited instead, as are other pro-inflammatory, antibody-independent B-cell functions. We should also keep in mind that drugs that we consider as mainly targeting B cells are in fact also affecting T cells – consider for example the depletion of $CD20^{dim}$ T cells by rituximab (Palanichamy et al 2014; *J Immunol* 193:580). Conversely, treatments that we consider as aimed at T cells, also have effects on B cells. For example, natalizumab affects the levels of circulating B cells with different naive/memory profiles depending on its effects on the mobilization of hematopoietic stem cells (Mattoscio et al 2015; *Neurology* 84:1473). In addition, fingolimod promotes a regulatory phenotype and function of B cells (Gruetzke et al 2015; *Ann Clin Transl Neurol* 2: 119) and reduces the repertoire diversity of newly produced T as well as B cells (Chiarini et al 2015; *Mult Scler* 21:726). The most effective disease-modifying treatments, either licensed for use (alemtuzumab) or experimental (hematopoietic stem cell transplantation), potently deplete both T cells and B cells, the latter recovering more quickly in subsequent months (Jones and Coles 2014; *Exp Neurol* 262:37; Sullivan et al 2010; *Biol Blood Marrow Transplant* 16: S48; Mancardi et al 2015; *Neurology* 84:981).

In conclusion, on the basis of the above mentioned observations, it would be unwise to exclusively target B cells in MS. We are in fact not even able to do so – and until more crucial disease mechanisms are clarified, we probably should not.