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# Age-Stratified Treg Responses During Viral Infections of the Central Nervous System: A Literature Review

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## ABSTRACT

Regulatory T cells (Tregs) play a vital role in limiting inflammation and resolving the immune response after a viral infection. Within the central nervous system (CNS), Tregs are especially important for the protection of neurons, which have limited regenerative capacity, and the preservation of myelin sheaths, which support neuronal function and survival. Nevertheless, viral infections of the CNS often result in enduring neurological dysfunction, especially in more vulnerable age groups such as newborns and the elderly. Although it is appreciated that Treg activity changes with age, it is unclear how these age-dependent changes impact viral CNS infections. In this review, we explore Treg development over the life of the host and discuss evidence for age-dependent Treg responses to peripheral viral infections. We also discuss the CNS-specific roles of Tregs, where both immunomodulatory and neuroprotective functions can contribute to preservation of brain cells. Finally, we examine the current evidence for Treg activity in neurotropic infections in the context of age, and highlight gaps in our understanding of Treg function in younger and older hosts. Overall, a better understanding of age-dependent Treg activity in the CNS may reveal opportunities for therapeutic interventions tailored to the most vulnerable ages.

## 1 | Introduction

Many viruses (e.g., measles virus [MV], West Nile virus [WNV], Zika virus [ZIKV], Herpes simplex viruses [HSV]) can invade and infect the central nervous system (CNS), leading to irreparable damage to neural circuits and death of neurons in some cases [1]. These neurotropic infections can be lethal and are more often associated with a poor prognosis in vulnerable age groups, such as newborns, young children, and the elderly [2–4]. It is well-established that effector T cells (e.g., CD4 helper and CD8 cytotoxic T cells) play important roles in the antiviral response in the brain [5]. For instance, T cells produce interferon-γ (IFN-γ), which is a key cytokine for noncytolytic viral clearance from neurons [6]. CD4 T cells also stimulate

**Abbreviations:** 5-HT, 5-hydroxytryptamine; A2AR, adenosine A2A receptor; Areg, amphiregulin; BALF, bronchoalveolar lavage fluid; CCL20, C-C chemokine ligand 20; CCN3, cellular communication network factor 3; CCR4, C-C chemokine receptor type 4; CCR6, C-C chemokine receptor type 6; CD25, cluster of differentiation 25; CD28, cluster of differentiation 28; CD4, cluster of differentiation 4; CD45, cluster of differentiation 45; CD47, cluster of differentiation 47; CD69, cluster of differentiation 69; CD73, cluster of differentiation 73; CD8, cluster of differentiation 8; CD80, cluster of differentiation 80; CD86, cluster of differentiation 86; CTLA4, cytotoxic T-lymphocyte-associated protein 4; dLN, draining lymph node; DT, diphtheria toxin; DTR, diphtheria toxin receptor; FOXP3, Forkhead box P3; GATA3, GATA-binding protein 3; HMPV, human metapneumovirus; HSCs, hematopoietic stem cells; HSV, herpes simplex virus; IAV, influenza A virus; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; JHMV, JHM strain of mouse hepatitis virus; LCMV, lymphocytic choriomeningitis virus; mAb, monoclonal antibody; MBP, myelin basic protein; MCMV, murine cytomegalovirus; MHC-II, major histocompatibility complex class II; MHV, mouse hepatitis virus; MPP, 1-methyl-4-phenylpyridinium; MS, multiple sclerosis; MV, measles virus; NMDA, N-methyl-D-aspartate; NSC, neural stem cell; OPC, oligodendrocyte precursor cell; PBMC, peripheral blood mononuclear cells; pTregs, peripheral regulatory T cells; ROR-γT, RAR-related orphan nuclear receptor – γT; RSV, respiratory syncytial virus; RTE, recent thymic emigrants; SASP, senescence-associated secretory phenotype; SIRPA, signal regulatory protein alpha; Tcon, conventional T cells; TCR, T cell receptor; TGF-β, transforming growth factor-β; Th1, T helper 1 cells; Th17, T helper 17 cells; Th2, T helper 2 cells; TMEV, Theiler's murine encephalomyelitis virus; Tregs, regulatory T cells; TSDR, Treg-specific demethylated region; tTregs, thymic regulatory T cells; T-bet, T-box expressed in T cells; WNV, West Nile Virus.

B-cells to produce virus-specific IgG antibodies in the brain, which may help to prevent viral recurrence [6, 7]. However, overexuberant immune responses can also destroy neural cells, and a fine balance must be struck between controlling the virus and limiting immunopathogenesis in the CNS [5]. Regulatory T cells (Tregs) help to balance the antiviral immune response by modulating effector T cell activity and promoting tissue repair. However, how Treg activity is affected by the age of the host during neurotropic infections, and the ultimate impact on neurological outcomes, is not yet clear. Identifying potential age-specific differences in Treg function in the CNS may then be important to support the development of personalized immunotherapies against neurotropic viruses.

Developmental changes in the immune system occur throughout the life of the host, modifying the proportion, stability, survival, and function of many immune cells [8]. Some of these developmental changes also alter the susceptibility of the host to infections [8]. Tregs range from a predominantly naïve state in newborns, to a more memory-like phenotype in adults, and finally to a deviant phenotype in the elderly [9–11]. The age-specific roles of Tregs have been studied in humans and animal models of peripheral viral infections. However, few studies have explored how Treg development impacts antiviral responses and tissue repair in the CNS, which may be especially important in the developing and aged brain. In this review, we examine the potential age-dependent role of Tregs during neurotropic infections. Given the paucity of information in this space, we gather insights from studies of Treg development, Treg activity in peripheral viral infections, and Treg responses in neuroinflammatory diseases to better define the potential roles of Tregs in CNS infections.

## 2 | Hallmark Features of Tregs

Tregs are a subset of CD4 T cells with a characteristic immunosuppressive phenotype. Forkhead box P3 (FOXP3) is a transcription factor that is responsible for this immunosuppressive state. Mutations in the human *FOXP3* gene lead to a lymphoproliferative autoimmune condition called immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) in males [12]. Similarly, scurfy mice with a nonsense mutation in the *FOXP3* gene spontaneously developed a lymphoproliferative disease [13]. FOXP3 is thus used as a marker to distinguish Tregs from the pool of conventional CD4 T cells. Tregs also express the interleukin-2 (IL-2) receptor-α chain or CD25. IL-2 signaling through CD25 is critical for Treg differentiation, proliferation, maintenance of FOXP3 expression, and retention of the immunosuppressive phenotype [14].

Tregs can suppress the activity of both innate and adaptive immune cells, although Treg-mediated suppression of conventional T cells (Tcon) is perhaps best understood (Figure 1A). IL-2 is important for the differentiation and survival of T cells broadly, but IL-2 is produced by activated Tcon cells and not by Tregs. The sequestration of IL-2 by Tregs acts as a sink that deprives Tcon cells of IL-2 and suppresses their proliferation [15]. Tregs also produce immunosuppressive cytokines such as IL-10, IL-35, and TGF-β when activated [16]. These cytokines can inhibit the release of Th1-promoting cytokines, inhibit pro-inflammatory cytokine release, and downregulate MHC-II expression [17, 18]. At the time of antigen presentation, Tregs also inhibit T cell activation by blocking the binding of CD28 on effector T cells and CD80/86 on dendritic cells (DCs). Tregs accomplish this inhibition through cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which competes with CD28 for CD80/86 on the DCs. Additionally, through the activity of ectonucleotidases (CD39 and CD73), Tregs hydrolyze ATP to the immunosuppressive adenosine, which suppresses effector T cells through their A2A receptors [19]. Thus, Tregs can suppress Tcon activity through multiple mechanisms, thereby limiting inflammation and autoimmune responses.

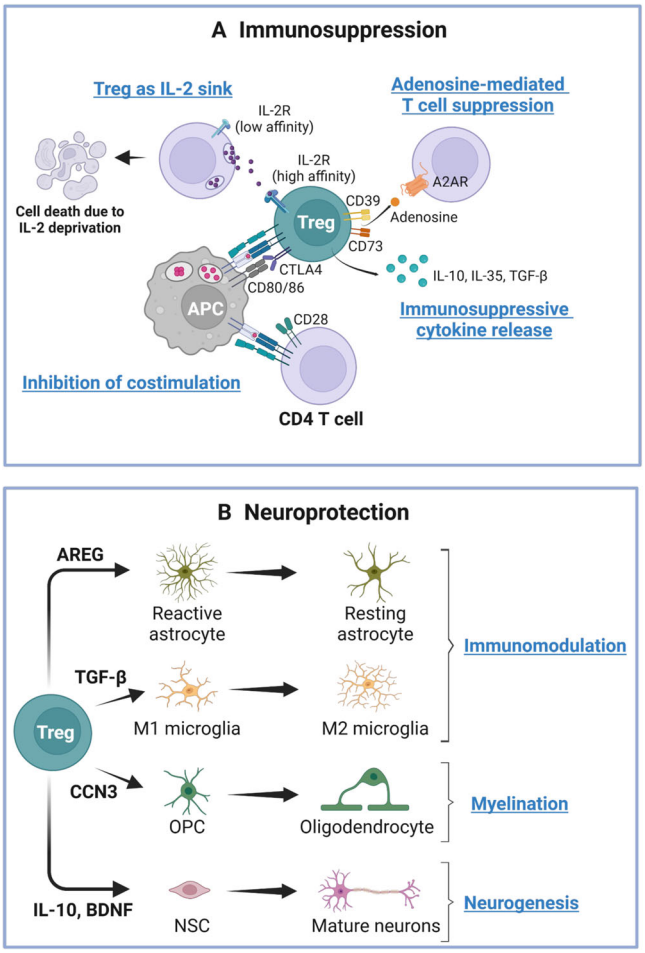


**FIGURE 1** | Immunosuppressive and neuroprotective functions of Tregs. (A) Tregs can suppress T cells through multiple mechanisms, including sequestration of IL-2, hydrolysis of ATP by ectonucleotidases (CD39 and CD73) to produce adenosine, release of immunosuppressive cytokines, and inhibition of costimulation between antigen-presenting cells (APCs) and T cells. (B) In the central nervous system, Tregs can protect neural cells by reducing activation of glia (astrocytes and microglia), promoting myelination through stimulation of oligodendrocyte differentiation, and stimulating neurogenesis. Created in BioRender. A2AR, adenosine A2A receptor; APC, antigen-presenting cells; AREG, amphiregulin; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CCN3, cellular communication network factor 3; CTLA4, cytotoxic T lymphocyte-associated protein 4; IL-2R, interleukin 2 receptor; NSC, neural stem cell; OPC, oligodendrocyte precursor cell; TGF-β, transforming growth factor-β.

In addition to well-established roles in immunomodulation, Tregs contribute to tissue regeneration and repair in many nonlymphoid tissues (recently reviewed in [20–22]). Reparative roles for Tregs have been identified in the brain, skin, lungs, skeletal muscle, and gastrointestinal tract, among others [23–27]. In part, the protective role of Tregs can be attributed to the resolution of the immune response and inflammation after infection or injury. However, it is increasingly appreciated that Tregs can modulate many nonimmune cells through the release of cytokines and growth factors, leading to tissue-specific repair responses. For instance, in a murine model of influenza infection, Tregs stimulated the repair of bronchial epithelial cells through the release of amphiregulin (Areg), which occurred independently of Treg-mediated suppressor functions [28]. Lung-resident Tregs have been further shown to directly stimulate proliferation of lung epithelial cells after acute lung injury, demonstrating that Tregs can promote tissue repair through specific interactions with tissue cells [29]. Tregs also stimulate tissue regeneration through modulation of stem cells in the skin, brain, and other sites [21, 23, 30]. For example, skin-resident Tregs promote the proliferation and differentiation of hair follicle stem cells through high Treg expression of Jagged-1, ultimately promoting hair regeneration [23]. Tregs even support host metabolism through modulation of adipose tissue, leading to enhanced glucose uptake by adipocytes and maintenance of insulin sensitivity [31, 32]. Overall, these studies support the notion that Tregs can protect and repair host tissues through specific interactions with non-lymphoid cells.

## 3 | CNS-Specific Functions of Tregs

In the CNS, the protective capacity of Tregs is of particular importance, as many neurons are nonrenewable and the capacity for regeneration is relatively limited. Brain-resident Tregs adopt a tissue-resident phenotype common to Tregs in other tissues (e.g., CD69 +), but also express genes that are CNS-specific, such as the serotonin receptor 5-$HT_7$, suggesting a responsiveness to neurotransmitters and tissue-specific specialization [33, 34]. Brain Tregs provide neuroprotection through multiple mechanisms (Figure 1B). Tregs can resolve gliosis in the inflamed brain through modulation of reactive astrocytes and microglia, shifting these cells to a more neuroprotective phenotype [33, 35, 36]. In In Vitro models of 1-methyl-4-phenylpyridinium (MPP) toxicity, which is used as a model of Parkinson's disease, Tregs protected neurons from cell death through direct cell-to-cell contact, potentially through binding between CD45 and CD47 on Tregs with galectin-1 and SIRPA on neurons, respectively [37, 38]. These findings suggest that Tregs protect existing neurons directly or through modulating glial cells to provide better neuronal support.

Tregs also induce the regeneration of neurons and oligodendrocytes in the brain through stimulation of stem cells. Neural stem cells (NSCs), which can differentiate into neurons and glial cells, are stimulated to proliferate by IL-10 from Tregs during ischemic brain injury [30]. Tregs also prompt the differentiation of oligodendrocyte precursor cells (OPCs), which are specialized precursor cells that give rise to oligodendrocytes. In a mouse model of stroke, Tregs released osteopontin to modulate microglial function, creating a more permissive environment for OPC differentiation and myelination [39]. In a model of toxin-induced demyelination, Tregs released soluble factors (e.g., CCN3) that directly induced differentiation of OPCs and enhanced remyelination [40]. Intriguingly, the ability of Tregs to stimulate myelination declines with age, perhaps contributing to the vulnerability of the brain to neurodegenerative disease later in life [41]. Collectively, these studies demonstrate that Tregs play a key role in protecting and repairing the brain after many neurotoxic insults.

## 4 | Age-Dependent Differences in Treg Production and Phenotype

The study of Treg ontogeny and aging has identified distinct phenotypes of Tregs at different stages of life [42, 43]. Depending on the age of the host, Tregs differ in their ability to proliferate, survive, migrate, and maintain a stable phenotype (Figure 2). Tregs emerge early during fetal development by the process of thymic selection [44]. During this process, some of the self-reactive thymocytes escape deletion and rather differentiate into $CD4^+CD25^+FOXP3^+$ Tregs, known as thymic Tregs (tTregs). These tTregs then leave the thymus to enter the circulation and populate the lymphoid tissues, leading to a high frequency of Tregs perinatally [45]. In addition to the tTregs, naïve T cells can differentiate into peripheral Tregs (pTregs) after migration from the thymus and TCR activation by non-inherited maternal antigens [46]. During the neonatal period, naïve CD4 T cells possess an intrinsic ability to differentiate into FOXP3-expressing Treg cells [47]. The heightened frequency of Tregs is sustained until the first few weeks after birth. These neonatal Tregs are important for establishing immune tolerance to self-antigens and commensal microorganisms and the appropriate modulation of the immune response against pathogens [48–50]. The frequency of Tregs then declines during older childhood and adulthood, mainly due to thymic involution, differentiation of naïve T cells to other T cell subtypes, and negative feedback from thymic re-entry of circulating Tregs [45].

In the elderly, the naïve CD4 T cell population declines, and tTregs accumulate in the blood, spleen, and lymph nodes [51]. The elevation in tTregs stems in part from the expansion of apoptosis-resistant tTregs at the expense of naïve CD4 T cells [11]. The decline in naïve CD4 T cells may also explain the reduced frequency of pTregs and effector T cells observed in aging hosts. Collectively, these changes lead to a net replacement of effector T cells by tTregs in elderly lymphoid organs.

Tregs also display age-dependent preferences for homing to nonlymphoid tissues. Upon exiting the thymus, Tregs home to nonlymphoid and tertiary lymphoid tissues in neonates, with an initial preference to populate barrier sites like the gut and the skin [9, 52]. At these sites, neonatal Tregs play important roles in the generation of immune tolerance to commensal microbes. The bias of Tregs to home toward the gut is explained by heightened expression of gut-homing integrins ($\alpha4\beta7$) and the limited expression of chemokine receptors for extra-gut homing (CCR4) on Tregs from human infants. In early childhood, there is then a switch to CCR4 dominance between 1.5 and 3 years old, causing the majority of the naïve Tregs to express CCR4

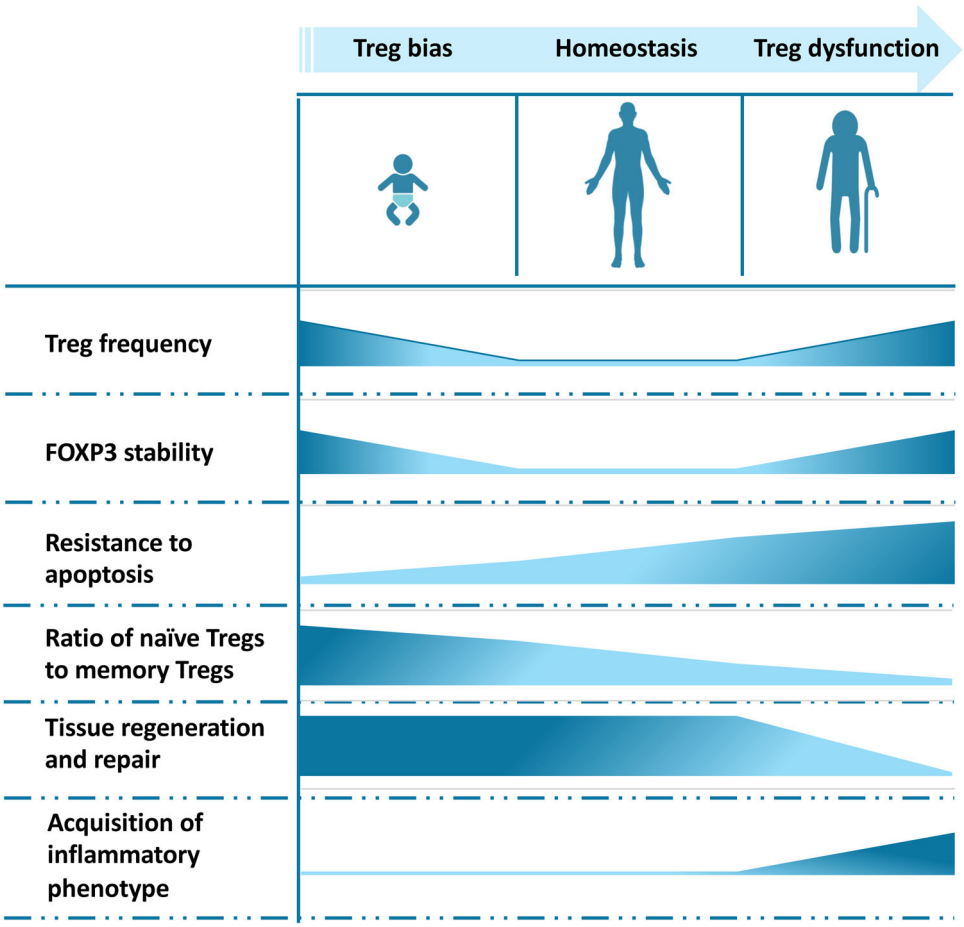


**FIGURE 2** | Developmental changes in Tregs over the lifetime of the host.

and leading to an associated decline in gut homing through adulthood [9, 53]. Similarly, in the skin, murine studies revealed that the enrichment of neonatal Tregs is attributed to preferential expression of CCR6, which facilitates Treg migration to CCL20 expressed by the skin. The induction of CCL20 expression was dependent upon the colonization of the neonatal skin by the microbiota [54]. This early-life colonization by skin commensal bacteria triggered the accumulation of highly activated Tregs, supporting the development of healthy host-commensal relationships [52]. Importantly, this tolerance was not established when skin from adult mice was colonized with commensal bacteria, suggesting that the tolerance to the skin microbiota requires a neonate-like Treg phenotype [52].

Neonatal and adult Tregs also differ in the stability of FOXP3. The expression of FOXP3 in adult Tregs is less stable than in neonates, which is evident from FOXP3 downregulation upon repeated TCR stimulation in adults [47]. Transcription of the *FOXP3* gene is controlled by the degree of demethylation at the Treg-specific demethylated region (TSDR), which is a CpG-rich region found in the first exon in the *FOXP3* locus. Demethylation of the TSDR is associated with more stable expression of FOXP3. Although there are no clear markers for Treg stability, studies have shown that Tregs that express the transcription factor HELIOS showed greater FOXP3 stability versus Tregs that were negative for HELIOS expression [55]. HELIOS$^{+}$ Tregs also had a greater frequency of demethylated TSDR compared to HELIOS$^{-}$ Tregs, indicating more stable FOXP3 transcription. FOXP3$^{+}$HELIOS$^{-}$ Tregs were absent in neonatal mice during the first 2 weeks of life, indicative of more stable FOXP3 expression, with adult levels of HELIOS expression observed only 1 week after weaning [55]. Similar to neonatal mice, older mice also showed more hypomethylation in the FOXP3 enhancer regions compared to adults, indicating greater FOXP3 expression and enhanced Treg stability later in life [56].

As the host ages, Tregs also become increasingly resistant to apoptosis and more likely to assume a memory-like phenotype. Neonatal Tregs are predominantly naïve (CD45RO$^{-}$) and require a strong activation signal for survival [9, 10]. In studies of African green monkeys, neonatal Tregs did not survive in the absence of a strong activating signal through the TCR, whereas adult Tregs were relatively resilient in the absence of stimulation [10]. In addition, Tregs from middle-aged (9–15 months) and elderly mice (18 months) become more resistant to apoptosis due to decreased expression of the proapoptotic molecule, Bim, suggesting older Tregs are less prone to cell death [11]. Tregs from older hosts also tend toward a memory-like phenotype. The adult Treg compartment is majorly comprised of long-lived effector/memory-like (CD45RO$^{+}$) Tregs and very few naïve (CD45RO$^{-}$) Tregs. In the elderly, this ratio of memory-like Tregs over naïve Tregs increases further due to several reasons. First, aging-associated thymic atrophy and myeloid bias of the hematopoietic stem cells (HSCs) leads to a decline in lymphoid precursors and poor thymic output of naïve T cells

[57, 58]. This decline in naïve T cells from the thymus results in fewer available precursors for pTregs [43]. Second, as mentioned above, circulating tTregs are expanded in the blood, lymph nodes, and spleen of older hosts. Return of these tTregs to the thymus suppresses the production of new tTregs [42]. This reduction in naïve Tregs and expansion of terminally differentiated memory Tregs is further associated with the narrowing of Treg clonal diversity [42]. As a consequence, this pool of oligoclonal Tregs may then suppress only certain effector T cells while sparing others, contributing to inflammation in elderly hosts [42]. Overall, these studies demonstrate that the naive Treg population dwindles over the life of the host, giving rise to a more stable memory-like oligoclonal Treg population.

## 5 | Age-Dependent Treg Responses During Peripheral Viral Infections

During a viral infection, Tregs modulate the balance between achieving viral clearance and preventing immune-mediated pathology. Tregs can contribute to this immune homeostasis during both acute and chronic viral infections by suppressing overzealous antiviral T cell responses [59]. However, in hosts with severe viral disease, the harmony between Tregs and effector T cells is often disrupted. Virus-specific induction of Tregs, either directly or indirectly, may contribute to this disruption as an immune evasion mechanism [60, 61]. However, age-dependent differences in Tregs may also further this imbalance, potentially leading to greater tissue damage or the establishment of chronic infections. In this section, we explore Treg responses in different age groups during viral infections outside of the CNS, as a greater body of research exists for Tregs in peripheral infections (Table 1).

In neonates, naïve T cells default toward the Treg lineage, leading to a relatively high proportion of Tregs. At the same time, many neonatal CD4 T cells are recent thymic emigrants (RTE), which are biased towards a Th2 phenotype and are a preferred precursor for pTregs compared to mature naïve T cells [46, 77, 78]. The Th2 bias of RTE is due to enrichment of Th2 polarizing cytokines and transcription factors, like IL-4 and GATA3, and suppression of Th1 polarizing cytokines and transcription factors like IFNγ and T-bet, respectively [77, 78]. Together, these features of neonatal T cells may contribute to a greater vulnerability to viral infections in early life. For instance, in a murine model of Herpes Simplex Virus Type 2 (HSV2) infection, Treg depletion in neonates led to a more profound increase in HSV-specific activated CD8 T cells and their cytotoxicity than in adults [63]. Treg depletion in neonates was also associated with increased expression of IFNγ in CD4 T cells and a reduction in viral titer in lymph nodes and the brain, suggesting that neonatal Tregs suppress effector T cell responses against HSV [63]. Thus, for some neonatal viral infections, Tregs may attenuate the effective antiviral immune response and allow for unrestricted viral spread.

Newborns and young children are also highly susceptible to respiratory viruses, such as influenza A virus (IAV), human metapneumovirus (HMPV), and respiratory syncytial virus (RSV) [79]. In these respiratory infections, Tregs can play an important, and occasionally contradictory, role. For instance, in influenza A virus (IAV) infection of neonatal mice, Tregs are critical for clearance of IAV from the lung. Depletion of Tregs was associated with higher viral load and a greater pro-inflammatory response in neonates, suggesting that Tregs were important for viral control [62]. In preliminary studies with HMPV, neonatal mice mounted a Th2-like response against the virus, which could be shifted to a Th1-like response upon Treg depletion, similar to the Th1 response seen in adult mice [80]. Interestingly, neonatal Tregs that were transferred into adult mice could induce a more Th1-like phenotype during HMPV infection, suggesting that neonatal Tregs can contribute to Th1 skewing in certain environments [80].

In RSV infection, the role of Tregs has been studied in greater detail. In RSV-infected infants, CD4 T cells are skewed toward a Th2 phenotype, with less IFNγ production from T cells compared to uninfected infants when stimulated Ex Vivo [81–83]. Tregs are also depleted in the peripheral blood of infants with severe RSV compared to age-matched uninfected infants, potentially due to greater Treg recruitment to the lungs [49, 84]. This idea is supported by studies in neonatal lambs, where Tregs rapidly enter the bronchoalveolar space after RSV infection [85]. In mouse models of RSV infection, the majority of Treg studies focus on young adult mice (6–8 weeks). In these studies, Tregs suppressed the Th2 response, promoted an early CD8 T cell response against RSV, and in some cases facilitated viral clearance [67–69]. Thus, despite evidence for rapid Treg infiltration in the bronchoalveolar space in neonates, it is not yet clear why a Th2 response predominates at this site during RSV infection. Studies characterizing age-related differences in Tregs while in the microenvironment of the bronchoalveolar space may help us determine how Tregs uniquely shape the neonatal immune responses against RSV.

In the elderly, the pool of Tregs expands, which is associated with suppression of the effector immune response and a decline in naïve T cells. This accumulation of older Tregs contributes to a heightened vulnerability to new viruses, to recurrences of latent or chronic infections, and to reduced vaccine efficacy in the elderly [86, 87]. Furthermore, aging impairs the tissue regeneration capacity of Tregs, leading to incomplete tissue repair during the resolution phase of tissue inflammation [41, 75]. For instance, during IAV infection in aged mice, the adoptive transfer of aged splenic Tregs was associated with greater lung injury and mortality compared to the transfer of young splenic Tregs [75]. In line with these observations, elderly Tregs expressed more pro-inflammatory cytokines while young adult Tregs expressed genes related to tissue repair upon IAV infection. Elderly mice also experience a substantial expansion of the Treg pool upon IAV infection, which is not observed in younger adult mice [66]. The dominance of deviant Tregs may also explain, in part, the poor vaccine efficacy in elderly hosts. In subjects $>60$ years of age vaccinated against IAV, non-responders showed a higher proportion of Treg cells before vaccination compared to responders [88]. Thus, age-associated immunosenescence and expansion of Tregs appear to be playing an important role in vulnerability to viral infections and muted responses to vaccines in the elderly.

**TABLE 1** | Age-dependent role of Tregs during CNS and peripheral viral infections.

| Role of Tregs during viral infections in neonates and juveniles | | | | | |
|---|---|---|---|---|---|
| **Animal model (age)** | **Virus (route of infection)** | **Treg manipulation** | **Outcome** | **Role of Tregs** | **Reference** |
| C57BL/6 mice (2–4 days) | IAV PR8 strain (IN) | Treg depletion by anti-CD25 mAb (PC61.5.3; IP) | • Increased IL-17$^{+}$ CD4 T cells in BALF<br>• Increased viral load and delayed clearance in the lungs | Immunosuppression; enhances viral control | [62] |
| C57BL/6 mice (1 week) | WT HSV2 186syn$^{+}$-1 strain (SC in hind footpad) | Treg depletion by anti-CD25 mAb (PC61; IP) | • Enhanced HSV-specific CD8 T cell cytotoxicity in dLN<br>• Reduced viral titer in the LN and brain | Immunosuppression; limits viral control | [63] |
| C57BL/6 mice (2 weeks) | Rodent-adapted recombinant MV CAM/RB strain (IC) | Treg expansion by superagonistic anti-CD28 mAb (D665; IP)<br>Treg depletion in *FOXP3*$^{DTR}$ mice treated with DT (IP) | • Increased virus spread and persistence in the brain<br>• Improved brain infiltration of antigen-specific CD8 T cells<br>• Fewer infected neurons | Immunosuppression; limits viral control | [64] |
| SJL/J mice (4 weeks) | TMEV Daniels strain (IC) | Acute stage: Ex Vivo induced Tregs (IP) on day of infection<br>Chronic stage: Ex Vivo induced Tregs (IP) 3–4 weeks postinfection | • Greater weight loss and impaired righting reflexes<br>• Less perivascular cuffing and T cell infiltration in the brain<br>• More IL-10 and IL-4- producing cells in the spleen<br>• Greater viral load<br>• Improved righting reflex scores<br>• Less perivascular cuffing in spinal cord<br>• More IL-10-producing CD4 T and B cells in the spleen<br>• No effect on viral load | Immunosuppressive; but the impact on viral control and pathology depends on the stage of the infection | [65] |
| **Role of Tregs during viral infections in adults** | | | | | |
| **Animal model (age)** | **Virus (route of infection)** | **Treg manipulation** | **Outcome** | **Role** | **Reference** |
| C57BL/6 mice (4 months) | IAV PR8 H1N1 strain (IV) | -- | • Lower percentage of Tregs in spleen versus aged mice (18–22 months)<br>• Timely expansion of virus-specific splenic CD8 T cells versus aged mice | Young adult Tregs promote more efficient CD8 T cell response compared to aged Tregs | [66] |

(Continues)

**TABLE 1** | (Continued)

| Role of Tregs during viral infections in adults | | | | | |
|---|---|---|---|---|---|
| **Animal model (age)** | **Virus (route of infection)** | **Treg manipulation** | **Outcome** | **Role** | **Reference** |
| CB6F1 mice (6–10 weeks) | RSV A2 strain (IN) | Treg depletion by anti-CD25 mAb (PC61; IP) | • Delayed viral clearance from lungs<br>• Delayed RSV-specific CD8 T cell trafficking to the lungs | Anti-inflammatory and immunomodulatory; role in viral control is uncertain, but may enhance early CD8 T cell responses against the virus | [67] |
| C57BL/6 mice (6–10 weeks) | RSV A2 strain (IN) | Treg depletion in *FOXP3*$^{DTR}$ mice treated with DT (IP) | • Greater influx of eosinophils and neutrophils in BALF<br>• Enhanced Th2 (e.g., IL-5) and limited Th1 responses<br>• Increased GATA3$^{+}$FOXP3$^{+}$ phenotype within repopulated Tregs<br>• No effect on viral clearance | | [68] |
| BALB/c or C57BL/6 mice (6–10 weeks) | RSV A2 strain (IN) | Treg depletion in *FOXP3*$^{DTR}$ mice treated with DT (IP) | • Delayed recovery and sustained weight loss<br>• Increased macrophages and neutrophils in BALF<br>• Less virus in the lungs | | [69] |
| | | Treg expansion with IL-2/anti-IL-2 complex | • Accelerated recovery<br>• Decreased neutrophils, CD4 T and CD8 T cells<br>• No effect on virus levels | | |
| C57BL/6 mice (6–12 weeks) | WNV TX-2002-HC strain (SC in hind footpad) | Treg depletion in *FOXP3*$^{DTR}$ mice treated with DT (IP) | • Increased pro-inflammatory CD4 and CD8 T cells in the dLN and brain<br>• Dominant short-lived effector cells in the spleen<br>• Impaired brain-resident CD8 memory T cell formation | Immunosuppressive; production of tissue-resident memory CD8 T cells | [70] |
| C57BL/6 mice (6–8 weeks) | MCMV RM461 strain (ICV) | Treg depletion in *FOXP3*$^{DTR}$ mice treated with DT (IP) | • Increased pro-inflammatory CD4 and CD8 T cell infiltration in the brain and dLN<br>• Fewer brain-resident memory CD8 T cells<br>• Decreased granzyme B production by CD8 T cells in the brain | Immunosuppressive; production of tissue-resident memory CD8 T cells | [71] |

(Continues)

**TABLE 1** | (Continued)

| Role of Tregs during viral infections in adults | | | | | |
|---|---|---|---|---|---|
| **Animal model (age)** | **Virus (route of infection)** | **Treg manipulation** | **Outcome** | **Role** | **Reference** |
| C57BL/6 mice (6 weeks) | Neuroattenuated variant of JHMV (rJ2.2) strain of MHV (IC) | Adoptive transfer of viral antigen (M-133)-specific Tregs, M-133-specific Tcon cells, and/or bulk Tregs | • M-133 and bulk Treg cotransfer: Increased ratio of M-133 Tregs:bulk Treg in brain<br>• Tcon co-transferred with M-133: M-133 Tregs inhibited Tcon expansion and egress from LN<br>• M-133 Tregs improved survival without affecting viral clearance | Immunosuppressive with no impact on viral control; bias for antigen-specific Tregs over bulk Tregs during neurotropic infection | [72] |
| C57BL/6 mice (5–7 weeks) | JHMV neurotropic strain of MHV (IP) | Adoptive transfer of viral antigen (M-133)-specific Tregs | • M133 Tregs were more suppressive than bulk Tregs<br>• Decreased morbidity/mortality from encephalitis<br>• M133 Tregs persisted as memory cells | Bias for antigen-specific Tregs over bulk Tregs during neurotropic infection; balance between antiviral immune response and neuroprotection | [73] |
| C57BL/6 mice (6 weeks) | Neuroattenuated variant of JHMV (rJ2.2) strain of MHV (IC) | Adoptive transfer of Tregs | • Improved clinical scores; less weight loss and demyelination<br>• Decreased CD4 and CD8 T cells in the brain<br>• No change in the kinetics of viral clearance in the brain | Immunosuppression; protection against demyelination | [74] |
| **Role of Tregs during viral infections in aging hosts** | | | | | |
| **Animal model (age)** | **Virus (route of infection)** | **Treg manipulation** | **Outcome** | **Role** | **Reference** |
| C57BL/6 mice (18–22 months) | Mouse-adapted IAV A/WSN/33[H1N1] strain (IT) | Young adult Tregs (2–4 months) adoptively transferred (retroorbital) | • Reduced mortality<br>• Lung Tregs enriched with pro-repair genes | Aged Tregs were more pro-inflammatory and less protective | [75] |
| | | Aged adult Tregs (18–22 months) adoptively transferred (retroorbital) | • Greater mortality<br>• Lung Tregs with enriched pro-inflammatory genes and depressed pro-repair genes | | |
| C57BL/6 mice (18–22 months) | IAV PR8 H1N1 strain (IV) | – | • Active ($CD69^+$) tTregs expanded in the spleen with reduced CD25 expression<br>• Impaired trafficking (CD62L reduction)<br>• Delayed/reduced spleen CD8 T cell response | Aged Tregs expanded but did not traffic efficiently to the brain; poor virus control; Tregs less reliant on IL-2 for survival | [66] |

(Continues)

**TABLE 1** | (Continued)

| Role of Tregs during viral infections in aging hosts | | | | | |
|---|---|---|---|---|---|
| **Animal model (age)** | **Virus (route of infection)** | **Treg manipulation** | **Outcome** | **Role** | **Reference** |
| C57BL/6 mice (18–22 months) | WNV (SC in the footpad) | – | • CD4 T cells trafficked poorly to the brain, including FOXP3$^+$ Tregs | | [76] |

Abbreviations: BALF, bronchoalveolar lavage fluid; dLN, draining lymph node; DT, diphtheria toxin; HMPV, human metapneumovirus; HSV, herpes simplex virus; IAV, influenza A virus; IC, intracerebral; ICV, intracerebroventricular; IN, intranasal; IP, intraperitoneal; IT, intratracheal; IV, intravenous; JHMV, JHM strain of mouse hepatitis virus; MCMV, murine cytomegalovirus; MHV, mouse hepatitis virus; MV, measles virus; PR8, Puerto Rico 8; RSV, respiratory syncytial virus; SC, subcutaneous; Tcon, conventional T cells; TMEV, Theiler's murine encephalomyelitis virus; WNV TX-2002-HC, West Nile Virus Texas 2022 Hall County.

## 6 | Age-Dependent Treg Responses During Neurotropic Infections

The central nervous system can be targeted by many diverse viruses, including arboviruses, herpesviruses, orthomyxoviruses, coronaviruses, picornaviruses, paramyxoviruses, and rhabdoviruses, among others [1, 89, 90]. These neurotrophic viruses can induce immediate and long-term neurological complications, owing partly to the pathology caused by the antiviral immune response [1]. Encephalitis and meningoencephalitis can develop during acute viral infection, whereas more long-term neurological sequelae can include seizures, cognitive deficits, retinopathy, and motor dysfunction [91]. Often these outcomes are more severe in newborns, young children, and the elderly [92, 93]. In addition to immunopathology, autoimmune responses against CNS antigens have been observed after viral infections. The development of N-methyl-D-aspartate (NMDA) receptor antibodies after HSV encephalitis and cell-mediated immune responses against myelin basic protein (MBP) during and after MV encephalomyelitis have been reported, suggesting the initiation of an autoimmune response against neurons and oligodendrocytes, respectively [94, 95]. Viral infections are even proposed as risk factors for the later development of neurodegenerative diseases, such as Alzheimer's Disease, and demyelinating disorders, such as multiple sclerosis (MS) [96, 97].

Although the brain was once considered to be an immune-privileged organ, there is sufficient evidence today that confirms the infiltration of innate and adaptive immune cells into the CNS during viral infections [98]. In the brain, the balance between viral clearance and cytotoxicity is especially tenuous, as excessive inflammatory responses can be toxic to non-regenerative neurons and other bystander cells. As seen in peripheral viral infections, Tregs have been reported to infiltrate the CNS, where they can play both beneficial and detrimental roles. This dichotomy in Treg responses has been extensively reviewed elsewhere for neurotropic infections [89]. However, a gap remains in our understanding of age-dependent Treg responses against viruses in the brain. Here, we consider the roles of Tregs in CNS infections in the context of different age groups (Table 1). There are a handful of studies that examine Tregs in the young brain during viral infection. In a model of HSV2 infection, neonatal mice had a relatively delayed and subdued CD8 T cell response in comparison to a rapid response in adults, with the neonatal mice ultimately succumbing to lethal encephalitis [99, 100]. In neonates, Treg depletion enhanced the function of CD8 and CD4 T cells from the lymph nodes and lowered viral titers in the brain, suggesting Tregs suppressed HSV2-specific T cells in the periphery and the CNS [63]. However, the authors note that the reduced viral load in the brain could be due to delayed dissemination of the virus from the periphery or enhanced clearance of the virus from the brain itself. Despite the lower viral load in the brain in the absence of Tregs, both Treg-depleted and nondepleted neonates developed similar symptoms and onset of encephalitis, suggesting that reducing the level of virus alone is not sufficient to prevent CNS disease in this model.

Tregs may also influence the establishment of persistent infections in the brains of young hosts. Using a juvenile model of

measles virus (MV) infection, where 2-week old mice survived infection in the context of an immature immune system, MV persisted in the brain for up to 10 weeks postinfection [101]. Tregs were found in the brain of persistently infected mice as early as 3 days postinfection and remained 4 weeks later. Experimental expansion of Tregs was associated with increased MV replication and spread in the brains of young mice. Meanwhile, Treg depletion increased the frequency of MV-specific CD8 T cells and diminished the number of MV-infected cells in the brain at 4 weeks, suggesting a reduction in the persistent infection [64]. Thus, while Tregs may limit immunopathology, Treg-mediated suppression of effector T cells may permit the establishment of persistent infections in the juvenile brain.

The role of Tregs in the brain may differ depending upon the stage of infection, as is seen in Theiler's murine encephalomyelitis virus (TMEV) infection of juvenile mice [65]. TMEV infection is characterized by an acute phase, where neurons are predominately infected, followed by a chronic phase, where immune-mediated demyelination develops. During acute TMEV infection, infusion of Tregs provided modest improvements in inflammation, but ultimately increased weight loss and viral load in the brains of young mice [65]. Similarly, Treg inactivation during the acute phase decreased the viral load in the brain, possibly due to sustained elevation in virus-specific CD8 T cells [102]. During the chronic phase, late-stage infusion of Ex Vivo-induced Tregs did not affect viral clearance, but reduced perivascular cuffing and improved the righting reflex score, which is used as a measure of motor neuron function [65]. Although more studies are warranted, these results suggest that Tregs may be detrimental during acute TMEV infection, when viral control is needed in the brain, but protective in the later demyelinating stages.

There are also studies that examine Tregs in the brains of young adult mice (e.g., 6–8 weeks old), which have provided insight into additional functions of Tregs in CNS infections. For instance, in murine cytomegalovirus (MCMV) infection, Tregs contributed to the maintenance of long-lived memory T cells [70, 71]. Memory T cells are important in the CNS since their establishment is associated with more rapid and potent viral control upon reinfection or reactivation. During infection with a neurotropic strain of murine hepatitis virus (JHMV strain), virus-specific Tregs and memory Tregs were found in adult mice [72, 73]. These viral epitope-specific Tregs were more suppressive than nonspecific Tregs; however, they did not suppress the initial activation of epitope-specific Tcon cells and thus did not negatively affect viral clearance. The epitope-specific memory Tregs were long-lived with stable FOXP3 expression. Similar studies exploring such roles for Tregs in maintaining memory responses are not yet available in neonatal or elderly neurotropic infections. However, in the periphery, neonatal mice infected with RSV or Lymphocytic Choriomeningitis Virus (LCMV) did not develop robust memory T cells in the lungs and blood, respectively [103–105]. Intriguingly, JHMV infection is also associated with chronic demyelination, and transfer of Tregs preserves myelination after infection, which highlights that Treg activity influences both immunological and neurological aspects of the disease [74, 106].

In aging hosts, there is conflicting evidence for both Treg dysfunction (e.g., heightened cytokine expression) and neuroprotective activity in neurodegenerative diseases, although relatively little is known about how Tregs respond to viruses in the aging brain [107–109]. In older mice (18–22 months), West Nile Virus (WNV) infection is associated with an attenuated virus-specific CD4 T cell response in the brain and draining lymph nodes compared to the spleen and nondraining lymph nodes [76]. Treg numbers in the brains of these older mice were also low despite the existence of a higher proportion of precursor cells in the periphery. These findings suggest a possible defect in trafficking from the lymph nodes to the brain in aged mice. Importantly, depletion of Tregs however was fatal in this model, suggesting Tregs ultimately played a protective role in aging mice during WNV infection, as has been observed in many neurodegenerative conditions [76, 108]. Whether the protective capacity of aged Tregs is as robust as young Tregs against neurotropic viruses remains to be explored.

## 7 | Current Challenges and Future Directions

Currently, there are no Treg-based therapeutics for viral CNS infections. However, Treg therapies are in development for a variety of neuroinflammatory, autoimmune, and neurodegenerative diseases (recently reviewed in [110]) (Table 2). Initial therapeutic approaches primarily used low-dose IL-2 to expand Tregs In Vivo. Other studies focused on infusion of Ex Vivo-expanded autologous or cord blood-derived allogeneic Tregs to treat neuroinflammation. However, these approaches expanded Tregs nonspecifically or offered only a small proportion of antigen-specific Tregs [111]. To improve the efficiency of Treg-based therapies, ongoing preclinical and early clinical studies are exploring platforms to expand antigen-specific Tregs, to produce Tregs with engineered T-cell receptors, or to design chimeric antigen receptor-Tregs (or CAR-Tregs). Whether such therapeutic approaches could apply to CNS infections is an open question that is complicated by our limited knowledge of Treg activity in young and elderly hosts. More basic research is warranted into the function of Tregs in neurotropic infections before we can reposition novel Treg-based therapies toward viral infections in the brain.

The study of age-dependent Treg responses has the potential to unveil developmental variables that influence the outcomes of CNS infections. Despite advances in our understanding of Treg activity in the brain, there are outstanding questions that remain. For instance, it is unclear how age-related shifts in peripheral Treg proportions, phenotypes, and activity influence the antiviral immune response in the brain. Another important question is whether the regenerative capacity of Tregs is modified by neurodevelopmental changes in the brain, where the activity of NSCs and OPCs is also age-dependent. More direct studies of functional differences between young and old Tregs, such as the heterochronic adoptive transfer studies published for viral lung infections [75], are needed to better define mechanisms of CNS disease and identify strategies for therapeutic intervention in these vulnerable age groups.

**TABLE 2** | Treg-based therapeutic approaches for neurological conditions in preclinical studies and clinical trials.

| Study ID/source | Condition | Intervention | Approach | Phase/status | Sponsor | Location |
|---|---|---|---|---|---|---|
| NCT04220190<br>NCT06169176 | Amyotrophic lateral sclerosis (ALS) | RAPA-501 | Autologous hybrid TREG/Th2 cell therapy | II/III (recruiting) | Rapa Therapeutics | USA |
| NCT05468073 | Alzheimer's Disease (AD) | Proleukin | In Vivo Treg expansion with low dose IL-2 | II (recruiting) | Centre Hospitalier St Anne | France |
| NCT04133233 | Bipolar depression | ILT101 | In Vivo Treg expansion with low dose IL-2 | II (completed) | Assistance Publique - Hôpitaux de Paris | France |
| NCT03039673 | ALS | Riluzole | In Vivo Treg expansion with low dose IL-2 | II (completed) | Centre Hospitalier Universitaire de Nīmes | France |
| NCT03865017 | Alzheimer's Disease (AD) | GB301 | Autologous Treg cell therapy | I/II (unknown status) | VT Bio | Australia |
| NCT05695521 | ALS | CK0803 | Allogeneic umbilical cord blood-derived Treg cell therapy | I (recruiting) | Cellenkos | USA |
| NCT06395038 | Frontotemporal Disorder (FTD) | IL2 plus abatacept (CTLA4-IgG) | In Vivo Treg expansion with low dose IL-2 | I (recruiting) | The Methodist Hospital Research Institute | USA |
| NCT06566261 | Progressive multiple sclerosis (MS) | ABA-101 | TCR-engineered, autologous Treg cell therapy | I (recruiting) | Abata Therapeutics | USA |
| Company pipeline | Neuroinflammation | BTx-001 | Genetically reconfigured Treg cell therapy | Preclinical | Bastion Therapeutics | UK |
| Company pipeline | Parkinson's Disease (PD) | CK0803 | Allogeneic umbilical cord blood-derived Treg cell therapy | Preclinical | Cellenkos | USA |
| Company pipeline | ALS and MS | CAR-Tregs | CAR-Tregs allow direct targeting of antigens without requiring antigen presentation by APCs | Preclinical | Poltreg S.A. | Poland |

### Author Contributions

Vivek R. Singh and Lauren A. O'Donnell conceptualized and wrote the initial draft. Vivek R. Singh created the tables and figures. Vivek R. Singh and Lauren A. O'Donnell revised the final manuscript. Both authors approved the final version of the manuscript.


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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The authors have nothing to report.

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