Tissue-resident CD8 T cells in central nervous system inflammatory diseases: present at the crime scene and ...guilty

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Tissue-resident CD8 T cells in central nervous system inflammatory diseases: present at the crime scene and …guilty

Doron Merkler[1,2], Ilena Vincenti[1], Frederick Masson[3] and Roland S Liblau[3,4]

Tissue-resident memory T cells (T_{RM}) represent a subset of antigen-experienced T cells that are constantly retained in a given tissue with limited trafficking through the circulation. These cells are characterized by expression of molecules enabling their tissue anchoring and downregulation of molecules promoting tissue egress. They reside at sites of previous antigen encounter and their number increases with age. T_{RM} have been shown to provide rapid and efficient protection against tissue reinfection and T_{RM} density correlates with efficient antitumor responses. Intriguingly, the density of CD8 T_{RM} is increased in the central nervous system (CNS) of patients with neuroinflammatory diseases such as multiple sclerosis, or suffering from neurodegenerative diseases. In this review, we discuss current knowledge regarding the diversity of CNS-resident CD8 T cells and their role in CNS autoimmunity. Given their likely contribution to the protracted course of several inflammatory diseases of the CNS, their therapeutic targeting becomes an important challenge.

Addresses
[1] Department of Pathology and Immunology, University of Geneva, Geneva, Switzerland
[2] Division of Clinical Pathology, Geneva University Hospital, 1211 Geneva, Switzerland
[3] Toulouse Institute for infectious and inflammatory diseases (Infinity), University of Toulouse, CNRS, INSERM, UPS, 31024 Toulouse, France
[4] Department of Immunology, Toulouse University Hospital, 31300 Toulouse, France

Corresponding author: Doron Merkler (doron.merkler@unige.ch)

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Introduction

Memory T cells ensure a key role in immune surveillance and in protective immunity against reinfection and tumor control. Thereby, memory T cells represent a functionally heterogeneous pool of cells, which are classically segregated according to their patrolling routes within the body. Circulating-memory T cells consist of central-memory T cells (T_{CM}) and effector-memory T cells (T_{EM}) that patrol in the bloodstream, lymphoid organs, and, for T_{EM}, transiently in nonlymphoid organs. In contrast, tissue-resident memory T cells (T_{RM}), the focus of this review, are sessile in a wide range of non-lymphoid tissues, but may re-enter the bloodstream upon recall responses, revealing a recirculatory potential of T_{RM} progeny [1,2].

With regard to the central nervous system (CNS), T_{RM} are generated in mice following acute CNS infection with vesicular stomatitis virus [3] or lymphocytic choriomeningitis virus (rLCMV) [4]. Similarly, T_{RM} are found during persistent infection with murine polyomavirus (MuPyV) [5], murine cytomegalovirus [6], adenovirus [7], bacterial infection such as neuroinvasive Listeria monocytogenes [8], and the intracellular parasite *Toxoplasma gondii* [9]. In humans, the residence behavior of memory T cells is challenging to prove, particularly in the CNS. Thus, identification of T_{RM} often relies either on the detection of canonical T_{RM} markers, such as CD69, CD103, or CD49a [10], or on the analysis of their transcriptional signature [11•,12•]. Notably, whereas CD103 expression defines resident memory T cells in epithelial tissues, T_{RM} from the CNS comprise both CD103 + and CD103-subsets [13].

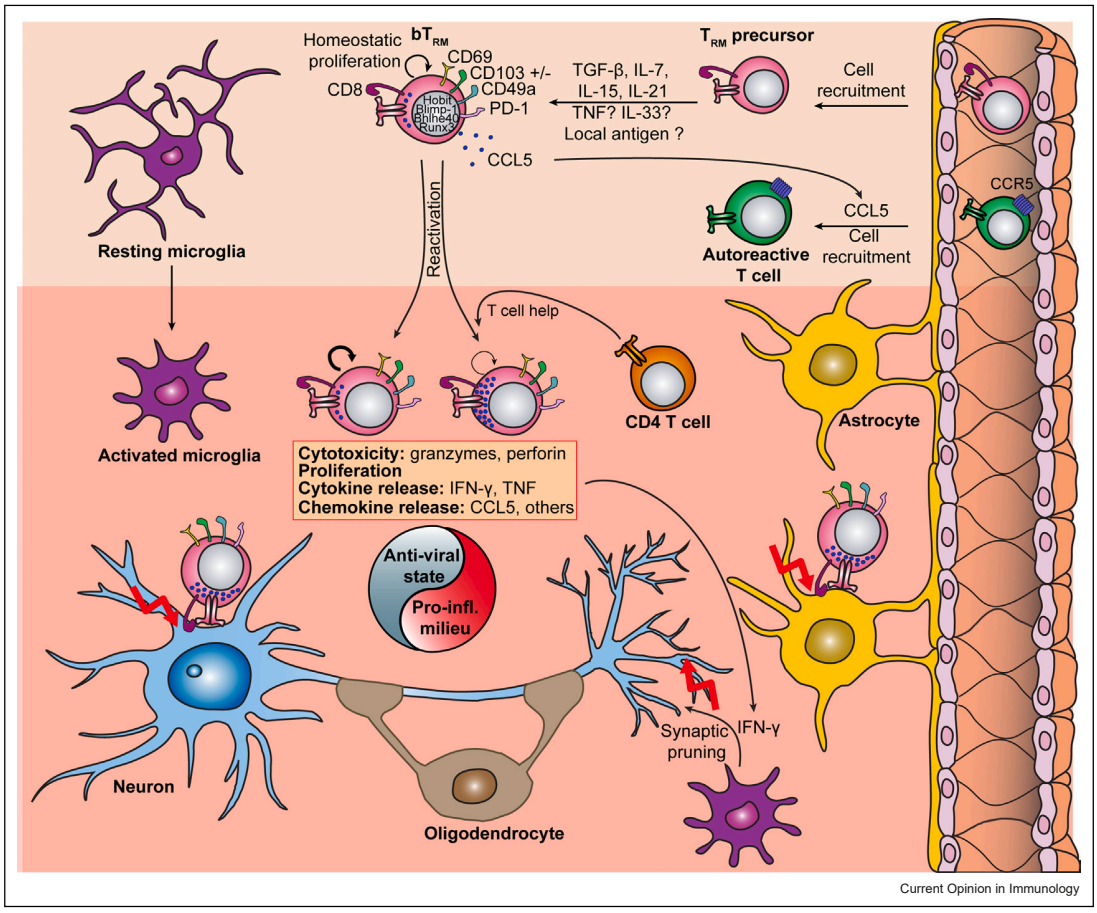
Beyond their role in protective immunity, recent studies suggest that T_{RM} are also implicated in organ-restricted chronic inflammatory diseases, some of which involve the CNS (Table 1). The role of T_{RM} in CNS autoimmune conditions as well as in neurodegenerative disorders only starts to be uncovered. Most of our understanding regarding T_{RM} establishment, maintenance, and function is derived from experimental model systems and focused on CD8 T_{RM}. Although less is known about CD4 T_{RM}

Table 1

Human chronic CNS diseases in which CD8 + T_{RM} were reported.

Chronic CNS diseases	T_{RM} phenotype	References
Multiple Sclerosis	CD8 + CD69 + CD103 + /–	[11•,39•,64•–66]
Neuromyelitis optica	CD8 + CD69 + CD103 + /–	[39•]
Paraneoplastic neurologic syndromes	CD8 + CD69 + CD103 + /–	[38•]
Rasmussen Encephalitis	CD8 + CD103 +	[67,68]
Alzheimer	CD8 + CD69 + CD103 + /–	[63]
Parkinson	CD8 + CD69 + CD103 + /–	[63,69•]
Dementia	CD8 + CD69 + CD103 + /–	[63]
Bipolar disorder	CD8 + CD69 + CD103 + /–	[63]

Figure 1



Schematic outline summarizing CD8 T_{RM} in CNS inflammation. T_{RM} precursor cells recruited within the CNS differentiate into brain T_{RM} (bT_{RM}) upon sensing of microenvironmental cues. The core signature of bT_{RM} includes expression of CD69, CD49a, PD-1, and transcription factors Hobit, Blimp-1, Bhlhe40, and Runx3. In addition, both CD103 + and CD103–bT_{RM} subsets exist. Resting bT_{RM} undergo homeostatic proliferation and constitutively produce the chemokine CCL5, attracting CCR5 + autoreactive T cells within the CNS. Upon bT_{RM} reactivation, the heterogeneous pool of bT_{RM} progeny consists of cells with a high proliferative capacity and cells with a high cytotoxic capacity. CD4 T-cell help is necessary for the acquisition of the highly cytotoxic program. Activated bT_{RM} release pro-inflammatory mediators such as IFN-γ and TNF, as well as chemokine such as CCL5. Altogether, bT_{RM} induce a damaging proinflammatory milieu that can be protective in case of a viral reinfection. bT_{RM}-derived IFN-γ induces synaptic pruning by activated microglia, leading to neuronal damage. Activated autoreactive bT_{RM} can directly attack astrocytes and neurons, and, possibly other cells such as oligodendrocytes.

within the CNS, new functions are emerging for this subset [14]. Here we review the current state of the field, emphasizing the origin of CD8 T_{RM}, their reactivation mechanisms, and how they can be implicated in chronic inflammatory diseases of the CNS.

Mechanism of tissue-resident memory T cells differentiation and maintenance in the central nervous system

T_{RM} preferentially arise from CD127–KLRG1– early effector cells [15–17]. T_{RM} commitment most likely occurs in inflamed tissues upon sensing of tissue-specific microenvironmental cues by precursor cells (Figure 1). Additionally, recent evidence suggests that early T_{RM} precursors are already skewed toward the T_{RM} fate in lymphoid organs [18,19].

TGF-β promotes T_{RM} differentiation by inducing CD103 upregulation and subsequent retention of CD103 + T_{RM} in epithelial tissues [20,21]. Interestingly, TGF-β is also critical for the development of CD103–T_{RM} of the lung [22,23]. During West Nile virus (WNV) infection of the brain, TGF-β production by regulatory T cells similarly induced CD103 upregulation on infiltrating CD8 T cells [24]. Recently, a study of human peripheral blood mononuclear cells (PBMC) suggested that hypoxia synergizes with TGF-β for CD103 induction [25]. CD103 expression has been shown to facilitate cell retention through the interaction with its ligand E-cadherin in epithelia. Despite the absence of E-cadherin expression in the brain parenchyma, expression of CD103 by brain T_{RM} was associated with an increased T_{RM} retention within the CNS tissue [13,26]. During experimental persistent viral infection of the brain, CD4 T-cell-derived IL-21 supports T_{RM} formation [27], while CD4 T-cell help is not required to clear virus from the brain after CNS acute LCMV infection [4]. Additional microenvironmental signals that presumably promote T_{RM} differentiation comprise IL-7, IL-15, TNF, and IL-33 [20,28–31] (Figure 1). Conflicting results have been reported regarding the requirement of local antigen encounter in the CNS for the development of T_{RM} [7,27,32]. Additionally, IL-1β signaling seems to be required for migration of WNV-specific T cells across the blood–brain barrier (BBB) [33], but its role for T_{RM} differentiation remains to be addressed. Finally, costimulatory signals such as ICOS and CD28 can impact T_{RM} differentiation and functions [16,34].

T_{RM} display a distinct transcriptional signature [35,36] but also share some transcriptional overlap with T_{EM} and T_{CM} [37]. Notably, although sharing a common core signature, there is a phenotypical and a functional heterogeneity among T_{RM} from the brain [38•,39•], specifically regarding proliferative and effector capabilities. The core transcriptional program defining T_{RM} comprises the expression of *Hobit*, *Blimp-1*, *Runx3*, and *Bhlhe40* [35,36,40] (Figure 1). Intriguingly, a polymorphism in the *Runx3* gene has been associated with risk to develop multiple sclerosis (MS) [41]. The restrictive environment of nonlymphoid tissues reduces metabolite availabilities. Therefore, T_{RM} have evolved a particular metabolic reprogramming that depends on exogenous free fatty acid uptake to survive [42], and have been shown to adapt their residency program to facilitate organ-specific fatty acid uptake [43]. The transcription factor Notch is required for T_{RM} survival in the lung [44], however, its requirement to establish T_{RM} in other tissues remains elusive. The hallmark of T_{RM} also comprises the downregulation of *Klf2*, *S1pr1*, and *S1pr5* [35,45], all involved in tissue egress. In addition, T_{RM} in murine CNS typically express PD-1 [6,13], the implication of which remains to be explored. The corresponding ligand, PD-L1, is expressed on astrocytes, microglia, and neurons upregulate PD-L1 expression following MuPyV infection in the CNS [46], suggesting a regulatory role of neural cells for T_{RM} activity. In line with this, *in vitro* experiments found that PD-L1 from glial cells induces upregulation of CD69 and CD103 on activated CD8 T cells [47].

Although considerable progress is being made in our understanding of the regulation of T_{RM} function and retention in the CNS, open questions remain to be addressed. In particular, it will be important to gain further knowledge regarding the local cellular source and the temporal regulation of the essential signals, leading to T-cell residence in the CNS.

Evidence for tissue-resident memory T cells in protective immunity of the central nervous system

The presence of T_{RM} in the CNS accelerates clearance of LCMV during acute reinfection and controls persistent infection [4,5,32]. T_{RM} are involved in protective immunity via several mechanisms. They rapidly express proinflammatory cytokines following pathogen encounter, exerting a sensing and alarming function that induces an 'anti-viral state' and that promotes the recruitment of immune cells to the infected tissue [48,49]. In addition, upon reactivation, T_{RM} rapidly expand in the CNS and give rise to effector cells [3,4]. These effector cells can clear virus in an interferon-gamma-(IFN-γ-) and perforin-dependent manner, even in the absence of circulating T cells or NK cells, showing that T_{RM} can serve as an autonomous immunological barrier against infection of the CNS [4]. While circulating-memory T cells are also sufficient to protect against fatal outcome following LCMV intracranial challenge [4], protective immunity during challenge with rabies virus is only achieved when resident memory T cells are pre-

established in the CNS [50,51]. This suggests that the need for T_{RM} in protective anti-infectious immunity may vary, depending on the infection context, ranging from being sufficient to necessary.

Beyond their protective function during infection, T_{RM} are also supposed to play a role in immune surveillance of cancer. Indeed, T_{RM} are found in human tumors [52–57] and tumor-specific T_{RM} surveying the skin prevent the development of melanoma cells into macroscopic lesions in a mouse model of cutaneous melanoma [58]. In the CNS, CD8 T cells with a T_{RM} phenotype have been found in gliomas [26,59], which showed TCR specificity against different virus epitopes, including influenza-A-, Epstein–Barr virus, and cytomegalovirus [60]. Accordingly, delivery of virus-derived peptides in a glioblastoma mouse model reactivated T_{RM} from explant tumors and improved survival [60]. Additionally, tumor-cell lysate vaccination in low-grade gliomas has been shown to elicit tumor-specific T cells with a T_{RM} phenotype in the tumor microenvironment [61]. The potential use of T_{RM} to target pathogens and malignant tumors in the CNS therefore appears to be a most appealing avenue of research for the coming years.

Tissue-resident memory T cells in chronic inflammatory disease of the central nervous system

Role of tissue-resident memory T cells in harmful response in the central nervous system

CD8 T cells with a T_{RM} phenotype are detected in the healthy and aging human brain [62,63]. Furthermore, due to the parenchymal localization of T_{RM} and their surveying attributes, it is tempting to speculate that they are involved in inflammatory disease affecting the CNS. In this regard, CD8 T cells expressing CD69 and/or CD103 are described in MS [11•,64•–66] and in neuromyelitis optica spectrum disorders [39•]. CD8 T cells expressing CD103 are also detected in brain-infiltrating lymphocytes from resected lesions of Rasmussen encephalitis (RE), a highly inflammatory disease of possible autoimmune etiology affecting mostly children, and in which neurons are likely the immunological targets of CD8 T cells [67,68].

Additionally, T_{RM} have been found in paraneoplastic neurological disorders [38•], as well as in neurodegenerative conditions such as Alzheimer's and Parkinson's diseases [63,69•,70]. The fact that T_{RM} are also found in neurodegenerative diseases raises the question how these cells may be involved in the pathogenesis of neurodegeneration. In Parkinson's disease, CD8 T_{RM} infiltration in the substantia nigra paralleled the progression of dopaminergic neuron death and was present already in early disease stages, even before synucleinopathy was evident [69]. Likewise, clonally expanded CD4 T_{RM} secreting inflammatory mediators and stimulated with a phosphorylated α-synuclein epitope were found in patients suffering from Lewy body dementia and T_{RM}-like CD4 T cells could be detected in their CSF and postmortem substantia nigra [70]. Altogether, this suggests that T_{RM} may contribute or even foster disease evolution in such neurodegenerative diseases. Regardless of whether the disease is primarily considered as neuroinflammatory or neurodegenerative, T_{RM}-mediated tissue damage could happen in two principal ways, either in a bystander manner and/or via cognate antigen recognition.

With regard to a bystander involvement of T_{RM} in CNS autoimmune disease, it was shown that following transient LCMV infection in young mice, brain T_{RM} contributed to a proinflammatory tissue microenvironment in which their constitutive expression of the chemokine CCL5 facilitated the recruitment of circulating autoreactive T cells later in life [66] (Figure 1). Analogously to mice, CCL5 was also detected in the normal-appearing white matter of MS patients. Furthermore, it has been shown that T_{RM} expressed IFN-γ after flavivirus infection and drove synaptic pathology in a bystander manner via microglia activation [71•].

In experimental models of viral and autoimmune encephalitis, CNS-infiltrating effector CD8 T cells attack neurons in an antigen-dependent manner [38•,72] (Figure 1). With prolonged disease duration, such infiltrating CD8 T cells can become tissue-resident and progressively drive neuronal alterations and loss behind the BBB independently to their circulating counterparts [38•]. Furthermore, TCRβ sequencing from RE brain resections identified sequence similarity between the CDR3 from the most abundant clonotypes with that of T-cell clones specific for two immunodominant human cytomegalovirus (HCMV) epitopes [73]. This finding suggests that autoreactive T cells in RE might be cross-reacting with HCMV epitopes. Since T_{RM} are described in RE [67,68], one might speculate that cross-reactive T_{RM} are implicated in RE disease pathology. Analogously, in a mouse model of CNS autoimmune disease, virus-specific T_{RM} that cross-react with a cognate neo-self-antigen in glial cells were reactivated and precipitated CNS disease in the absence of infection [39•] (Figure 1).

Furthermore, as brain T_{RM} accumulate following CNS pathogen infections, one could speculate that they could contribute to the aging process and cognitive decline through their intrinsic proinflammatory properties. Indeed, in experimental models of aging, T cells expressing T_{RM} marker (CD69) were found within old

neurogenic niche and contribute to loss of self-renewal through an IFN-γ-dependent mechanism [74]. T_{RM} from aged brains were likewise shown to promote inflammation following ischemic stroke [62].

These data suggest that T_{RM} can play an important role in the immunopathology of various chronic inflammatory processes of the CNS and, thereby, contribute to neurological decline.

Tissue-resident memory T cells cooperation with other immune cells in central nervous system inflammation

During persistent CNS infection with MuPyV and in a model of neuronal autoimmunity, CD8 T_{RM} require CD4 T-cell help to become independent from circulating cells for their maintenance [27,38•,75], revealing an essential role of CD4 T cells for CD8 T_{RM} homeostasis during chronic antigen exposure. Local reactivation of T_{RM} upon antigen encounter in the CNS results in the rapid recruitment of immune cells from the circulation and the vicinity, including CD8 T cells, CD4 T cells, B cells, and border-associated macrophages [39•].

Secretion of IFN-γ appears to be a major T_{RM} effector mechanism fostering the recruitment of various immune cells to the CNS, the local activation of microglial cells, and local interactions between neural cells such as neurons and glial cells and T cells and phagocytes. In the acute phase of brain MuPyV infection, microglial activation is mediated by CD8 T-cell-derived IFN-γ [46]. Similarly, IFN-γ from infiltrating CD8 T cells mediates microglial-dependent synaptic pruning during a mouse model of autoimmune encephalitis [72]. In a model of vaccine-induced autoimmune narcolepsy, lack of IFN-γ by autoimmune CD8 T cells prevents the loss of neurons and attenuates microglial activation [76]. Thus, T_{RM} and infiltrating leukocytes likely cooperate to sustain brain inflammation and inflict tissue damage.

T_{RM} reactivation in the lungs does not depend on conventional antigen-presenting cells, by contrast to circulating-memory cells [77]. Likewise, in a murine CNS autoimmune model, T_{RM} are reactivated by antigen-expressing glial cells [39•]. In this model, functional reactivation of CD8 T_{RM} requires the help of recruited CD4 T cells. Unhelped T_{RM} showed an altered transcriptional signature characterized by increased *Tcf7* expression and reduced expression of cytotoxic genes (Figure 1), which was associated with reduced T_{RM} killing ability and prevented disease onset. Similarly, in a model of neuron-targeted autoimmune disease, help provided locally by CD4 T cells sustains the expression of cytotoxic molecules by T_{RM} [38•].

Thus, it is becoming evident that CD8 T_{RM} communicate with other immune and nonimmune cells within the CNS microenvironment. In particular, CD4 T cells play critical supporting roles for T_{RM} function.

Future perspectives and therapeutic implications

Besides their beneficial role in the protection against neurotropic pathogens and tumors, it is now clear that T_{RM} have the potential to play a deleterious role in human chronic CNS inflammatory or neurodegenerative diseases, ranging from MS, paraneoplastic neurological disorders to Alzheimer's and Parkinson's diseases, and are likely involved in the process of brain aging. T_{RM} drive a compartmentalized immune response in the CNS, leading to pathology that can operate autonomously behind the BBB in the absence of contributions of the circulating CD8 T-cell pool. The role played by local T_{RM} activation, regardless of its mechanisms, in the waxing and waning presentation of some chronic inflammatory diseases of the CNS, remains to be evaluated.

Importantly, high-throughput transcriptomic analyses have revealed the existence of a tissue-residency program enabling T_{RM} to survive in nonlymphoid tissues by rewiring their metabolic program, effector functions, and adhesion-molecule patterns. More studies are therefore necessary to take advantage of this unique tissue-residency program to uncover potential vulnerabilities specific to CNS T_{RM}. This will require improving our understanding of the signals required for their differentiation, long-term maintenance, and positioning within the CNS tissue, as well as unraveling the cellular niche promoting their survival and their interactions with other partners such as CD4 T cells and microglial cells.

The identification of a pathogenic contribution for T_{RM} cells in chronic inflammatory diseases of the CNS, and possibly in neurodegenerative diseases [38•,39•], raises several key questions related to their ontogeny, their regulation, their interactions with other cell types within the CNS, and, ultimately, their therapeutic targeting.

Indeed, while current treatment options in CNS inflammatory diseases rely on the use of systemic immunosuppressors or molecules blocking T-cell migration to the CNS (such as Fingolimod and Natalizumab), there is an urgent need to consider T_{RM} as a key cellular target at the nexus of many chronic CNS inflammatory diseases. The development of therapies targeting T_{RM} is, however, facing multiple challenges. First, T_{RM} act behind a selective BBB potentially restricting access to drugs delivered in the bloodstream, and as T_{RM} can be deeply embedded within the brain parenchyma, this could also reduce drug accessibility. Second, future pharmacological approaches would need to target

specifically pathogenic T_{RM} cells while sparing the circulating T-cell compartment, including potentially beneficial T cells such as regulatory T cells.

Two non-mutually exclusive approaches to target T_{RM} are (i) to interfere with their differentiation or migration to the tissue, and (ii) to inhibit their survival or functions within the CNS. With regard to the first approach, understanding the molecular mechanisms underpinning the differentiation of effector CD8 T cells into T_{RM} or their precursors in the periphery and/or in the CNS would be required to manipulate this cell type [78]. In that respect, recent studies related to the identification of T_{RM} precursors, based on the expression of the *Hobit* transcription factor, provide valuable information on the developmental pathway and markers of early T_{RM} cells [19].

However, at the time of diagnosis, it is likely that a population of T_{RM} has already seeded the CNS and targeting T_{RM} within the CNS would probably be essential. The identification of molecular features unique to CNS T_{RM}, and of the signals and niches that allow their survival and long-term retention within the CNS, should reveal potential therapeutic targets.

Several targets can already be envisioned, such as HOBIT, CD69, and CD103 (T_{RM}-enriched molecules), cytokines supporting T_{RM} survival (IL-21, IL-15), and tissue-retention (TGF-β), or key T_{RM}-derived inflammatory mediators (such as IFN-γ and CCL5). However, a difficult challenge is to inhibit/neutralize these targets locally, in the CNS, without affecting their expression systemically. Administration of antisense RNA or blocking/neutralizing antibodies through the CSF could be an option. Strategies combining the prevention of effector T-cell homing to the CNS (such as S1P-receptor functional antagonists or anti-alpha4 integrin mAb) with inhibition of their CNS residence seem reasonable to act both on the source and the existing pool of pathogenic T_{RM}.

As always, targeting specific immune pathways or cells is a trade-off, as it may lessen protection against infection and cancer [52,79].

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- • of special interest
- •• of outstanding interest

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