Journal of Pathology
J Pathol 2013; **229:** 332–346
Published online 28 November 2012 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4106

INVITED REVIEW

Harnessing monocyte-derived macrophages to control central nervous system pathologies: no longer 'if' but 'how'

Ravid Shechter and Michal Schwartz

Department of Neurobiology, Weizmann Institute of Science, 76100, Rehovot, Israel

**Correspondence to: Professor Michal Schwartz, Department of Neurobiology, The Weizmann Institute of Science, 76100 Rehovot, Israel. e-mail: michal.schwartz@weizmann.ac.il*

Abstract

The central nervous system (CNS) tissues, including the brain, the eye, and the spinal cord, are immune-privileged, secluded from the circulation by a complex of barriers, and equipped with their own myeloid cell population, the resident microglia. Based on the classical perspective of immune–brain interactions and on the contribution of such interactions to the progression of multiple sclerosis, an autoimmune inflammatory disease of the CNS, infiltrating macrophages were traditionally viewed as an enemy of the nervous system. However, over the past two decades, research has revealed the pivotal role of monocyte-derived macrophages in CNS repair, and opened up a new era in understanding and treating CNS pathologies. Here, we gather current knowledge regarding macrophage broad spectrum of activities in the CNS, whose two poles correspond to the classical pro-inflammatory M1 and the 'alternatively-activated' M2 cells previously described in various non-CNS pathologies, and their diverse, multi-functional contribution in various neurological conditions, ranging from acute traumas to neurodegenerative disorders, and autoimmune diseases. The diverse functions are manifested by induction and resolution of inflammation as well as their involvement in neural tissue regeneration and renewal, matrix remodelling, debris clearance, and angiogenesis. A special focus is devoted to current evidence suggesting that resident microglia and infiltrating monocyte-derived macrophages are functionally non-redundant cell types. Taken together, these recent advances reveal a dramatic therapeutic opportunity for controlled harnessing of macrophages for repair of the damaged CNS following acute insults, in neurodegenerative conditions, and in psychiatric disorders.

Keywords: neuroimmunology; CNS pathology; macrophages; microglia; neurodegenerative disease; spinal cord injury; monocytes

Received 22 August 2012; Revised 9 September 2012; Accepted 11 September 2012

No conflicts of interest were declared.

Introduction

The central nervous system (CNS), including the brain, the spinal cord and the retina, are immune-privileged sites. The first milestone demonstrating this unique immunological attribute of the CNS was the observation made by Medawar in 1948 revealing the prolonged survival of allografts transplanted to the brain, relative to their rapid rejection when grafted to the skin [1]. This immune-privileged nature of the CNS was originally attributed to the inability of leukocytes to access immune-privileged sites, a concept further supported by studies showing that the CNS is an anatomically separate compartment, sealed from the circulation. These findings are consistent with the existence of complex barriers separating the CNS from the circulation, which limit the access of soluble factors, a fact that was assumed to imply exclusion of immune cell entry as well.

Until recently, this dogma was generally accepted, and infiltration of immune cells, predominantly monocytes (which locally differentiate to macrophages within their target tissue), to such privileged organs was viewed as a negative by-product of barrier breakdown and as detrimental for tissue healing. Major support for this neuro-destructive paradigm of macrophage function came from extensive research in the context of the autoimmune-mediated CNS neurodegenerative disease multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE); in these diseases, immune cells, including macrophages, were found to attack the myelin compartment, leading to axon degeneration. The negative outcomes associated with inflammation resulted in the widespread clinical use of anti-inflammatory drugs in CNS pathologies, ranging from MS [2] to head trauma, spinal cord injury [3], and Alzheimer's disease [4]. This view of the CNS as an immunologically autonomous system is apparently also supported by the fact that the CNS is equipped with its own phagocyte cells, the resident microglia [5–12]. Many similarities are evident between activated microglia and macrophages recruited under pathological conditions. As the damaged CNS is loaded with activated microglia, the entry of blood-derived macrophages was considered to be redundant.

However, experiments over the last decade have exposed key weaknesses in this prevailing dogma, revealing a much more complex story. First, in contrast to their destructive, nerve-attacking role, macrophages, through their phagocytic activity in the form of Wallerian degeneration, were found to be essential for peripheral nerve regeneration [13]. Such phagocytosing macrophages even modulate autoimmune responses [14]. *In vitro* studies in the 1990s demonstrated that supplementation of macrophages to the CNS counteracts its growth-inhibitory milieu and can further directly influence the survival of neurons via tropic effects [15]. However, while in the peripheral nervous system (PNS), macrophage-mediated phagocytosis of axons was viewed as essential for regeneration, in the context of the CNS, despite sporadic evidence of their potential benefit, the overall role of macrophages was considered to be negative.

Our research group pioneered a paradigm shift in the perception of the effect of monocyte-derived macrophages on the CNS, based on a provocative experiment in which *ex vivo* activated macrophages, defined as an 'alternatively activated', were introduced to the injured parenchyma of rodents with spinal cord injuries; these cells were shown to enhance functional recovery [16]. Subsequently, a similar approach was tested in clinical trials in human patients, as a therapeutic manoeuvre [17]; trials using this approach will soon resume, with some technical modifications. Over the past two decades, intensive research in the field of neuroimmunology has revealed the potential beneficial role of macrophages in additional CNS pathologies, ranging from acute insults to neurodegenerative diseases [18,19], and recently, even in neurodevelopmental mental disorders [20]. It was further discovered, similar to the situation outside the CNS and as previously described in cancer, that macrophages are functionally heterogeneous within the pathological CNS, exhibiting a growing list of essential properties beyond their phagocytic capacity; macrophages secrete neurotropic factors; promote inflammation induction and resolution; and promote angiogenesis, regeneration, and cell replacement, as well as regulating matrix remodelling. Revealing such pivotal roles for haematopoietic-derived macrophages, and for circulating immune cells in general, may account for the underlying mechanism explaining the failure of anti-inflammatory drugs in many neurodegenerative conditions [21]. The shift in the understanding of macrophages in the CNS is reflected in recent approaches to the treatment of CNS disorders; rather than seeking means for macrophage elimination or prevention of their CNS infiltration, current efforts have shifted to identifying means for boosting their controlled recruitment.

Here, we review progress over the last two decades in understanding the role of macrophages in the CNS, providing the basis for our comprehensive view of the functional role of macrophages in CNS repair, acknowledging their heterogeneity. By summarizing our current knowledge of various CNS pathologies, ranging from acute insults to neurodegenerative disease, age-related dementia, mental disorders, and autoimmune-mediated diseases, we will describe the revolution in the field of CNS macrophages.

The macrophage activation spectrum in CNS neurodegeneration

Plasticity and diversity have long been known to be hallmarks of the monocyte–macrophage differentiation pathway [22–27]. In the CNS, macrophages display a spectrum of activation stages and a range of activities, which are in many respects similar to those occurring in cancer [26,27]. The two extreme phenotypes of macrophages are defined as M1 (the classical, pro-inflammatory macrophages) and M2 (the 'alternatively activated'/resolving anti-inflammatory cells); yet, in between lies a full spectrum of activation states which share some overlapping properties with those of the poles – either M1 or M2 (Figure 1). Similar to the situation in cancer [26,27], the macrophage response to neurodegeneration can promote beneficial effects, unless it is dysregulated and becomes pathological. Thus, none of the phenotypes is intrinsically 'good' or 'bad'; they all have beneficial potential if recruited to the correct location, at the right dose, at the appropriate time, and are eliminated when their function is complete. However, all of these cells can be detrimental if they persist, exceed optimal levels, or are not recruited at the optimal time.

While surveying the role of macrophages in various types of CNS disease or injury, we will summarize current evidence suggesting that resident microglia and infiltrating monocyte-derived macrophages are not redundant cells. Importantly, over the years, these cells were in many cases erroneously referred to in a generalized way as either 'macrophages' or 'microglia', without specifically addressing their origin; in this review, when their origin is not clear, we will refer to these cells collectively as either 'phagocytes' or 'myeloid cells'.

Macrophage heterogeneity in CNS repair following acute injury

Following acute traumatic insult to the CNS, the surrounding healthy neural tissue, initially spared from the injury but located adjacent to the damaged tissue, undergoes degeneration, leading to further neurological loss after the initial injury [5,28]. Among the mechanisms leading to such a spread of damage are vascular insults such as haemorrhage and ischaemia, excitotoxicity, calcium-mediated secondary injury, fluid–electrolyte disturbances, and inflammation (mediated mainly by myeloid cells), which, over the years, have received major attention as obstacles to repair, causing exacerbation of damage via neurotoxicity [5,28]. The limited regenerative nature of the

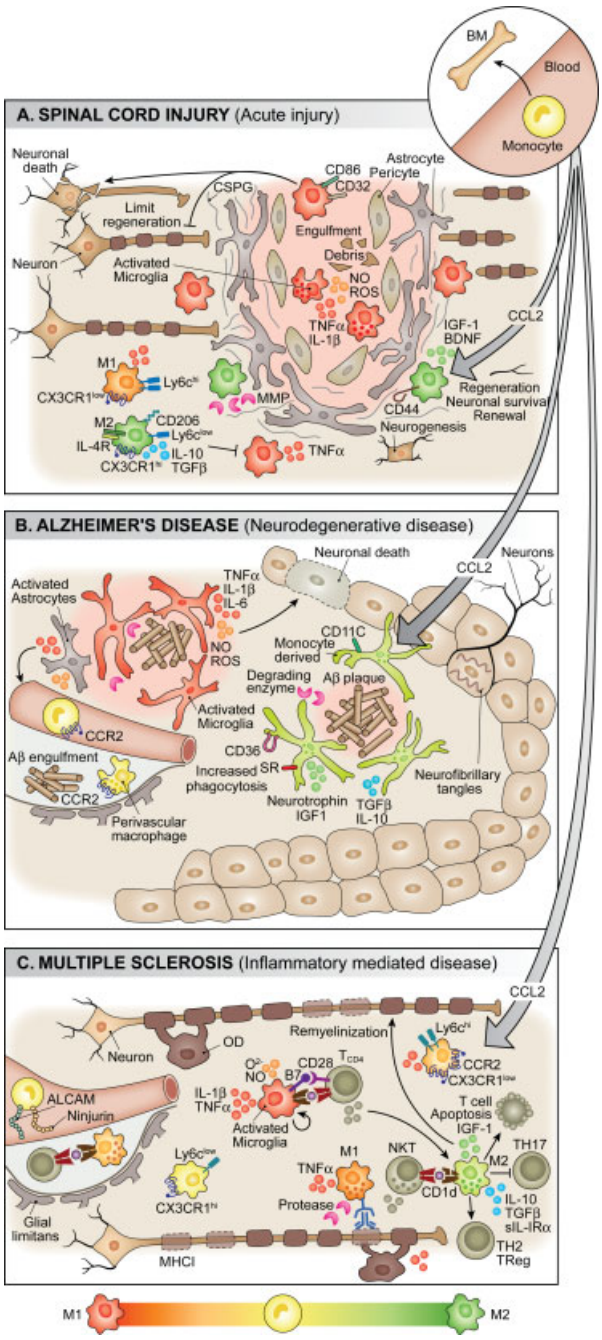

Figure 1. Macrophage heterogeneity in CNS neurodegenerative conditions. Illustrative scheme summarizing the characteristics of the blood-derived macrophage response, distinct from the response of resident microglia, in various CNS pathologies. Macrophages shown in orange have an M1-like phenotype, while those in green are skewed to M2-like activity. (A) Spinal cord injury, an acute trauma characterized by glial scar formation and microgliosis. Monocytes display pro-inflammatory M1 properties (neurotoxic and growth inhibitory) and subsequently M2-like resolving/anti-inflammatory characteristics in a regulated stepwise programme. M2-like cells also contribute neuro/axonal-tropic support as well as scar-degrading capacities. (B) Alzheimer's disease (AD), a neurodegenerative disease in which amyloid plaques are formed. AD is characterized by microglial activation. Blood-derived cells exhibit increased phagocytic capacity, neurotropic support, and anti-inflammatory characteristics. (C) Multiple sclerosis, a CNS autoimmune disease, is mediated by lymphocytes and dominated by a pro-inflammatory M1 response, although M2-like resolving macrophages are evident. Re-activation of self-reactive T cells by macrophages at the CNS border is indicated.

damaged CNS is attributed to the hostile environment at the lesion site predominated by the axonal growth-inhibitory glial scar, and pro-inflammatory radicals/mediators.

The diverse contributions of macrophages to neurological outcome following CNS trauma

Earlier observations attributed a negative role to macrophages/microglia in secondary tissue damage following CNS injury, leading to the widespread use of anti-inflammatory drugs for the treatment of victims of acute spinal cord injury [3,29–31]. Over the years, this issue has been repeatedly challenged. For example, targeted depletion of CD95L in myeloid cells reduces the infiltration of macrophages and neutrophils into the injured spinal cord, with an improvement of locomotor recovery [32]. Furthermore, anti-inflammatory treatment with FK506 or minocycline, a synthetic tetracycline derivative, decreases phagocytic activation and lesion size after injury and confers variable degrees of neuroprotection in spinal cord injury, traumatic brain injury, and stroke [33–35]. Similarly, early depletion of presumed peripheral macrophages using clodronate diminishes secondary tissue damage and was shown to have some beneficial effect [36].

Concomitantly, beneficial roles of macrophages have also been reported. Our team has shown that transplantation into the injured spinal cord or optic nerve of macrophages which were pre-activated *in vitro* by co-culture with peripheral nerve promotes neuronal survival and functional recovery [16]. These so-called 'alternatively *ex vivo* activated macrophages' exhibit enhanced phagocytic ability, increased capacity to secrete trophic factors, reduced pro-inflammatory bias, and increased proteolytic activity. Notably, it was found that the number of cells transplanted, the timing of their administration post-injury, and the site of their injection critically determine the neurological outcome. A phase I study using autologous macrophages activated *ex vivo* with autologous dermis as a treatment for complete spinal cord injury supported the safety of the treatment and its therapeutic potential in humans [37]. However, a phase II study in complete spinal cord injury patients failed to show a significant benefit, calling for additional study and protocol adjustments [38]. Other treatments based on the transplantation of autologous bone marrow-derived cells, with and without pre-activation/differentiation, were tested, and additional similar treatments, with some modifications, are currently being evaluated in pre-clinical phases [39,40]. In the eye, activated macrophages induced by lens injury were found to promote regeneration after optic nerve injury [41]. Using a conditional ablation strategy, and adoptive transfer experiments, in addition to a bone-marrow (BM) chimera model, we demonstrated a neuroprotective role of blood-derived monocytes in the spontaneous response to spinal cord or retinal injury [19,42]. Moreover, administration of naïve (non-activated) bone marrow-derived monocytes expressing

the hallmark marker of all monocytes, CD115, reduces secondary degeneration and promotes locomotion following spinal cord injury as well as ganglion cell rescue following glutamate toxicity, further supporting the therapeutic relevance of these cells [19,42].

The apparently conflicting findings resulted in a spirited controversy in the field, with some researchers viewing macrophages as detrimental and others emphasizing their beneficial role. Based on recent data, we suggest, as discussed below, that this discrepancy reflects the functional heterogeneity of the participating innate immune cells, their origin, and their dynamics in the process of CNS repair.

Origin heterogeneity of the phagocytic cells at the lesion site: microglia and monocyte-derived macrophages

Upon traumatic brain injury, microglial processes rapidly and autonomously converge at the site of injury without cell body movement, establishing a potential barrier between the healthy and the injured tissue, along with the astrocytes. This rapid microglial chemotactic response was found to be guided by extracellular ATP release from damaged cells [43,44]. ATP-stimulated microglia were shown to secrete brain-derived neurotropic factor (BDNF), a known survival factor which was shown in this case to cause a collapse of the neuronal transmembrane anion gradient [45]. At the site of the injury, the activated innate phagocytic cells include, in addition to the activated microglia, the macrophages which are derived from their circulating monocyte precursors upon their entry to the CNS parenchyma following the insult. Yet, over the years, these phagocytic cells were often erroneously referred to as either 'macrophages' or 'microglia' without specifically addressing their origin; to date, activated microglia and macrophages in the injured CNS cannot be clearly distinguished by their morphology or specific antigenic markers. Thus, it was suggested that the monocyte-derived cells be viewed as a subset of microglia when detected in the CNS; however, recent data have highlighted their distinction. The infiltrating monocyte-derived macrophages are often localized mainly to the lesion area [19], without spreading to the remote parenchyma [19]; these cells avoid lesion core invasion, concentrating at the margins of the injury site [19]. In contrast, amoeboid microglia, an activated form of resident microglia with retracted processes and extensive phagocytic activity, are distributed at the lesion core and margins [19,46]. Independent studies showed that monocyte-derived macrophages preferentially infiltrate into the grey matter [47–49]. The spatial organization of the infiltrating myeloid progenitor cells around the lesion site is regulated by the glial scar matrix, chondroitin sulphate proteoglycan (CSPG), which has a direct impact on macrophage functionality [46,50].

In retrospect, it became evident that part of the long-held debate in the literature regarding the role of microglia/macrophages in traumatized CNS reflected the fact that earlier experiments did not distinguish between resident microglia and blood-derived macrophages, and did not consider the dynamic changes in the course of the repair process in the subsets of monocyte-derived macrophages, as will be explained below.

Macrophage subset polarity in acute CNS injury

Phagocytic cells at the site of trauma were traditionally suggested to have a negative role in secondary tissue degeneration, via the secretion of pro-inflammatory cytokines such as IL-1β and TNFα, as well as increased production of reactive oxygen and nitrogen species. Although it is undoubtedly true that some phagocytes indeed exhibit this phenotype, a much more complex picture appears when the injury site is studied in more detail, revealing a spectrum of phagocyte phenotypes and activities. At least one subset of infiltrating monocytes at a critical time point after the injury has a unique, non-redundant, and essential anti-inflammatory role, characterized by pronounced expression of IL-10, a factor essential for microglial resolution, limiting inflammation, preventing secondary degeneration, and promoting motor function repair [19]. In contrast to the infiltrating monocytes, which can become resolving cells, resident microglia are generally pro-inflammatory, producing pronounced levels of pro-inflammatory cytokines and radicals, and do not acquire anti-inflammatory properties, at least during the dynamic phase of the repair. Using CX_3CR1 KO mice, it was recently shown that deficiency in CX_3CR1 signalling enhances recovery after spinal cord injury [51]. The CX_3CR1^{high} sub-population (which is classically identified in the brain with microglia known to express very high levels of this chemokine receptor [52,53]) was suggested to secrete pro-inflammatory mediators and oxygen radicals [51]. Using fluorescence-activated cell sorting analysis of macrophages at the CNS lesion (distinguished from the microglia by using head-shielded bone marrow chimeric mice, which allows these two cell types to be unambiguously identified), we recently found distinct subsets within the recruited monocyte-derived macrophage populations which correspond based on established markers, to pro-inflammatory cells and anti-inflammatory 'alternatively activated' (M2)/resolving (anti-inflammatory) population and to share similarities with the tumour-associated macrophages [TAMs; the monocytic fraction of the myeloid-derived suppressor cells (MDSCs)] identified in cancer.

Characterization of the overall phenotypic polarization in the contused mouse spinal cord suggested that most myeloid cells correspond to the classical M1 subtype, determined according to CD86+ and CD16/32+, with only a transient (few days) and small population (< 40% in the first days, reducing to less than 10% thereafter) exhibiting a phenotype reminiscent of the 'alternatively activated' M2 polarization, defined

as Arginase 1 (Arg1) and mannose receptor (CD206)-positive [54]. M2-like cells secreting IL-10 were also recently found at the lesion site following brain trauma [55]. Although these cells are a minority, their elimination results in worse motor recovery and in spread of damage following spinal cord injury [19]. In addition, supplementation of monocytes which were shown to acquire locally resolving/M2-like phenotype, manifested by their IL-10 secretion, to spinally injured animals augments repair [19]. *In vitro* studies have shown that classical M1-polarized macrophages can directly induce neuronal death, probably via iNOS activity (and may thereby contribute to secondary degeneration) [54]. The low number of cells reminiscent of the 'alternatively activated' M2 macrophages after spinal cord trauma probably explains the prolonged pro-inflammatory response, which has detrimental effects on tissue viability if not terminated on time (Figure 1A).

Multiple roles of macrophages in acute CNS trauma beyond inflammation induction and resolution

Varied roles of macrophages have long been reported in cancer and more recently in non-CNS wounds, supporting not only inflammation induction and resolution, but also participation in many other processes including matrix remodelling, angiogenesis, and cell renewal [22–27]. In the injured CNS, macrophages were shown to be a source for tropic support [41,46,56,57] and can stimulate axonal regeneration [41] and survival [42], as well as modulation of scar deposition [50]. The specific phenotype responsible for each function is still not clear. Using CD11b-TK(mt-30) mice, in which myeloid cells may be pharmacologically depleted, it was shown that myeloid cells support axonal regeneration and functional recovery by creating a growth-permissive milieu for injured axons, supporting the clearance of inhibitory myelin debris, neurotrophin synthesis, and blood vessel formation/maintenance [58]. Similarly, $CD14^+$ peripheral blood monocytes were found to participate in the repair of the vascular barrier after brain injury [59]. Monocyte-derived macrophages contribute to degradation of the glial scar matrix CSPG, via its proteolysis, a remodelling activity that requires matrix-degrading enzymes such as matrix metalloproteinase (MMP) 13 [50]. Neuron survival and axonal regeneration have also been reported to be facilitated by macrophages; macrophages secrete IGF-1, BDNF, NGF, and oncomodulin, a specific macrophage-derived, Ca^{2+} binding growth/trophic factor [41,46,56,57]. Macrophage regenerative capacity is differentially regulated by the cell subset; *in vitro* polarized M1 macrophages cause retraction of dystrophic axons of adult dorsal root ganglion neurons. Moreover, M1 macrophage-conditioned medium induces stunted, short neurites with multiple branches, whereas M2 macrophage-conditioned medium promotes extensive, long neurites [54]. Monocytes also orchestrate cell renewal. Inhibition of monocyte infiltration following glutamate toxicity in the eye reduces the numbers of proliferating retinal progenitor cells (RPCs) in the ciliary body, whereas enhancement of the circulating monocyte pool leads to increased RPC colonization [42]. Activated macrophages can serve as an *in vivo* source of ferritin for $NG2^+$ cells – oligo-progenitors – which induces their proliferation and differentiation into new oligodendrocytes [60]. Thus, it seems that phagocytes in general and specifically, defined macrophage populations, mainly with M2-like phenotype or similar activation state(s), can support multiple reparative functions whose nature is just starting to be revealed (Figure 1A).

Macrophages in chronic neurodegenerative disorders – an ancient foe becomes a future friend

The involvement of macrophages in neurodegenerative disease which are not inflammatory in their aetiology has only recently begun to be appreciated. Originally these diseases were believed to involve only the neural tissue compartment; however, in recent years, it has been shown that microglia/macrophages could support disease progression or remission by multiple functional activities ranging from secreting inflammatory mediators to debris engulfment and providing neurotropic support [18,61–65]. Moreover, recently the contribution of systemic factors in these diseases was revealed, disproving the previous assumption that neurodegenerative disorders are CNS-autonomous. These new findings provided the basis for therapeutic avenues based on harnessing systemic myeloid cells in neurodegenerative diseases.

The case of Alzheimer's disease

Alzheimer's disease (AD) is an age-dependent neurodegenerative disease whose clinical features include loss of memory, progressive impairment of cognition, and various behavioural symptoms. The neuropathological characteristics of Alzheimer's disease include the accumulation of extracellular amyloid-β plaques (collectively termed Aβ) that comprise aggregated, cleaved products of amyloid precursor protein (APP) and neuron intracellular neurofibrillary tangles that are composed of hyperphosphorylated forms of the microtubule-binding protein tau.

Alzheimer's disease is characterized by neuroinflammation [66]. Susceptibility-linked gene variants were found in inflammatory pathways, and epidemiological studies revealed a protective effect for non-steroidal anti-inflammatory agents against later development of Alzheimer's disease. However, in several clinical trials studying established Alzheimer's disease, the administration of non-steroidal anti-inflammatory agents had no effect or even a detrimental one on disease progression, highlighting a possible protective role of inflammation in this disorder [21]. Neuropathological characterization of tissues taken

from AD patients revealed the presence of numerous inflammatory mediators, as well as an inflammatory cellular reaction, consisting of mainly myeloid cells (microglia, monocytes, and perivascular macrophages) and almost no adaptive immune cells, highlighting the role of the myeloid lineage in AD.

Microglia and macrophages in AD

Microglia were originally suggested to be responsible for pathological β-amyloid (Aβ) protein deposition [67–69] and neuronal loss [70]. However, ablation of the majority of parenchymal microglia using an inducible suicide gene approach in mouse models of AD suggested that neither amyloid plaque formation and maintenance nor amyloid-associated neuritic dystrophy depends on the presence of microglia [71]. *In vivo* multi-photon imaging showed that microglial activation is a secondary event to amyloid aggregation [72]. While they play only a minor role in amyloid clearance, microglia may become activated by protein aggregates and thus contribute to secondary degeneration via the release of neurotoxic factors.

The significant contribution of peripheral myeloid cells to AD brains was a subject of intense research. Originally, using bone marrow chimera, it was suggested that abundant myeloid cells are attracted from the bloodstream to the proximity of amyloid plaques; these cells were suggested to differentiate to microglia and were thus termed blood-derived microglia [18]. With the discovery that microglia are derived from yolk-sac cells [14], this terminology was understood to be inaccurate, and these cells are better described as blood-derived macrophages. The capacity of monocytes to enter the AD brain, without pre-conditions, was shown in adoptive transfer experiments in non-irradiated mice [73]. Using a myeloid-specific ablation system, it was shown that blood-derived cells, and not their resident counterparts, eliminate amyloid deposits efficiently by a cell-specific phagocytic mechanism [18]. The effective amyloid clearance mediated by infiltrating monocytes, and not by microglia, may be explained by microglial lysosomes being less acidic than macrophage lysosomes, resulting in reduced activity of lysosomal enzymes [74]. Accelerated CNS tissue pathology and early demise were reported in a mouse model of Alzheimer's disease that was unable to recruit monocytes to the CNS as a result of deficiency of CCR2, a receptor specific for the monocyte chemoattractant protein family of chemokines [75,76]. Similarly, a dominant role was attributed to MCP-1/CCL2, the ligand for CCR2, in chronic inflammation in the human AD brain [77]. The recruitment of peripheral immune cells, probably via MCP-1 induction, might be induced by intracerebral expression of pro-inflammatory cytokines, such as IL-1β [78]; such neuroinflammation was associated with decreased cerebral amyloid burden [79].

A recent study demonstrated an additional aspect of the complexity of macrophage heterogeneity in AD by suggesting distinct spatiotemporal roles for specific myeloid sub-populations in disease pathogenesis. $CCR2^{+}$ blood-derived myeloid cells were shown to be recruited to regions of Aβ plaques and the cerebrovascular compartment. The recruitment of mononuclear phagocytes from the periphery to parenchymal plaques was shown to be dependent on CCR2 expression and preconditioning of the brain (for example, irradiation), whereas perivascular macrophage recruitment to vascular β-amyloid deposits from the circulation occurs even in the absence of CCR2, though this receptor is needed for Aβ clearance [80]. Stimulation of perivascular macrophage turnover reduces cerebral amyloid angiopathy load independently of clearance by microglia [81]. These newly identified key players are phagocytes located in the perivascular spaces, where they are important for immune surveillance and in the transport of Aβ across the blood–brain barrier (BBB) [82]. Altogether, these findings indicate multiple phagocytic phenotypes, origins, and activities in AD, in which the microglia are insufficient for mediating amyloid engulfment, while macrophages, located within the parenchyma or at its perivascular spaces, are better equipped for this task (Figure 1B).

Macrophages as a therapeutic avenue in AD

Similar to the case of CNS acute injury discussed above, the involvement of circulating immune cells suggests the possibility of manipulating systemic immunity as a powerful approach to treat AD and to eliminate Aβ from the CNS. Vaccination was tested in the APP mouse model of AD using glatiramer acetate (GA) in a regimen that is distinct from the daily protocol used for multiple sclerosis (MS), resulting in decreased plaque formation and induction of neurogenesis [61]. The treatment skews the phenotype of microglia/macrophages to dendritic-like ($CD11c^{+}$/MHC-II^{+}) cells providing tropic support via the production of IGF-1 [83] and induces the recruitment of bone marrow-derived cells [84]. Inducible depletion of CD11c cells by diphtheria toxin significantly increases the accumulation of amyloid plaques, abrogating the benefit of the treatment. Notably, treatment with GA in complete Freund's adjuvant also has a beneficial effect on disease progression in a mouse model of amyotrophic lateral sclerosis (ALS), a neurodegenerative disease of motor neurons [85], whereas adjuvant-free GA does not alter the survival of these mice and even results in earlier appearance of disease symptoms and, in a different immunization regimen, in shorter life expectancy [86,87]. Immunization with a myelin oligodendrocyte glycoprotein (MOG)-altered peptide, loaded on dendritic cells, reduces parenchymal and perivascular amyloid plaque burden [84]. The changes are associated with a skewed local innate immune response, manifested by an increased number of macrophages that engulf Aβ. Surprisingly, these phagocytes, in contrast to classical M1 cells, express reduced pro-inflammatory cytokine

(TNFα) levels; in fact, these cells possess similarities with the M2/'alternative' phenotype, as such treatment results in increased anti-inflammatory (IL-10) cytokine and growth factor (IGF-1 and TGFβ) levels and increased matrix degradation enzyme expression [88]. Systemic immune activation by specific blocking of TGFβ–Smad2/3 innate immune signalling in peripheral myeloid cells increases the infiltration of Aβ-containing peripheral macrophages around cerebral vessels and amyloid plaques and attenuates AD-like pathology [89]. Importantly, the beneficial effect of restricting cerebral amyloid, achieved by removing TGFβ immunosuppression signalling from blood-derived macrophages, does not come at the cost of increased inflammation in the brain; on the contrary, these blood-derived Aβ phagocytotic cells display an anti-inflammatory profile [89]. Thus, these beneficial phagocytes manifest an intermediate phenotype somewhere between classical M1 and M2, with properties of both cell types. Intracerebral pro-inflammation signals such as IL-1β or IL-6 may also be beneficial, facilitating the recruitment of blood leukocytes without causing neutrotoxicity. Rather, these cells reduce cerebral amyloid pathology, possibly via the augmentation of phagocytic cells [79,90]. Although phagocytic activity is a hallmark of M1, other reports suggest that M2 are efficient phagocytes. The full phenotype of the recruited/activated phagocytes was not defined and may also reflect an intermediate state. Systemic M-CSF administration, a powerful treatment to mobilize monocytes, increases CNS infiltration of bone marrow-derived myeloid cells, reduces plaques, and attenuates the cognitive decline associated with Aβ burden in a mouse model of AD [91]. The combined effects of haematopoietic progenitor cell mobilization from bone marrow by granulocyte colony-stimulating factor and chemotaxis into the brain using intracerebral injection of stromal cell-derived factor-1α in an Alzheimer's disease mouse model enhance neurogenesis, improve cognition, and increase BM-derived macrophage activation with an alternative neuroprotective phenotype [92]. These results indicate that boosting macrophage recruitment to AD brains can attenuate symptoms by enhancing amyloid engulfment and providing other supportive functions (Figure 1B).

Multiple macrophage phenotypes even in multiple sclerosis

The benefit of monocyte-derived macrophages in acute and chronic neurodegenerative conditions does not negate the well-established pathological role of macrophages in multiple sclerosis (MS); even in MS, in which pro-inflammatory neurotoxic, myelin-attacking macrophages predominate, some macrophages with the properties of an alternative phenotype are present, as described below. In addition, we will describe how this disease, although inflammatory in nature, can benefit from macrophages of the correct phenotype.

Pathogenic macrophages in MS

Macrophages are involved in the pathogenesis of demyelination in MS, an inflammatory disease in which the myelin sheaths around the axons (the nerve extensions involved in their communication) in the CNS are damaged, leading to demyelination. Thus, a correlation was found between macrophage numbers and myelin degradation [93]. However, this linkage, although roughly accurate, is somewhat misleading. Since total macrophage counts do not account for phenotypic heterogeneity, reliance on macrophage numbers was actually a setback in understanding the roles of CNS macrophages in other non-inflammatory diseases. Nevertheless, macrophages do have a proven role in initiating EAE, the animal model of MS, as their depletion significantly inhibits disease [94]. MHC class II-expressing macrophages are responsible for reactivation of pathogenic T cells at the CNS borders, subarachnoid spaces of the meninges, and perivascular spaces of the BBB; such reactivation is needed for lymphocyte subsequent border crossing and parenchymal invasion [95]. Notably, microglial cells become competent APCs for T cells only after inflammation is established, which induces their expression of MHC and co-stimulatory molecules. Macrophages were also shown to secrete inflammatory mediators and to suppress Treg expansion via a sialoadhesin–silic acid interaction [96]. Thus, multiple pathogenic roles have been attributed to the phagocytic cells in MS.

Origin heterogeneity of phagocytes in MS

The origin of the macrophages seen at the EAE plaque has been an ongoing enigma. As early as the 1990s, it was shown that microglia and macrophages both occupy MS lesions [97]. Using a combination of parabiosis and myeloablation (thereby replacing circulating progenitors without affecting CNS-resident microglia), a correlation was shown between monocyte infiltration and progression to the paralytic stage of EAE [98]. MCP-1, the major CCR2 ligand in mice with EAE, was suggested more than a decade ago to have a major role in the establishment of this pathology [99]. Only recently were $CCR2^{+}$/Ly-$6C^{hi}$ monocytes shown to be rapidly recruited to the inflamed CNS and to play a crucial role in the effector phase of the disease [100,101]. Inhibition of MCP-1-CCR2 chemokine receptor-dependent recruitment of monocytes to the CNS blocked EAE progression, suggesting that these infiltrating cells are essential for pathogenesis. Using double *Cx3cr1*^{GFP}/*CCR2*^{RFP} transgenic mice [in which CNS microglia were labelled with high GFP (but not CCR2-RFP) and blood monocytes were traced with RFP and GFP], it was shown that both Ly$6c^{high}$/CX_3CR1^{low} and Ly$6c^{low}$/CX_3CR1^{high} monocyte-derived macrophages are seen at the demyelinized lesions in EAE, while only the former, which are the predominant population in this pathology, are recruited in a CCR2-dependent

manner and are believed to contribute to activation of resident microglia, further accelerating inflammation [52]. This finding hints at macrophage phenotypic heterogeneity even in a disease that was considered to be purely inflammatory.

M2-like macrophages in MS

Recent data have indeed highlighted the functional heterogeneity of macrophages even in this pathology; macrophages with the characteristic phenotype of M2 alternatively activated macrophages, $CD163^+$, Arg-1^+, were found in MS brain [102,103]. As in the case of other neurological diseases, heterogeneous macrophages (which may correspond to M1-like and M2-like macrophages or in between) are believed to differentiate from infiltrating monocytes in MS, and the balance between them was proposed to predict the development of relapses, suggesting the functional participation of the alternatively activated cells [104]. Activation of invariant NKT cells, via IL-4 and CD1d, was shown to promote differentiation of monocytes to induce an M2 character [105], whereas CCL22 was shown to promote differentiation towards possessing the character of the more classical M1 [104]. In MS, myelin engulfment by phagocytes skews the cells towards anti-inflammatory properties, in which myelin-phagocytosing cells were reported to inhibit TCR-triggered lymphocyte proliferation in an antigen-independent manner via an increase in NO production [106]. Although classically monocytes [and more specifically $CCR2^+$ inflammatory ($Ly6c^{high}$) ones] were suggested to contribute to MS pathology [100,101], other studies have shown that $CD11b^+/Ly6c^{high}$ are immature monocytes with suppressive activities (NO synthase 2, Arg1, causing T-cell apoptosis [107]), reminiscent of TAMs/MDSCs often found to infiltrate tumours [108]. Such cells are induced by IFN-γ, GM-CSF, and TNFα [109]. Although further characterization is required to reveal the full spectrum of their activities and their similarities to the other subsets identified in CNS neurodegeneration and other non-CNS systems, these findings provide additional evidence of macrophage heterogeneity (Figure 1C).

Macrophages in MS control remyelination

Phagocytic cells, including macrophages, are known to attack the myelin sheet in MS, leading to demyelination. However, remyelination, which occurs during remissions, revealed a novel role for macrophages in promoting this healing process. Similarly, minocycline treatment strongly inhibits phagocyte accumulation at the MS lesions, resulting in reduced remyelination and a suppressed oligodendrocyte progenitor cell response [110]. In a recent study using parabiosis in which old and young mice were paired, it was shown that remyelination following experimentally induced demyelination in old mice necessitates, in addition to other soluble factors [111], the recruitment to the repairing lesion of blood-derived monocytes from the young parabiotic partner [112]. *In vitro* studies demonstrated that while Th1-derived cytokines, such as IFN-γ, confer on microglia/macrophages a phenotype that impairs oligodendrogenesis, IL-4, an M2 skewing cytokine, reverses this phenotype and overcomes the blockage of IGF-1 production [83]. In a rodent EAE model, injection of IL-4-activated microglia/macrophages into the cerebrospinal fluid results in increased oligodendrogenesis in the spinal cord and improves clinical symptoms [83] (Figure 1C).

Macrophages as a therapeutic avenue even in MS

Treatment with GA, when administered daily, promotes the development of anti-inflammatory type II monocytes, characterized by increased secretion of interleukin (IL)-10, TGFβ, and sIL-1Rα, and decreased production of the pro-inflammatory cytokines IL-12, TNF, and IL-1β [113,114]. These type II monocytes skew the phenotype of lymphocytes, the main pathological compartment in EAE. Adoptive transfer of type II monocytes reverses EAE, suppresses Th17 cell development, and promotes both Th2 differentiation and expansion of Treg cells in recipient mice, highlighting their powerful immunosuppressive nature and their direct therapeutic relevance [113,114]. Similarly, adaptive transfer of alternatively activated myeloid cells displaying characteristics of the M2 subset, prepared either by *in vitro* activation of bone marrow-derived myeloid cells with IL-4 [115] or using M2-skewed blood monocytes [104], mitigates EAE. Thus, it appears that even in a pathology that is inflammatory in its aetiology, in which macrophages are the pathological effector cells, specific macrophages with the desired phenotype, resembling the M2 or resolving phenotype previously described, can mitigate disease. Under such conditions, in which macrophages are extensively recruited, it may even be possible to skew the phenotype of the previously recruited inflammatory cells.

Multiple macrophage/microglia phenotypes in CNS-cell renewal

Microglia and macrophages contribute to the process of neural progenitor cell (NPC) proliferation and differentiation (neurogenesis, oligodendrogenesis) occurring at the site of neuronal damage following various pathological conditions (Figure 2). Two classical neurogenic niches are present in the adult brain [116]: the sub-granular zone (SGZ) of the hippocampus, participating in memory and learning skills; and the sub-ventricular zone (SVZ) and its projection via the rostral migratory stream (RMS) to the olfactory bulb, participating in novel odour discrimination. In recent years, novel roles have been attributed to immune involvement in the regulation of adult neurogenesis within their natural physiological niches and in ectopic

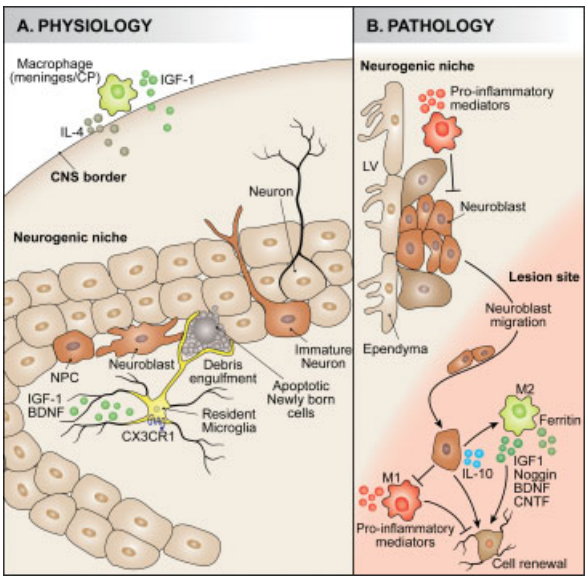

Figure 2. The multiple functions of microglia/macrophages at the neurogenic niches. (A) The participants under physiological conditions. The neurogenic niche at the sub-granular zone of the hippocampus is shown. Resident microglia have an active role as waste managers to eliminate cellular debris from apoptosing newborn cells and to provide trophic support via the secretion of growth factors. At the CNS borders, macrophages can contribute to regulation of neurogenesis via trophic support. (B) The many effects under pathology. Although often distant from the damaged area, neurogenic niches are affected in many pathologies. Pro-inflammatory macrophages and microglia can destroy the architecture of the sub-ventricular zone (SVZ), inhibit neurogenesis, and promote glial differentiation via pro-inflammatory mediators. Neuroblasts from the SVZ were also shown to migrate to the site of damage. At the damage site, M1-like cells inhibit NPC differentiation to neurons or oligodendrocytes, while M2-like cells promote differentiation via the secretion of growth factors and ferritin. The cross-talk with the neuroblast is bi-directional, in which the neural progenitor also acts as an immune-modulating cell via the secretion of anti-inflammatory cytokines.

niches under pathological conditions [117]. Cells of the immune system, including microglia/macrophages, can be beneficial or detrimental to such a process. This cross-talk between NPCs and immune components within the brain has been reviewed in detail elsewhere, and this interaction is suggested to harbour significant reparative potential [117,118].

Microglia/macrophages support adult neurogenic niches

Microglia are located within the neurogenic niches and have become appealing candidates for modulating neurogenesis in both the healthy and the injured brain. Microglial inflammation was originally suggested to inhibit neurogenesis and was thus defined as 'the enemy within' [119–121]. However, progress in the field has revealed the complex and heterogeneous microglial participation even in this process. *In vitro* studies revealed that microglia are capable of secreting factor(s) essential for neurogenesis [122,123]. It was further shown that skewing of macrophages (achieved by classical Th1 or Th2 cytokines) distinctly affects neural differentiation [124]. Moreover, the persistence of microglial activation (acute or chronic) also differentially affects NPC fate [125]. *In vivo*, it was shown that microglia become activated, increasing IGF-1 and MHCII expression, when hippocampal neurogenesis is induced by an enriched environment, suggesting their activation in response to the challenge [126]. Microglia were shown to modulate hippocampal neural precursor activity in response to exercise and ageing, an effect that is suggested to be mediated by the CX_3CL1–CX_3CR1 axis [127]. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis, in which microglia assume the role of waste management to eliminate cellular debris from apoptosing newborn cells [128]. Resident and recruited olfactory epithelial macrophages participate in the regulation of the survival, cell proliferation, degeneration, and replacement of olfactory sensory neurons [129,130]. CX_3CL1/fractalkine was also reported to regulate the monocyte-derived cellular response in the mouse olfactory epithelium, in which monocyte-derived cells depend on CX_3CL1 signalling for intraepithelial migration and apical dendrite expression [131]. A recent study attributed a role in learning and memory capacity, which is highly regulated by hippocampal neurogenesis, to meningeal myeloid cells (which are constitutively replaced by blood precursors); this function is specifically dependent on their M2-like phenotype (directed by IL-4-secreting T cells) and their ability to secrete BDNF [132]; however, their direct involvement in hippocampal neurogenesis was not tested (Figure 2).

Changes in classical neurogenesis, although anatomically remote from the site of neuronal damage, accompany many CNS disorders. Inflammation is known to modulate various steps in adult neurogenesis, affecting NPC proliferation, survival, differentiation, functional integration, and synaptogenesis. Inflammation-induced sub-ventricular zone (SVZ) dysfunction was reported to lead to olfactory deficits in a targeted mouse model of multiple sclerosis [133]. Blood-derived macrophages as well as activated microglia were reported to preferentially accumulate within the SVZ of EAE mice, to secrete pro-inflammatory mediators, and to derange SVZ cytoarchitecture [134]. Diminished adult neurogenesis underlies the pathogenesis of HIV1-associated dementia and was suggested to be mediated by HIV-infected macrophages inducing glial differentiation of the NPCs [135]. The classical niches also remotely support the damaged site, at which persistent migration from the SVZ towards the affected area was reported [136,137] (Figure 2).

Bi-directional cross-talk

NPCs can act as immunomodulating cells by producing IL-10 [138], skewing the immune response towards regulatory and reparative activities, reminiscent of M2

cells, or sharing properties with them. Therefore, transplantation of NPCs in various CNS pathologies, ranging from acute insults to autoimmune diseases and neurodegenerative disorders, provides an additional major advantage as immunological players, beyond cell replacement, whose efficacy is limited [56,139]. As such, transplanted NPCs were reported to 'instruct' phagocytic cells in the injured spinal cord, skewing the inflammatory macrophages towards more M2-like characteristics [140]. In addition, NPCs seem to use the same guiding molecules as immune cells, to secrete cytokines, and to express classical immune receptors. For example, NPCs respond to SDF-1 guiding their migration to the site of damage [136] and express innate receptors such as Toll-like receptors (TLRs) that regulate their fate in the classical neurogenic niches and in response to insults [141,142] (Figure 2).

Projecting the M1–M2 model to the CNS

Macrophage heterogeneity corresponds to a spectrum of activities whose two poles are the pro-inflammatory M1 and the 'alternatively activated'/resolving M2 phenotypes; in between, a full spectrum of activation states displaying overlapping properties with the two poles (M1 and M2) is suggested (extensively reviewed elsewhere [22–27]). To date, there are insufficient markers to discriminate between each of the intermediate activation states, sometimes resulting in the erroneous classification of the identified cells to one of the poles. However, these cells display a huge array of possible phenotypes and seem to be involved in almost every conceivable function; they participate in inflammation induction as well as resolution, angiogenesis, matrix remodelling, debris clearance, tumour invasion and seeding, pathogen killing, tissue regeneration, cell rescue, cell renewal, and others. Depending on the circumstances and the tissue needs, these polarized cells can have either beneficial or pathological consequences.

The multiple roles of macrophages within the CNS have precedent in the well-accepted models of the diverse roles of different macrophage populations in tumours. The effect of macrophages on tumour progression is illustrated by the 'yin–yang' scheme of Biswas and Mantovani [26] describing the beneficial or pathological interaction between macrophages (either M1 or M2/TAM) and tumour cells, while emphasizing the cross-talk of M1 and M2 with other immunological components. We suggest that a similar beneficial or pathological outcome is applicable when describing the neurological output of diverse macrophage activities. However, one should recall that a full spectrum of activation states, sharing overlapping characteristics with both poles, lies in between the classical M1 and M2 cells, complicating the picture. In our scheme, we mainly consider the extreme states and suggest that the M1–M2 polarization in the CNS regulates intercellular interactions with CNS tissue-specific cells and thereby determines the overall effect of such interactions on CNS degeneration and repair (Figure 3A). M2 macrophages in the CNS resolve microglial and astrocyte pro-inflammatory milieus, promote neuroprotection and axonal regeneration, and support cell renewal from progenitors. In contrast, M1 macrophages promote an inflammatory response of the CNS glia (both resident microglia and astrocytes), causing axon degeneration and neuronal death, and promote BBB permeability and activation, leading to enhanced inflammation and tissue damage. Taking into account their multi-functional activity, it seems on face value as if M2 macrophages support CNS repair, while M1 macrophages accelerate its degeneration. Importantly, however, the current view also suggests that M1 macrophages are necessary in some conditions as long as they are kept under control; they are undoubtedly essential for inflammation induction, regulation of scar formation, and debris clearance – all repairing essential events. However, if prolonged, an uncontrolled pro-inflammatory response is detrimental to the neural tissue. No less important, a dysregulated M2 response might be detrimental as well when its timing, dosing or location is not optimally controlled. Thus, a much more complex scenario rather than a simple dichotomy of bad–good or M1–M2 is evident *in vivo*.

Another level of complexity is added via the multiple functions of these cells. M1–M2 macrophages are best defined by virtue of their inflammatory nature; a more complex picture is evident when the other properties of these cells are considered. To best describe macrophage heterogeneity, we wish to adapt the scheme of Condeelis and Pollard that correlates such multiple functions of macrophages [143] to the well-appreciated six traits of malignancy [144], thereby emphasizing the crucial multi-functional roles of macrophages in the processes resulting in tumourigenesis. As a corollary to this model, we suggest that in CNS pathology, macrophages adopt diverse phenotypes (of which their poles are the classical M1 and M2), each supporting a specific role that facilitates six features of tissue repair. These features of tissue repair, and the characters of the macrophages participating in each of them, predominantly overlap with the occurrence in cancer. While in cancer the overall activities of macrophages support malignancy, in CNS tissue damage macrophages have the potential to support cell survival, regeneration, and renewal, and if malfunctioning, tissue degeneration (Figure 3B).

Harnessing monocytes to fight off neurodegenerative conditions

As summarized above, until two decades ago, the only cross-talk between the brain and the immune system, which suggested having a negative output, was appreciated only under inflammatory-associated pathologies. However, with time, it has become clear that the interconnections between these systems can no

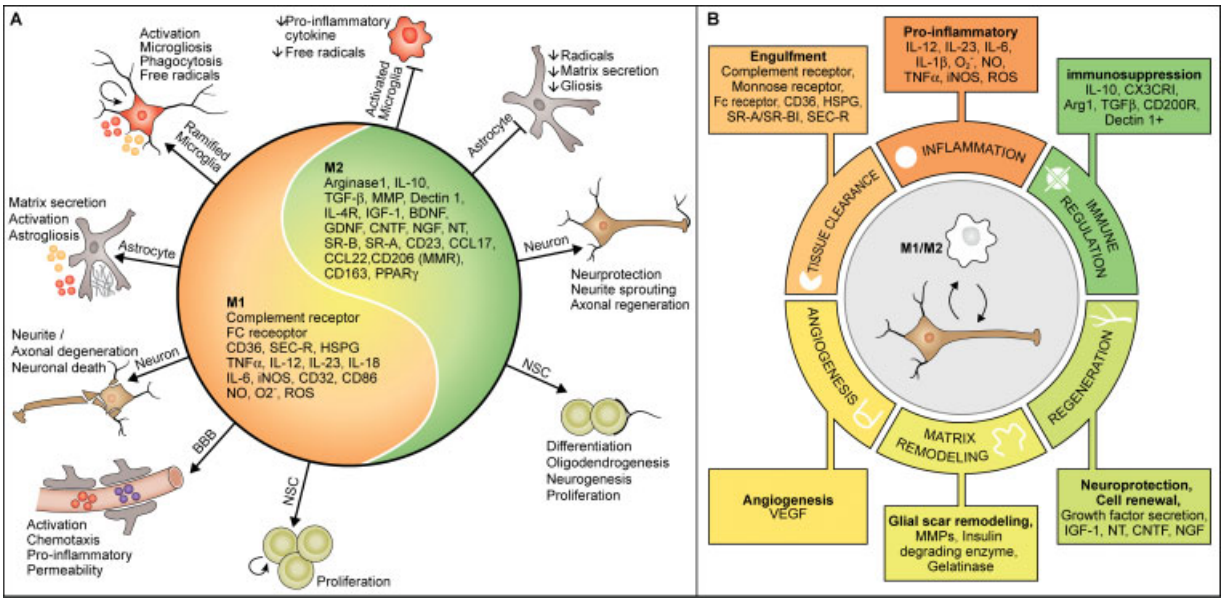

Figure 3. The multiple functions of CNS macrophages – M1/M2 model. (A) The 'yin–yang' scheme of Biswas and Mantovani summarizing the M1–M2 immunological interactions and overall effects on tumour progression, compared with the activities of M1-like and M2-like cells within the CNS. The specific consequences of polarized macrophages on cells of the CNS, such as neurons, astrocytes, microglia, BBB, and NSC, are indicated. The red and green shading reflects a simplified view of the overall functional outputs of M1/M2, respectively. (B) CNS adaptation of the Condeelis and Pollard scheme of macrophage contribution to the six traits of malignancy. The analogous contribution of diverse macrophage phenotypes to the six equivalent traits of CNS pathology is summarized. Macrophages can promote inflammation or its resolution, can support matrix remodelling by degradation, and can promote tissue angiogenesis, regeneration and cell renewal, as well engulfment of debris, pathogens, or dying cells.

longer be ignored, calling for a new interdisciplinary approach. As macrophages/microglia are an efficient effector arm of the immune system involved in many CNS pathologies, they have gained great attention. Although some lines of evidence as early as the 1990s highlighted their therapeutic value and potential reparative capacity, these findings were generally viewed as enigmatic and even provocative. Recently, however, research on myeloid cells in the CNS has been markedly changed by employing many of the tools of immunological research and projecting the knowledge accumulated in other systems, such as tumours. These methodologies have yielded unexpected results which challenge the traditional view of macrophages in the CNS. As the distinction between bone marrow-derived myeloid cells and the CNS-resident microglia became clear, macrophages returned to the spotlight as unique players. Their functions became even more intriguing with the discovery that cells with distinct origins exhibit non-redundant roles in many pathologies. Bone marrow-derived macrophages seem to be more involved in CNS pathologies than originally thought, with a spectrum of properties and activities ranging from devastating to beneficial; they are no longer considered the invading enemy, but are recognized for their multiple reparative capacities. Currently, therapeutic efforts in various pathologies ranging from acute traumas [19,42] to chronic neurodegenerative diseases [18] and neurodevelopmental disorders [20] and even inflammatory-mediated disease [113] are aimed at harnessing these multi-functional cells.

As discussed above, the phenotype of the recruited cells and the magnitude of their infiltration critically affect the neurological outcome. In MS, an autoimmune disease, monocytes are massively recruited but exhibit predominantly M1 (or similar) pro-inflammatory neurocytotoxic activity. In such an inflammatory disease, patients could benefit from M2/resolving skewing, possibly even of the previously recruited cells, thereby turning the foe into a friend. The situation in neurodegenerative disease is different; in the case of either acute insults or neurodegenerative disease and even mental disorders, these resolving monocytes have reparative effects but their recruitment is, at best, limited and in some cases even unachievable. Such non-inflammatory neurodegenerative conditions would thus benefit from inducing or augmenting monocyte infiltration to the CNS. According to our current understanding, these plastic cells, once introduced to the neuropathological CNS, acquire a reparative phenotype and provide neurotropic support, increased debris clearance, and anti-inflammatory/resolving capacities. Thus, it seems that the limitation in neurodegenerative conditions is not necessarily the acquisition of the correct phenotype, but the failure to recruit sufficient numbers of the right phenotype; the physiological protective mechanism of the CNS barrier system, protecting it from pathogens and the changing environment of the circulation, becomes an obstacle to repair in neurodegenerative disease. Importantly, revealing the mechanisms of spontaneous, though limited recruitment of 'healing' monocytes should

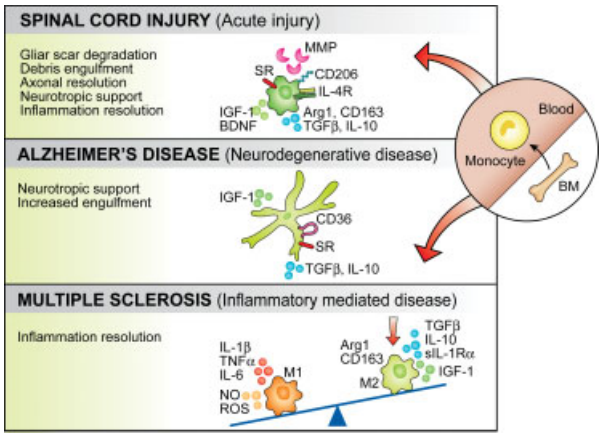

Figure 4. The ultimate monocyte-based therapy for CNS neurodegeneration. Schematic presentation of recommended therapeutic approaches based on Figure 1. In multiple sclerosis, in which monocytes massively recruit and acquire an M1 phenotype, therapeutic avenues should consider skewing the already recruited cells towards an M2 phenotype. Under non-inflammatory conditions, which include acute traumas, neurodegenerative disease, and even mental disorders, induction/augmentation of monocyte recruitment could promote healing. These plastic cells acquire the desired phenotype as determined by the needs of the tissue.

pave the way to their optimal augmented/induced recruitment. Understanding how to harness these cells holds great potential as a therapeutic approach to the degenerating CNS, ranging from neurodegenerative (acute and chronic) conditions [18,19] to even neuropsychiatric disorders [20] (Figure 4).

Author contribution statement

The manuscript was written under the supervision of MS and is the outcome of the collaborative efforts of MS and RS.

References

1. Medawar PB. Immunity to homologous grafted skin; the fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye. *Br J Exp Pathol* 1948; **29:** 58–69.
2. Boster A, Edan G, Frohman E, *et al*. Intense immunosuppression in patients with rapidly worsening multiple sclerosis: treatment guidelines for the clinician. *Lancet Neurol* 2008; **7:** 173–183.
3. Bracken MB, Shepard MJ, Collins WF, *et al*. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med* 1990; **322:** 1405–1411.
4. McGeer PL, McGeer E, Rogers J, *et al*. Anti-inflammatory drugs and Alzheimer disease. *Lancet* 1990; **335:** 1037.
5. David S, Kroner A. Repertoire of microglial and macrophage responses after spinal cord injury. *Nature Rev Neurosci* 2011; **12:** 388–399.
6. Prinz M, Priller J, Sisodia SS, *et al*. Heterogeneity of CNS myeloid cells and their roles in neurodegeneration. *Nature Neurosci* 2011; **14:** 1227–1235.
7. Ransohoff RM, Cardona AE. The myeloid cells of the central nervous system parenchyma. *Nature* 2010; **468:** 253–262.
8. Saijo K, Glass CK. Microglial cell origin and phenotypes in health and disease. *Nature Rev Immunol* 2011; **11:** 775–787.
9. Graeber MB. Changing face of microglia. *Science* 2010; **330:** 783–788.
10. Rivest S. Regulation of innate immune responses in the brain. *Nature Rev Immunol* 2009; **9:** 429–439.
11. Ransohoff RM, Perry VH. Microglial physiology: unique stimuli, specialized responses. *Annu Rev Immunol* 2009; **27:** 119–145.
12. Hanisch UK, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neurosci* 2007; **10:** 1387–1394.
13. Vargas ME, Barres BA. Why is Wallerian degeneration in the CNS so slow? *Annu Rev Neurosci* 2007; **30:** 153–179.
14. Ginhoux F, Greter M, Leboeuf M, *et al*. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* 2010; **330:** 841–845.
15. Mallat M, Chamak B. Brain macrophages: neurotoxic or neurotrophic effector cells? *J Leukoc Biol* 1994; **56:** 416–422.
16. Rapalino O, Lazarov-Spiegler O, Agranov E, *et al*. Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. *Nature Med* 1998; **4:** 814–821.
17. Schwartz M, Yoles E. Immune-based therapy for spinal cord repair: autologous macrophages and beyond. *J Neurotrauma* 2006; **23:** 360–370.
18. Simard AR, Soulet D, Gowing G, *et al*. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. *Neuron* 2006; **49:** 489–502.
19. Shechter R, London A, Varol C, *et al*. Infiltrating blood-derived macrophages are vital cells playing an anti-inflammatory role in recovery from spinal cord injury in mice. *PLoS Med* 2009; **6:** e1000113.
20. Derecki NC, Cronk JC, Lu Z, *et al*. Wild-type microglia arrest pathology in a mouse model of Rett syndrome. *Nature* 2012; **484:** 105–109.
21. Schwartz M, Shechter R. Systemic inflammatory cells fight off neurodegenerative disease. *Nature Rev Neurol* 2010; **6:** 405–410.
22. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. *Nature Rev Immunol* 2005; **5:** 953–964.
23. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. *Immunity* 2010; **32:** 593–604.
24. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. *Nature Rev Immunol* 2008; **8:** 958–969.
25. Pollard JW. Trophic macrophages in development and disease. *Nature Rev Immunol* 2009; **9:** 259–270.
26. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nature Immunol* 2010; **11:** 889–896.
27. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell* 2010; **141:** 39–51.
28. Popovich PG, Longbrake EE. Can the immune system be harnessed to repair the CNS? *Nature Rev Neurosci* 2008; **9:** 481–493.
29. Young W. Methylprednisolone and spinal cord injury. *J Neurosurg* 2002; **96:** 141–142.
30. Bracken MB, Shepard MJ, Holford TR, *et al*. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. *J Neurosurg* 1998; **89:** 699–706.
31. Editorial. Steroids after spinal cord injury. *Lancet* 1990; **336:** 279–280.
32. Letellier E, Kumar S, Sancho-Martinez I, *et al*. CD95-ligand on peripheral myeloid cells activates Syk kinase to trigger their recruitment to the inflammatory site. *Immunity* 2010; **32:** 240–252.

33. Wells JE, Hurlbert RJ, Fehlings MG, *et al*. Neuroprotection by minocycline facilitates significant recovery from spinal cord injury in mice. *Brain* 2003; **126:** 1628–1637.
34. Sanchez Mejia RO, Ona VO, Li M, *et al*. Minocycline reduces traumatic brain injury-mediated caspase-1 activation, tissue damage, and neurological dysfunction. *Neurosurgery* 2001; **48:** 1393–1399; discussion 1399–1401.
35. Arvin KL, Han BH, Du Y, *et al*. Minocycline markedly protects the neonatal brain against hypoxic-ischemic injury. *Ann Neurol* 2002; **52:** 54–61.
36. Popovich PG, Guan Z, Wei P, *et al*. Depletion of hematogenous macrophages promotes partial hindlimb recovery and neuroanatomical repair after experimental spinal cord injury. *Exp Neurol* 1999; **158:** 351–365.
37. Knoller N, Auerbach G, Fulga V, *et al*. Clinical experience using incubated autologous macrophages as a treatment for complete spinal cord injury: phase I study results. *J Neurosurg Spine* 2005; **3:** 173–181.
38. Lammertse DP, Jones LA, Charlifue SB, *et al*. Autologous incubated macrophage therapy in acute, complete spinal cord injury: results of the phase 2 randomized controlled multicenter trial. *Spinal Cord* 2012; **50:** 661–671.
39. Yoon SH, Shim YS, Park YH, *et al*. Complete spinal cord injury treatment using autologous bone marrow cell transplantation and bone marrow stimulation with granulocyte macrophage-colony stimulating factor: phase I/II clinical trial. *Stem Cells* 2007; **25:** 2066–2073.
40. Kumar AA, Kumar SR, Narayanan R, *et al*. Autologous bone marrow derived mononuclear cell therapy for spinal cord injury: a phase I/II clinical safety and primary efficacy data. *Exp Clin Transplant* 2009; **7:** 241–248.
41. Yin Y, Henzl MT, Lorber B, *et al*. Oncomodulin is a macrophage-derived signal for axon regeneration in retinal ganglion cells. *Nature Neurosci* 2006; **9:** 843–852.
42. London A, Itskovich E, Benhar I, *et al*. Neuroprotection and progenitor cell renewal in the injured adult murine retina requires healing monocyte-derived macrophages. *J Exp Med* 2011; **208:** 23–39.
43. Davalos D, Grutzendler J, Yang G, *et al*. ATP mediates rapid microglial response to local brain injury *in vivo*. *Nature Neurosci* 2005; **8:** 752–758.
44. Koizumi S, Shigemoto-Mogami Y, Nasu-Tada K, *et al*. UDP acting at P2Y6 receptors is a mediator of microglial phagocytosis. *Nature* 2007; **446:** 1091–1095.
45. Coull JA, Beggs S, Boudreau D, *et al*. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature* 2005; **438:** 1017–1021.
46. Rolls A, Shechter R, London A, *et al*. Two faces of chondroitin sulfate proteoglycan in spinal cord repair: a role in microglia/macrophage activation. *PLoS Med* 2008; **5:** e171.
47. Popovich PG, Hickey WF. Bone marrow chimeric rats reveal the unique distribution of resident and recruited macrophages in the contused rat spinal cord. *J Neuropathol Exp Neurol* 2001; **60:** 676–685.
48. Fry EJ, Ho C, David S. A role for Nogo receptor in macrophage clearance from injured peripheral nerve. *Neuron* 2007; **53:** 649–662.
49. Zhu Z, Ni B, Yin G, *et al*. NgR expression in macrophages promotes nerve regeneration after spinal cord injury in rats. *Arch Orthop Trauma Surg* 2010; **130:** 945–951.
50. Shechter R, Raposo C, London A, *et al*. The glial scar–monocyte interplay: a pivotal resolution phase in spinal cord repair. *PLoS One* 2011; **6:** e27969.
51. Donnelly DJ, Longbrake EE, Shawler TM, *et al*. Deficient CX3CR1 signaling promotes recovery after mouse spinal cord injury by limiting the recruitment and activation of Ly6Clo/iNOS+ macrophages. *J Neurosci* 2011; **31:** 9910–9922.
52. Saederup N, Cardona AE, Croft K, *et al*. Selective chemokine receptor usage by central nervous system myeloid cells in CCR2-red fluorescent protein knock-in mice. *PLoS One* 2010; **5:** e13693.
53. Cardona AE, Pioro EP, Sasse ME, *et al*. Control of microglial neurotoxicity by the fractalkine receptor. *Nature Neurosci* 2006; **9:** 917–924.
54. Kigerl KA, Gensel JC, Ankeny DP, *et al*. Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. *J Neurosci* 2009; **29:** 13435–13444.
55. Zhang Z, Zhang ZY, Wu Y, *et al*. Lesional accumulation of CD163(+) macrophages/microglia in rat traumatic brain injury. *Brain Res* 2012; **1461:** 102–110.
56. Ziv Y, Avidan H, Pluchino S, *et al*. Synergy between immune cells and adult neural stem/progenitor cells promotes functional recovery from spinal cord injury. *Proc Natl Acad Sci U S A* 2006; **103:** 13174–13179.
57. Dougherty KD, Dreyfus CF, Black IB. Brain-derived neurotrophic factor in astrocytes, oligodendrocytes, and microglia/macrophages after spinal cord injury. *Neurobiol Dis* 2000; **7:** 574–585.
58. Barrette B, Hebert MA, Filali M, *et al*. Requirement of myeloid cells for axon regeneration. *J Neurosci* 2008; **28:** 9363–9376.
59. Glod J, Kobiler D, Noel M, *et al*. Monocytes form a vascular barrier and participate in vessel repair after brain injury. *Blood* 2006; **107:** 940–946.
60. Schonberg DL, Goldstein EZ, Sahinkaya FR, *et al*. Ferritin stimulates oligodendrocyte genesis in the adult spinal cord and can be transferred from macrophages to NG2 cells *in vivo*. *J Neurosci* 2012; **32:** 5374–5384.
61. Butovsky O, Koronyo-Hamaoui M, Kunis G, *et al*. Glatiramer acetate fights against Alzheimer's disease by inducing dendritic-like microglia expressing insulin-like growth factor 1. *Proc Natl Acad Sci U S A* 2006; **103:** 11784–11789.
62. Beers DR, Henkel JS, Xiao Q, *et al*. Wild-type microglia extend survival in PU.1 knockout mice with familial amyotrophic lateral sclerosis. *Proc Natl Acad Sci U S A* 2006; **103:** 16021–16026.
63. Appel SH, Beers DR, Henkel JS. T cell-microglial dialogue in Parkinson's disease and amyotrophic lateral sclerosis: are we listening? *Trends Immunol* 2010; **31:** 7–17.
64. Beduneau A, Ma Z, Grotepas CB, *et al*. Facilitated monocyte–macrophage uptake and tissue distribution of superparmagnetic iron-oxide nanoparticles. *PLoS One* 2009; **4:** e4343.
65. Persidsky Y, Zheng J, Miller D, *et al*. Mononuclear phagocytes mediate blood–brain barrier compromise and neuronal injury during HIV-1-associated dementia. *J Leukoc Biol* 2000; **68:** 413–422.
66. Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? *Nature Med* 2006; **12:** 1005–1015.
67. Wisniewski HM, Wegiel J, Wang KC, *et al*. Ultrastructural studies of the cells forming amyloid fibers in classical plaques. *Can J Neurol Sci* 1989; **16:** 535–542.
68. Akiyama H, Arai T, Kondo H, *et al*. Cell mediators of inflammation in the Alzheimer disease brain. *Alzheimer Dis Assoc Disord* 2000; **14** (Suppl 1): S47S53.
69. Frackowiak J, Potempska A, LeVine H, *et al*. Extracellular deposits of A beta produced in cultures of Alzheimer disease brain vascular smooth muscle cells. *J Neuropathol Exp Neurol* 2005; **64:** 82–90.
70. Fuhrmann M, Bittner T, Jung CK, *et al*. Microglial Cx3cr1 knockout prevents neuron loss in a mouse model of Alzheimer's disease. *Nature Neurosci* 2010; **13:** 411–413.

71. Grathwohl SA, Kalin RE, Bolmont T, *et al*. Formation and maintenance of Alzheimer's disease beta-amyloid plaques in the absence of microglia. *Nature Neurosci* 2009; **12:** 1361–1363.
72. Meyer-Luehmann M, Spires-Jones TL, Prada C, *et al*. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. *Nature* 2008; **451:** 720–724.
73. Lebson L, Nash K, Kamath S, *et al*. Trafficking CD11b-positive blood cells deliver therapeutic genes to the brain of amyloid-depositing transgenic mice. *J Neurosci* 2010; **30:** 9651–9658.
74. Majumdar A, Chung H, Dolios G, *et al*. Degradation of fibrillar forms of Alzheimer's amyloid beta-peptide by macrophages. *Neurobiol Aging* 2008; **29:** 707–715.
75. El Khoury J, Toft M, Hickman SE, *et al*. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. *Nature Med* 2007; **13:** 432–438.
76. Naert G, Rivest S. CC chemokine receptor 2 deficiency aggravates cognitive impairments and amyloid pathology in a transgenic mouse model of Alzheimer's disease. *J Neurosci* 2011; **31:** 6208–6220.
77. Janelsins MC, Mastrangelo MA, Oddo S, *et al*. Early correlation of microglial activation with enhanced tumor necrosis factor-alpha and monocyte chemoattractant protein-1 expression specifically within the entorhinal cortex of triple transgenic Alzheimer's disease mice. *J Neuroinflammation* 2005; **2:** 23.
78. Shaftel SS, Carlson TJ, Olschowka JA, *et al*. Chronic interleukin-1beta expression in mouse brain leads to leukocyte infiltration and neutrophil-independent blood brain barrier permeability without overt neurodegeneration. *J Neurosci* 2007; **27:** 9301–9309.
79. Shaftel SS, Kyrkanides S, Olschowka JA, *et al*. Sustained hippocampal IL-1 beta overexpression mediates chronic neuroinflammation and ameliorates Alzheimer plaque pathology. *J Clin Invest* 2007; **117:** 1595–1604.
80. Mildner A, Schlevogt B, Kierdorf K, *et al*. Distinct and non-redundant roles of microglia and myeloid subsets in mouse models of Alzheimer's disease. *J Neurosci* 2011; **31:** 11159–11171.
81. Hawkes CA, McLaurin J. Selective targeting of perivascular macrophages for clearance of beta-amyloid in cerebral amyloid angiopathy. *Proc Natl Acad Sci U S A* 2009; **106:** 1261–1266.
82. Mucke L. Neuroscience: Alzheimer's disease. *Nature* 2009; **461:** 895–897.
83. Butovsky O, Landa G, Kunis G, *et al*. Induction and blockage of oligodendrogenesis by differently activated microglia in an animal model of multiple sclerosis. *J Clin Invest* 2006; **116:** 905–915.
84. Butovsky O, Kunis G, Koronyo-Hamaoui M, *et al*. Selective ablation of bone marrow-derived dendritic cells increases amyloid plaques in a mouse Alzheimer's disease model. *Eur J Neurosci* 2007; **26:** 413–416.
85. Habisch HJ, Schwalenstocker B, Danzeisen R, *et al*. Limited effects of glatiramer acetate in the high-copy number hSOD1-G93A mouse model of ALS. *Exp Neurol* 2007; **206:** 288–295.
86. Meininger V, Drory VE, Leigh PN, *et al*. Glatiramer acetate has no impact on disease progression in ALS at 40 mg/day: a double-blind, randomized, multicentre, placebo-controlled trial. *Amyotroph Lateral Scler* 2009; **10:** 378–383.
87. Haenggeli C, Julien JP, Mosley RL, *et al*. Therapeutic immunization with a glatiramer acetate derivative does not alter survival in G93A and G37R SOD1 mouse models of familial ALS. *Neurobiol Dis* 2007; **26:** 146–152.
88. Koronyo-Hamaoui M, Ko MK, Koronyo Y, *et al*. Attenuation of AD-like neuropathology by harnessing peripheral immune cells: local elevation of IL-10 and MMP-9. *J Neurochem* 2009; **111:** 1409–1424.
89. Town T, Laouar Y, Pittenger C, *et al*. Blocking TGF-beta–Smad2/3 innate immune signaling mitigates Alzheimer-like pathology. *Nature Med* 2008; **14:** 681–687.
90. Chakrabarty P, Jansen-West K, Beccard A, *et al*. Massive gliosis induced by interleukin-6 suppresses Abeta deposition *in vivo*: evidence against inflammation as a driving force for amyloid deposition. *FASEB J* 2010; **24:** 548–559.
91. Boissonneault V, Rivest S. [The hematopoietic cytokine M-CSF as a cure for Alzheimer's disease]. *Med Sci (Paris)* 2009; **25:** 666–668.
92. Shin JW, Lee JK, Lee JE, *et al*. Combined effects of hematopoietic progenitor cell mobilization from bone marrow by granulocyte colony stimulating factor and AMD3100 and chemotaxis into the brain using stromal cell-derived factor-1alpha in an Alzheimer's disease mouse model. *Stem Cells* 2011; **29:** 1075–1089.
93. Bruck W, Sommermeier N, Bergmann M, *et al*. Macrophages in multiple sclerosis. *Immunobiology* 1996; **195:** 588–600.
94. Tran EH, Hoekstra K, van Rooijen N, *et al*. Immune invasion of the central nervous system parenchyma and experimental allergic encephalomyelitis, but not leukocyte extravasation from blood, are prevented in macrophage-depleted mice. *J Immunol* 1998; **161:** 3767–3775.
95. Bartholomaus I, Kawakami N, Odoardi F, *et al*. Effector T cell interactions with meningeal vascular structures in nascent autoimmune CNS lesions. *Nature* 2009; **462:** 94–98.
96. Wu C, Rauch U, Korpos E, *et al*. Sialoadhesin-positive macrophages bind regulatory T cells, negatively controlling their expansion and autoimmune disease progression. *J Immunol* 2009; **182:** 6508–6516.
97. Li H, Cuzner ML, Newcombe J. Microglia-derived macrophages in early multiple sclerosis plaques. *Neuropathol Appl Neurobiol* 1996; **22:** 207–215.
98. Ajami B, Bennett JL, Krieger C, *et al*. Infiltrating monocytes trigger EAE progression, but do not contribute to the resident microglia pool. *Nature Neurosci* 2011; **14:** 1142–1149.
99. Huang DR, Wang J, Kivisakk P, *et al*. Absence of monocyte chemoattractant protein 1 in mice leads to decreased local macrophage recruitment and antigen-specific T helper cell type 1 immune response in experimental autoimmune encephalomyelitis. *J Exp Med* 2001; **193:** 713–726.
100. Mildner A, Mack M, Schmidt H, *et al*. CCR2+Ly-6Chi monocytes are crucial for the effector phase of autoimmunity in the central nervous system. *Brain* 2009; **132:** 2487–2500.
101. King IL, Dickendesher TL, Segal BM. Circulating Ly-6C+ myeloid precursors migrate to the CNS and play a pathogenic role during autoimmune demyelinating disease. *Blood* 2009; **113:** 3190–3197.
102. Zhang Z, Zhang ZY, Schittenhelm J, *et al*. Parenchymal accumulation of CD163+ macrophages/microglia in multiple sclerosis brains. *J Neuroimmunol* 2011; **237:** 73–79.
103. Boven LA, Van Meurs M, Van Zwam M, *et al*. Myelin-laden macrophages are anti-inflammatory, consistent with foam cells in multiple sclerosis. *Brain* 2006; **129:** 517–526.
104. Mikita J, Dubourdieu-Cassagno N, Deloire MS, *et al*. Altered M1/M2 activation patterns of monocytes in severe relapsing experimental rat model of multiple sclerosis. Amelioration of clinical status by M2 activated monocyte administration. *Mult Scler* 2011; **17:** 2–15.
105. Denney L, Kok WL, Cole SL, *et al*. Activation of invariant NKT cells in early phase of experimental autoimmune encephalomyelitis results in differentiation of Ly6C^{hi} inflammatory monocyte to M2 macrophages and improved outcome. *J Immunol* 2012; **189:** 551–557.
106. Bogie JF, Stinissen P, Hellings N, *et al*. Myelin-phagocytosing macrophages modulate autoreactive T cell proliferation. *J Neuroinflammation* 2011; **8:** 85.

107. Zhu B, Bando Y, Xiao S, *et al*. CD11b+Ly-6C(hi) suppressive monocytes in experimental autoimmune encephalomyelitis. *J Immunol* 2007; **179:** 5228–5237.
108. Youn JI, Nagaraj S, Collazo M, *et al*. Subsets of myeloid-derived suppressor cells in tumor-bearing mice. *J Immunol* 2008; **181:** 5791–5802.
109. Zhu B, Kennedy JK, Wang Y, *et al*. Plasticity of Ly-6C(hi) myeloid cells in T cell regulation. *J Immunol* 2011; **187:** 2418–2432.
110. Li WW, Setzu A, Zhao C, *et al*. Minocycline-mediated inhibition of microglia activation impairs oligodendrocyte progenitor cell responses and remyelination in a non-immune model of demyelination. *J Neuroimmunol* 2005; **158:** 58–66.
111. Villeda SA, Luo J, Mosher KI, *et al*. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* 2011; **477:** 90–94.
112. Ruckh JM, Zhao JW, Shadrach JL, *et al*. Rejuvenation of regeneration in the aging central nervous system. *Cell Stem Cell* 2012; **10:** 96–103.
113. Weber MS, Prod'homme T, Youssef S, *et al*. Type II monocytes modulate T cell-mediated central nervous system autoimmune disease. *Nature Med* 2007; **13:** 935–943.
114. Burger D, Molnarfi N, Weber MS, *et al*. Glatiramer acetate increases IL-1 receptor antagonist but decreases T cell-induced IL-1beta in human monocytes and multiple sclerosis. *Proc Natl Acad Sci U S A* 2009; **106:** 4355–4359.
115. Vaknin I, Kunis G, Miller O, *et al*. Excess circulating alternatively activated myeloid (M2) cells accelerate ALS progression while inhibiting experimental autoimmune encephalomyelitis. *PLoS One* 2011; **6:** e26921.
116. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell* 2008; **132:** 645–660.
117. Kokaia Z, Martino G, Schwartz M, *et al*. Cross-talk between neural stem cells and immune cells: the key to better brain repair? *Nature Neurosci* 2012; **15:** 1078–1087.
118. Martino G. How the brain repairs itself: new therapeutic strategies in inflammatory and degenerative CNS disorders. *Lancet Neurol* 2004; **3:** 372–378.
119. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 2003; **302:** 1760–1765.
120. Jakubs K, Bonde S, Iosif RE, *et al*. Inflammation regulates functional integration of neurons born in adult brain. *J Neurosci* 2008; **28:** 12477–12488.
121. Ekdahl CT, Claasen JH, Bonde S, *et al*. Inflammation is detrimental for neurogenesis in adult brain. *Proc Natl Acad Sci U S A* 2003; **100:** 13632–13637.
122. Walton NM, Sutter BM, Laywell ED, *et al*. Microglia instruct subventricular zone neurogenesis. *Glia* 2006; **54:** 815–825.
123. Choi SH, Veeraraghavalu K, Lazarov O, *et al*. Non-cell-autonomous effects of presenilin 1 variants on enrichment-mediated hippocampal progenitor cell proliferation and differentiation. *Neuron* 2008; **59:** 568–580.
124. Butovsky O, Ziv Y, Schwartz A, *et al*. Microglia activated by IL-4 or IFN-gamma differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. *Mol Cell Neurosci* 2006; **31:** 149–160.
125. Cacci E, Ajmone-Cat MA, Anelli T, *et al*. *In vitro* neuronal and glial differentiation from embryonic or adult neural precursor cells are differently affected by chronic or acute activation of microglia. *Glia* 2008; **56:** 412–425.
126. Ziv Y, Ron N, Butovsky O, *et al*. Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. *Nature Neurosci* 2006; **9:** 268–275.
127. Vukovic J, Colditz MJ, Blackmore DG, *et al*. Microglia modulate hippocampal neural precursor activity in response to exercise and aging. *J Neurosci* 2012; **32:** 6435–6443.
128. Sierra A, Encinas JM, Deudero JJ, *et al*. Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell* 2010; **7:** 483–495.
129. Borders AS, Hersh MA, Getchell ML, *et al*. Macrophage-mediated neuroprotection and neurogenesis in the olfactory epithelium. *Physiol Genomics* 2007; **31:** 531–543.
130. Borders AS, Getchell ML, Etscheidt JT, *et al*. Macrophage depletion in the murine olfactory epithelium leads to increased neuronal death and decreased neurogenesis. *J Comp Neurol* 2007; **501:** 206–218.
131. Ruitenberg MJ, Vukovic J, Blomster L, *et al*. CX3CL1/fractalkine regulates branching and migration of monocyte-derived cells in the mouse olfactory epithelium. *J Neuroimmunol* 2008; **205:** 80–85.
132. Derecki NC, Cardani AN, Yang CH, *et al*. Regulation of learning and memory by meningeal immunity: a key role for IL-4. *J Exp Med* 2010; **207:** 1067–1080.
133. Tepavcevic V, Lazarini F, Alfaro-Cervello C, *et al*. Inflammation-induced subventricular zone dysfunction leads to olfactory deficits in a targeted mouse model of multiple sclerosis. *J Clin Invest* 2011; **121:** 4722–4734.
134. Muzio L, Cavasinni F, Marinaro C, *et al*. Cxcl10 enhances blood cells migration in the sub-ventricular zone of mice affected by experimental autoimmune encephalomyelitis. *Mol Cell Neurosci* 2010; **43:** 268–280.
135. Peng H, Sun L, Jia B, *et al*. HIV-1-infected and immune-activated macrophages induce astrocytic differentiation of human cortical neural progenitor cells via the STAT3 pathway. *PLoS One* 2011; **6:** e19439.
136. Imitola J, Raddassi K, Park KI, *et al*. Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1alpha/CXC chemokine receptor 4 pathway. *Proc Natl Acad Sci U S A* 2004; **101:** 18117–18122.
137. Yan YP, Lang BT, Vemuganti R, *et al*. Persistent migration of neuroblasts from the subventricular zone to the injured striatum mediated by osteopontin following intracerebral hemorrhage. *J Neurochem* 2009; **109:** 1624–1635.
138. Yang J, Jiang Z, Fitzgerald DC, *et al*. Adult neural stem cells expressing IL-10 confer potent immunomodulation and remyelination in experimental autoimmune encephalitis. *J Clin Invest* 2009; **119:** 3678–3691.
139. Martino G, Pluchino S. The therapeutic potential of neural stem cells. *Nature Rev Neurosci* 2006; **7:** 395–406.
140. Cusimano M, Biziato D, Brambilla E, *et al*. Transplanted neural stem/precursor cells instruct phagocytes and reduce secondary tissue damage in the injured spinal cord. *Brain* 2012; **135:** 447–460.
141. Rolls A, Shechter R, London A, *et al*. Toll-like receptors modulate adult hippocampal neurogenesis. *Nature Cell Biol* 2007; **9:** 1081–1088.
142. Shechter R, Ronen A, Rolls A, *et al*. Toll-like receptor 4 restricts retinal progenitor cell proliferation. *J Cell Biol* 2008; **183:** 393–400.
143. Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell* 2006; **124:** 263–266.
144. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100:** 57–70.