As with so much in life, an appropriate immune response is composed of checks and balances. Too much inflammation or too little regulation is a bad thing and can lead to life-threatening disease, such as asthma or autoimmune conditions including multiple sclerosis (MS). For the past 20 years, a primary focus for immunologists has been the study of regulatory T (Treg) cells. CD4⁺ Treg cells originally identified by their high and continued expression of the interleukin (IL) IL-2 receptor, CD25, were subsequently distinguished by the transcription factor FoxP3. Natural Treg cells derived from the thymus and inducible Treg cells generated in the periphery from CD4⁺ T cells, both have suppressive functions required to maintain tolerance, preventing autoimmunity and limiting inflammatory responses. The importance of these cell populations is evident through a vast amount of work demonstrating that in their absence, immune responses can become highly pathological.¹

In view of this there is a real drive to utilize Treg cells in immunotherapy. Inhibition of Treg cell function to break tolerance for cancer treatment, or stimulation of Treg cell function on a cellular basis or by increasing numbers to induce tolerance and limit autoimmunity has enormous therapeutic potential. Such clinical promise was upended when it was discovered that under certain circumstances FoxP3⁺ Treg cells can become highly pathological.² Yet recent studies investigating the stability of FoxP3⁺ T cells from peripheral blood of MS patients suggests that Treg cells are prone to interferon (IFN)-γ production and would, therefore, not be an ideal therapeutic target. Such studies are limited as they are analyzing circulating cells rather than FoxP3⁺ cells at the site of inflammation.² In this issue of *Immunology and Cell Biology*, Zandee et al.,³ using a novel tissue bank of post-mortem brain tissue from patients who have died of non-neurological causes provide significant evidence that Treg cells in MS lesions retain their regulatory suppressive function.

MS, is a demyelinating autoimmune disease that can encompass a broad set of pathologies and is, somewhat unsatisfyingly, defined as having two or more lesions in the central nervous system (CNS) separated in time and space that cannot be attributed to any other clinical cause. Lesions are caused by autoimmune T cells targeting the myelin sheath around neurons. Further classification of MS is achieved by determining disease progression. Most patients have relapsing remitting disease, in which symptoms hit sporadically followed by periods of healing in which little to no symptoms are apparent. The healing involves the remyelination of neurons, a reduction in inflammatory cells in the CNS and disappearance of lesions as observed by magnetic resonance imaging. This state is frequently followed by secondary progressive MS (SPMS) where symptoms worsen over time. Zandee and colleagues accessed the UK Multiple Sclerosis Tissue Bank of post-mortem brain tissue from secondary progressive MS patients and control individuals who died of non-neurological causes. Of 10 patients with lesions, 7 had Treg cells present as identified by the co-expression of FoxP3 and the production of IL-10 by Treg cells. This type of tissue bank allows analysis of a greater range of lesions than tissue from patients who have died due to MS-related pathology. Thus, in lesions that are healed with evidence of remyelination, Treg cells are not found, and it is only in active lesions that IL-10-producing FoxP3⁺ cells dominate. The authors argue this supports a role for Treg cells retaining their suppressive qualities and only infiltrating in areas of active ongoing inflammation (Figure 1). This conclusion, rather than FoxP3⁺ Treg cells being a cause of the lesion, is also derived from previous murine studies in which Treg cell numbers decline as disease (experimental autoimmune encephalomyelitis) resolves.⁴ The production of IL-10 by Treg cells classically inhibits IL-12, and therefore the production of IFN-γ. In addition, it also stimulates alternatively activated or tissue remodeling macrophages that support oligodendrocyte differentiation and therefore remyelination.⁵

Further evidence of the suppressive quality of these cells comes from their expression of the IL-33 receptor ST2.⁶ Expression of ST2 also signals the reason for Treg cell recruitment as IL-33, a member of the alarmin group of cytokines is produced during tissue damage. In the intestine, ST2 expression by Treg cells is correlated with strong suppressive activity.⁷ Others have reported this pathway active in MS lesions⁸ with CNS resident cells, including oligodendrocytes responsible for myelination, expressing IL-33 while the receptor (ST2) is expressed within the lesion. This current study would now suggest that ST2 is expressed by regulatory cells and is a critical piece of the puzzle in stimulating Treg cell suppressive activity in the lesion (Figure 1). Whether or not a decrease in IL-33 occurs, as the lesion heals, would be worthy of study. Under these circumstances, reduced ST2 signaling could be a driving factor of Treg cell instability and could explain...
Vastly different clinical symptoms could be to classify MS as a spectrum of disease where occurring in MS. Indeed, there is movement but were still present. Therefore, it is still too does not maintain phenotype. Thus, although expression of a transcription factor alone γ not, can be driven to secrete IFN-γ 

Clearly, given the right stimuli (for example, dominant impact on the function of the cell. In which a T cell inhabits can have a 

Lastly, the location and local environment in which a T cell inhabits can have a 

To summarize, the results from this current study show IL-10-producing Treg cells present in active inflamed, but not remyelinating lesions of MS patients. It would support approaches where induction of Treg cells within the host would be a far superior therapeutic than the current drug treatments that inhibit all cells from entering the brain.

**CONFLICT OF INTEREST**
The author declares no conflict of interest.