


# Neuroimmune crosstalk and evolving pharmacotherapies in neurodegenerative diseases

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## Summary

Neurodegeneration is characterized by gradual onset and limited availability of specific biomarkers. Apart from various aetiologies such as infection, trauma, genetic mutation, the interaction between the immune system and CNS is widely associated with neuronal damage in neurodegenerative diseases. The immune system plays a distinct role in disease progression and cellular homeostasis. It induces cellular and humoral responses, and enables tissue repair, cellular healing and clearance of cellular detritus. Aberrant and chronic activation of the immune system can damage healthy neurons. The pro-inflammatory mediators secreted by chief innate immune components, the complement system, microglia and inflammasome can augment cytotoxicity. Furthermore, these inflammatory mediators accelerate microglial activation resulting in progressive neuronal loss. Various animal studies have been carried out to unravel the complex pathology and ascertain biomarkers for these harmful diseases, but have had limited success. The present review will provide a thorough understanding of microglial activation, complement system and inflammasome generation, which lead the healthy brain towards neurodegeneration. In addition to this, possible targets of immune components to confer a strategic treatment regime for the alleviation of neuronal damage are also summarized.

**Keywords:** complement system; immune system; inflammasome; microglia; neurodegenerative disease.

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; HD, huntington disease; MS, multiple sclerosis; SOD, superoxide dismutase; mTT, mutant huntingtin; CP, classical pathway; LP, lectin pathway; AP, alternative pathway; CNS, central nervous system; Fc, fragment crystallizable region; MBL, mannan-binding lectin; MASPs, MBL-associated serine proteases; MAC, membrane attack complex; TNF- $\alpha$ , tumour necrosis factor; IL-1 $\beta$ , interleukin-1 $\beta$ ; ROS, reactive oxygen species; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; TLR, Toll-like receptor; IRAK, IL-1R-associated kinase; NLR, NOD-like receptor; ASC, apoptosis-associated spec-like protein; PYD, N-terminal pyrin domain; CARD, caspase recruitment domain; NOD, nucleotide-binding oligomerization domain; LRR, leucine-rich repeats; GSDMD, gasdermin-D; DAMPs, damage-associated molecular pattern; PAMPs, pathogen-associated molecular pattern; PKR, protein kinase R; AIM2, absent in melanoma 2; A $\beta$ , amyloid-beta; SNPs, single nucleotide polymorphisms; CR1, complement receptor 1; CLU, clusterin; IHC, immunohistochemistry; TCC, terminal C5b-9 complement complex; DAP12, DNAX-activating protein of 12 kD; TREM-2, triggering receptor expressed on myeloid cells 2; SN, substantia nigra; Nox2, NADPH oxidase; CSF, cerebrospinal fluid;  $\alpha$ -syn,  $\alpha$ -synuclein; MMP, metalloproteinase; SIGLEC, sialic acid-binding Ig-like lectin; PET, positron emission tomography; LRRK2, leucine-rich repeat kinase; EGF, epidermal growth factor; IDE, insulin-degrading enzyme; ATG7, autophagy-related protein 7; mAbs, monoclonal antibodies; BBB, blood-brain barrier; PPAR- $\gamma$ , peroxisome-proliferated receptor gamma; MAPK, mitogen-activated protein kinase; LFA-1, lymphocyte function-associated molecule-1; LCA, leucocyte common antigen; CSF, colony-stimulating factor; MAIT, mucosal-associated invariant T; TRIF, TIR-domain-containing adaptor-inducing interferon- $\beta$ ; FOXP3, forkhead box transcription factor

## INTRODUCTION

Neuroinflammation is a hallmark of the vicious cycle of neurodegeneration.<sup>1</sup> It is responsible for the development and gradual progression of neurodegenerative conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), huntington disease (HD) and multiple sclerosis (MS). It is also an obvious consequence of cerebral ischaemia.<sup>2</sup> These proteinopathies show ramification of organelles and synaptic impairment of nervous system.<sup>2</sup> An epidemiological study carried out in 2016 revealed that about 276 million people were suffering from neurological disorders worldwide, and among them, every year, the extent of fatality was about 9 million people.<sup>3,4</sup> As dementia is one of the outcomes of neurological disorders, the estimated count of a global dementia patient is around 35 million, and if compelling measures are not identified, it will rise threefold by 2050.<sup>5</sup> Neurodegenerative diseases affect both the immune system and the central nervous system.<sup>6</sup> The immune system can also be constructive as it triggers repair of the damaged tissues, neurotrophic factor production and remyelination in response to toxins, trauma and injury, thus maintaining the functional integrity of the brain. During neurodegeneration, T cells, microglia, astrocytes, oligodendrocytes, inflammasomes and the complement system can induce neuroinflammation.<sup>7,8</sup> Microglia and inflammasomes act as a host defence mechanism against infections and dysfunctional neurons.<sup>9,10</sup> However, aggregation of amyloid- $\beta$ ,  $\alpha$ -synuclein, superoxide dismutase (SOD), mutant huntingtin (mHtt), etc. can cause aberrant activation of microglia, complement system and inflammasomes, which promotes the release of inflammatory cytokines leading to neuroinflammation.<sup>11,12</sup> The interplay between these two systems is of interest, albeit the mechanism is yet to be explored.<sup>13</sup> The present review focuses on the involvement of the immune system in regulating neurodegeneration and the available therapeutic approaches. Further, the detailed mechanism of immune component activation and how they contribute towards developing the pathology has been dealt with an elaborative summary of various therapeutic approaches of targeting immune components in neurodegenerative diseases.

## COMPLEMENT SYSTEM

The complement system is an element of the body's innate immunity whose components are primarily

synthesized in the liver and then enter into systemic circulation for activation.<sup>14,15</sup> These components cannot cross the blood-brain barrier; hence, neurons and glial cells synthesize them locally.<sup>16</sup> The complement system consists of more than 30 fluid phases to destroy pathogens and foreign cells.<sup>17</sup> The three pathways of complement system activation, that is classical (CP), lectin (LP) and alternative (AP), are mainly involved in protection against microbial infections, the connection of innate and adaptive immunity, and clearance of the debris of immune products.<sup>18,19</sup>

## Complement system in CNS

The complement system helps in maintaining homeostasis in the brain by acting against infections and by removal of waste products.<sup>20</sup> The classical pathway of the complement system starts with component C1q, which binds with the fragment crystallizable region (Fc region) of antibody.<sup>21</sup> Microglia is the primary source of C1q, which stimulates C1r and cleaves C1s to activate C1.<sup>21,22</sup> Activated C1 binds with C4 and cleaves it into C4a and C4b. C4b attaches itself to the surface of the pathogen and activates C2a and C2b. C2a and C4b together form C3 convertase (C4b2a and C3bBb).<sup>23</sup> The mannan-binding lectin (MBL) pathway attaches to the carbohydrates of the pathogen and activates MBL-associated serine proteases (MASPs). MASP-2 splits C4 and C2 to form C3 convertase.<sup>24</sup> The other complement system pathway, that is the alternative pathway, is an independent antibody pathway responsible for distinguishing between self and non-self. Hydrolysis of native C3 leads to activation of C3 (H<sub>2</sub>O), which associates with factor B (serine protease, which stimulates B cell to instigate inflammatory responses) and gives rise to C3 convertase.<sup>25</sup> Properdin can directly activate and amplify AP and is also accepted as a recognition factor for AP.<sup>26</sup> C3 convertase in all three pathways then splits into C3a and C3b. C3b attaches to C3 convertase to give rise to C5 convertase, which then activates membrane attack complex (MAC), resulting in phagocytosis.<sup>27</sup> However, this activation of the complement system is highly specific.<sup>28</sup>

## ROLE OF MICROGLIA IN NEURODEGENERATION

Microglia are the resident macrophages of the CNS, which play an important role in maintaining host defence

and at times can be detrimental to neurons.<sup>29</sup> These have self-renewal properties and are responsible for eliciting immunological responses in the CNS.<sup>30</sup> As per different neurological disorders, it undergoes proliferation and configurational changes to become reactive, which is known as microgliosis.<sup>31</sup> These reactive microglia, on the one hand, stimulate the release of neurotrophic factors and guide stem cells towards injury.<sup>32</sup> On the other hand, chronic activation of microglia secretes pro-inflammatory mediators such as tumour necrosis factor (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ) and reactive oxygen species (ROS), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), hydroxyl radicals (OH<sup>-</sup>) and superoxide anions (O<sup>2-</sup>), which are detrimental for neurons.<sup>33,34,35</sup> Once microglia are activated by Toll-like receptor (TLR), they stimulate the adaptor protein MyD88, which promotes autophosphorylation of IL-1R-associated kinase (IRAK) and releases pro-inflammatory cytokines.<sup>36</sup> Furthermore, it promotes the generation of ROS, leading to neuroinflammation.<sup>37</sup> In addition to this, microgliosis also involved in the synaptic loss in diseases such as AD and PD, which correlates with the gradual progression of dementia.<sup>38</sup> It has been observed that M1 microglia releases pro-inflammatory proteins such as IL-6, TNF- $\alpha$  and IL-1 $\beta$  at 24 hours post-stroke, which cause secondary injuries a few days afterwards. Unlike this, M2 microglia is anti-inflammatory and reported to be increased and proliferated in the core region at the same time. Modulation of TLRs or IFN- $\gamma$  causes activation of pro-inflammatory M1 phenotype, whereas anti-inflammatory M2 phenotype is activated by regulatory factors such as IL-4, IL-10, IL-13 and TGF- $\beta$ <sup>39</sup> (Figure 1).

## INFLAMMASOME-MEDIATED INFLAMMATION

The inflammasome is a complex protein that is responsible for the inflammation-mediated response. The three chief components of inflammasomes are NOD-like receptors (NLRs), apoptosis-associated spec-like protein (ASC) and pro-caspase-1.<sup>40</sup> NLRs, a tripartite structure, include N-terminal pyrin domain (PYD) or caspase recruitment domain (CARD), NACHT or NOD (nucleotide-binding oligomerization domain), and C-terminal leucine-rich repeats (LRRs).<sup>40</sup> Neurodegenerative diseases activate the NOD-like receptor (NLR) pyrin domain containing 1 and 3 (NLRP1 and NLRP3) inflammasome, ASC and pro-caspase-1 via either MAPK or NF- $\kappa$ B pathway. NLRP3 contributes to inflammation and injury in CNS and in neurodegenerative diseases such as AD, PD, MS and ALS, whereas both NLRP1 and NLRP3 play a role in the pathogenesis of ischaemic stroke.<sup>41</sup> Upon activation, the interaction of NLRP3 protein with ASC followed by the interaction of ASC with the CARD domain via PYD recruits pro-caspase-1 and forms the NLRP3-ASC-pro-caspase-1 complex (NLRP3 inflammasome).<sup>42</sup> It leads to the conversion of inactive pro-inflammatory cytokines

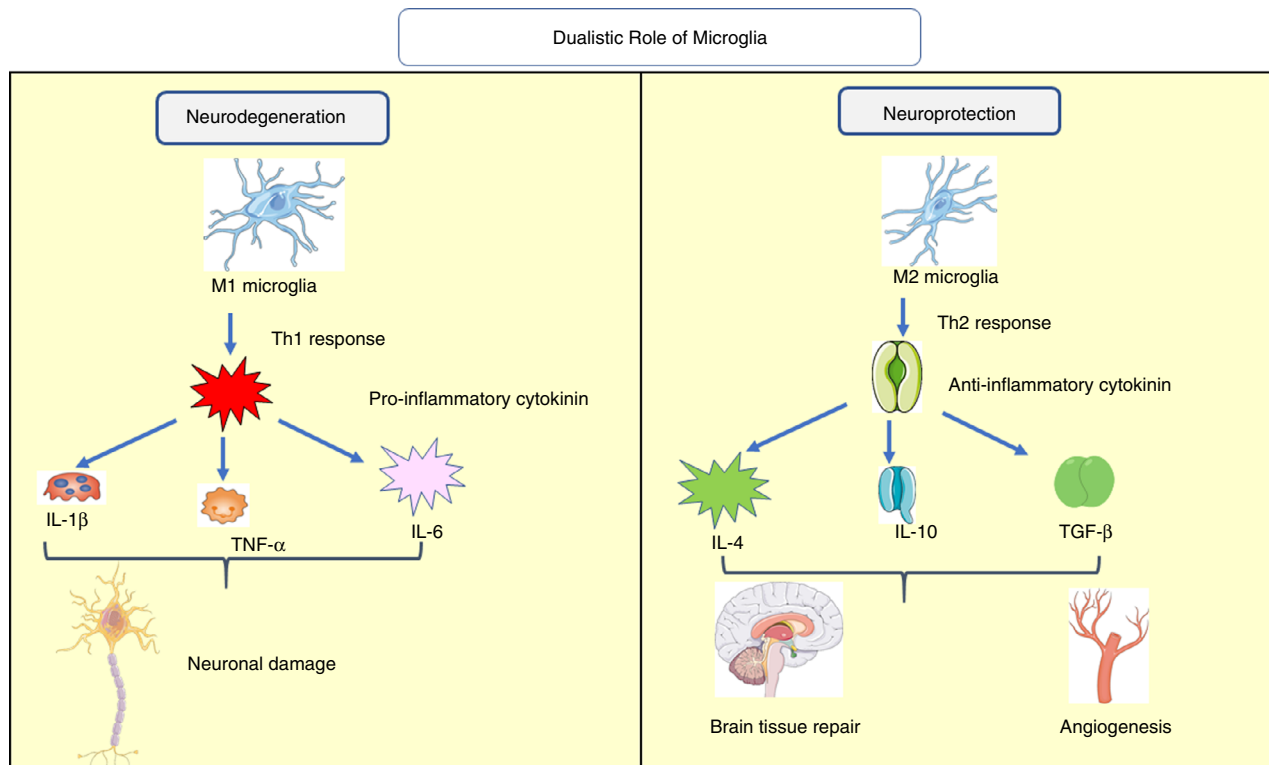
(pro-IL-1 $\beta$ , pro-IL-18) into active inflammatory cytokines (IL-1 $\beta$ , IL-18) and activation of caspase-1 that ultimately cause neuroinflammation and pyroptosis.<sup>43</sup> Pyroptosis is mediated by producing gasdermin-D (GSDMD), which is responsible for producing pores on the plasma membrane.<sup>44</sup> Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) such as energy depletion, ion flux (Ca<sup>2+</sup> influx, Na<sup>+</sup> influx, K<sup>+</sup> efflux, and Cl<sup>-</sup> efflux), cathepsin release, oxidized mitochondrial DNA release, PKR (protein kinase R) activation and ROS could activate inflammasome signalling<sup>45,46</sup> (Figure 2).

The immune response is a harmonized interplay of potential threat recognition by the innate immune system initially and response by the adaptive immune system afterwards.<sup>13,47</sup> Studies support that pattern recognition receptor (PRR) not only is involved in recognition of DAMPs and PAMPs, but it also informs and influences the adaptive immune response via TLRs.<sup>48</sup> PRRs include (nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin containing domain) NLRP-1, NLRP-3 NLRC-4 and absent in melanoma 2(AIM2).<sup>49,50</sup> Microglia express these PRRs whose increased expression causes inflammasome signalling activation.<sup>51</sup>

## DESTRUCTION OF IMMUNE MACHINERY IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

### Complement system: Associated pathways of activation

Alzheimer's disease (AD) is a neurodegenerative tauopathy that manifests as dementia and affects more than 6% of people older than 65 years.<sup>18,52</sup> AD is characterized by the formation of neurofibrillary tangles consisting of hyperphosphorylated tau and deposition of insoluble amyloid-beta (A $\beta$ ) plaque. In genomic studies, it has been identified that single nucleotide polymorphisms (SNPs) of genes encoding complement protein complement receptor 1 (CR1) and clusterin (*CLU*) are associated with the risk of late-onset AD.<sup>53,54</sup> CR1, a transmembrane protein that increases the phagocytosis of C3b, C4b and C1q, opsonized particles.<sup>55</sup> Interaction between *CLU* and A $\beta$  prevents proteolytic degradation of oligomers leading to plaque formation.<sup>56</sup> The co-localization of the classical pathway proteins (C1q, C3 and C4) with neurofibrillary tangles, amyloid fibrils and A $\beta$  deposits, particularly in the hippocampus, temporal cortex and amygdala, has been observed in Immunohistochemistry (IHC) study of post-mortem AD brains.<sup>55</sup> The terminal pathway marker of the complement system, terminal C5b-9 complement complex (TCC), is predominantly present in the cortex of the AD brain, which is associated with the formation of neurofibrillary tangles and aggregated A $\beta$ .<sup>18,57</sup> Dystrophic



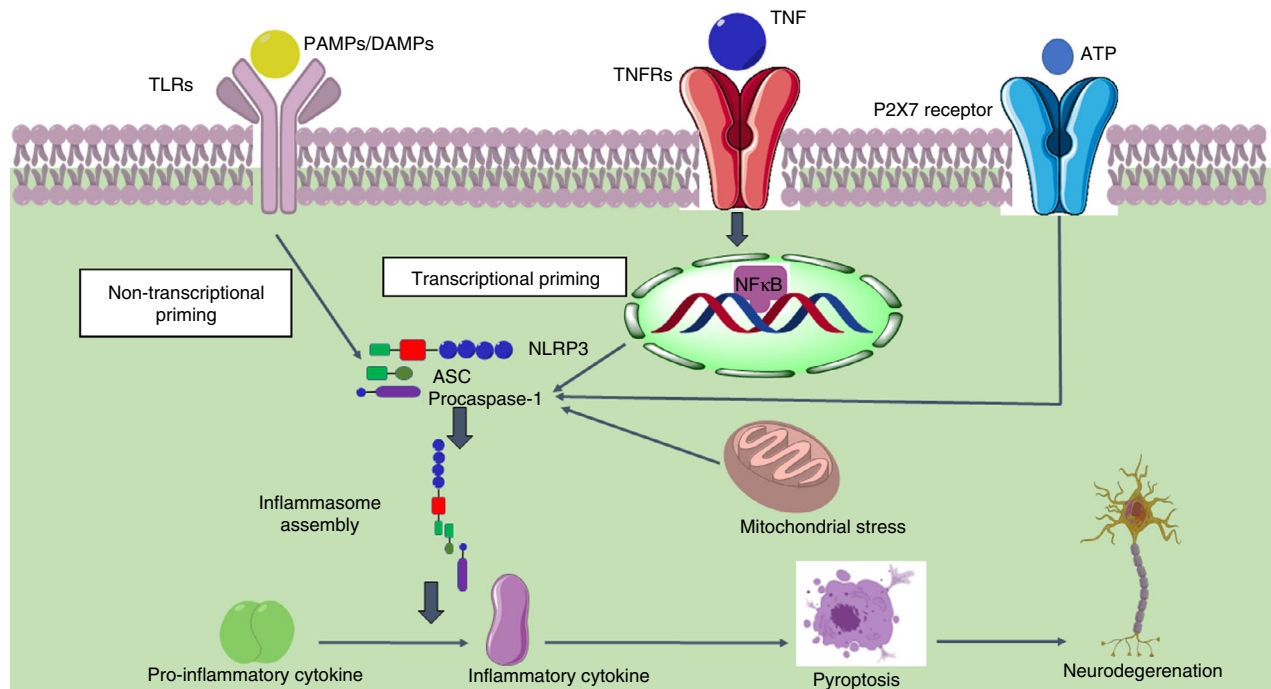
**FIGURE 1.** Dualistic role of microglia on the nervous system. M1 microglia produces pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$  and IL-6 through Th-1 response and leads to neurodegeneration. M2 microglia produces anti-inflammatory cytokines such as IL-4, IL-10 and TGF- $\beta$  via Th2 response. These anti-inflammatory cytokines help in brain tissue repair, angiogenesis and, thus, providing neuroprotection (IL – interleukin, TNF- $\alpha$  – tumour necrotic factor-alpha, TGF- $\beta$  – transforming growth factor-beta, Th1 – T helper cell 1) (Adapted from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence (<http://smart.servier.com/>))

neurites in A $\beta$  plaque and neurofibrillary tangles in neurons of the frontal cortex and hippocampus of AD brain express C5aR1 and C5L2 receptors predominantly. C5a fragment, generated by complement activation, is a chemotactic factor for glia.<sup>58</sup> C5a-CD88 (C5aR1) interaction has a detrimental effect in AD either by direct impact on a neuron or by indirectly activating the microglia, whereas the anti-inflammatory effect of activated C5L2 receptor is reported.<sup>58</sup>

Accumulation of toxic A $\beta$  leads to activation of the complement system by secretion of C1q from neurons and the production of C3 by astrocytes.<sup>14</sup> C1q binds to A $\beta$  plaque and C1q receptor (C1qR) on microglia, thus leads to synaptic pruning and initiates phagocytosis.<sup>59</sup> CD14, CD36, CD47,  $\alpha$ 6 $\beta$ 1 integrins, TLRs and RAGE receptors of microglia get activated by soluble A $\beta$  oligomer and A $\beta$  fibrils, which in turn instigate phagocytosis.<sup>59</sup> Binding of A $\beta$  oligomers to astrocytic TLR4 or CD36 receptors leads to the production of inflammatory cytokines or chemokines by activating NF- $\kappa$ B signalling.<sup>60</sup> Furthermore, this activated signalling cascade along with microglial post-phagocytic processes (lysosomal injury,

acidification of cytosol, etc.) contributes to the activation of NLRP-3 inflammasome.<sup>61</sup> C3 is further cleaved into C3a and C3b that ultimately produce MAC. C3b along with C3a contributes to the activation of DNAX-activating protein of 12 kD (DAP12), which stabilizes the triggering receptor expressed on myeloid cells 2 (TREM-2) to modulate microglial function leading to neuroinflammation.<sup>61</sup>

In the case of Parkinson's disease, the presence of Lewy bodies and melanized neurons in the substantia nigra (SN) is responsible for the activation of the classical complement system.<sup>62</sup> These depositions show positive staining in IHC for early complement activation C3b, C4d and C7 and late activation of C9.<sup>63</sup> Later on, positive staining in IHC of microglia-derived C1q and C5a levels was also found in SN.<sup>64</sup> Earlier studies have been reported that C1q also helps in removal of aggregated neuromelanin in the SN.<sup>65</sup> Lewy bodies and oligodendrocytes show MAC activation, which leads to phagocytosis in the SN in PD.<sup>66</sup> Microglial NADPH oxidase (Nox2) is stimulated by CR3, which suggests the role of the complement system in neuroinflammation-mediated loss of



**FIGURE 2.** Inflammasome-mediated neurodegeneration. PAMPs or DAMPs activate TLR and mediate non-transcriptional priming of the inflammasome. TNF activates the TNF receptor and increases the expression of NLRP3, ASC and pro-caspase-1 via NF- $\kappa$ B signalling. It also leads to the priming of inflammasome, which ultimately contributes to inflammasome assembly. It will further activate pro-caspase-1 into caspase-1, which converts the pro-inflammatory cytokines (pro-IL-1 $\beta$ , pro-IL-18) into inflammatory cytokines (IL-1 $\beta$ , IL-18). P2X7 receptor and mitochondrial stress also activate the inflammasome assembly. It will ultimately lead to pyroptosis and, thus, neurodegeneration (PAMPs – pathogen-associated molecular pattern, DAMPs – damage-associated molecular pattern, TNF – tumour necrosis factor, NLRP3 – nucleotide-binding domain, leucine-rich repeat-containing receptor (NLR) family pyrin domain containing 3, ASC – apoptosis-associated speck-like protein containing CARD, NF- $\kappa$ B – nuclear factor kappa-light-chain-enhancer of activated B cells, IL – interleukin, P2X7-P2 – purinergic receptor 2) (Adapted from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence (<http://smart.servier.com/>))

dopaminergic neurons.<sup>67</sup> Increased neuroinflammation in PD is marked by elevated C3 and factor H (FH) along with reduced A $\beta$ 42 in cerebrospinal fluid (CSF), which helps to correlate with cognitive and motor dysfunction.<sup>68</sup> In contrast to this study, Rozemuller et al<sup>69</sup> found negative double staining for  $\alpha$ -synuclein ( $\alpha$ -syn) and components of complement, suggesting that reactive microglia and the complement system are not involved in the formation of Lewy body in the cortex of PD patients.

### Implication of microglia

In AD, the structure of A $\beta$  oligomer is sensed by the microglia as DAMP and they are morphologically altered to the 'reactive' or 'primed' microglia state.<sup>13</sup> Activation of microglia has both degenerative and protective effects in AD.<sup>13</sup> On a negative aspect, activation of microglia can produce pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$  that act on the cholinergic neurons and induce apoptosis.<sup>70</sup> Conversely, it can also produce a proteolytic enzymes such as insulin-degrading enzyme (IDE),

matrix metalloproteinases (MMPs) and neprilysin to degrade A $\beta$  plaque to provide neuroprotection. Phagocytic function of microglia is inhibited by a mutation in the TREM-2 and CD33 protein.<sup>71</sup> TREM is a protein of immunoglobulin (Ig) superfamily, which is expressed in macrophages, microglia and dendritic cells of the brain, whereas CD33 is a cell-surface protein of the sialic acid-binding Ig-like lectin (SIGLEC) family, which majorly expressed in myeloid and lymphoid cells.<sup>72</sup> TREM-2 is involved in cell survival, phagocytosis, proliferation and production of inflammatory cytokines.<sup>73</sup> It has been observed in various studies that the risk of AD gets increased up to threefold to fourfold due to arginine to histidine mutation (R47H mutation) of TREM-2, which results in functional loss of the protein.<sup>74</sup> Other mutant variants of TREM-2 such as D87N, T96K and R62H have also been associated with AD generation.<sup>75,76</sup>

Progression of PD is the result of the infiltration of lymphocytes from the periphery to CNS, excessive activation of microglial cells and astrogliosis.<sup>77</sup> Researchers have observed early and prolonged activation of microglia

within the territory of damaged neuronal death using positron emission tomography (PET) scanning.<sup>78</sup> Reactive microglia phagocyte aggregated  $\alpha$ -syn and led to stimulation of Nox2 and generation of ROS to elevate dopaminergic neurodegeneration in SN.<sup>79</sup> Aggregation of  $\alpha$ -syn enables the upregulation of leucine-rich repeat kinase (LRRK2) along with activation of iNOS and CD68 through macroglia and the invading peripheral cells.<sup>80</sup> Activated microglia facilitate the release of pro-inflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-23, IL-12, epidermal growth factor (EGF) and TNF- $\alpha$  and chemokines such as CCL5, CCL2 and CXCL10 in the striatum, CSF and peripheral blood<sup>81,82,83</sup> (Figure 3). Interferon-gamma and TNF- $\alpha$  are also stimulated in the SN.<sup>84</sup> Increased levels of TNF- $\alpha$  in serum lead to four times of exacerbation in cognitive decline, which gives an idea about the role of inflammatory markers in cognitive function.<sup>85</sup> The release of IL-1 $\beta$  impairs the spatial navigational learning and cognitive functions in female C57BL/6 mice.<sup>86</sup> These cytokines then trigger iNOS and COX-2, which results in the generation of ROS.<sup>87,88</sup> A massive release of ROS leads to oxidative stress, which is responsible for aggravating neurodegeneration.<sup>89</sup>

### Inflammasome activation

AD is the most studied disease for understanding inflammasome signalling.<sup>90,91</sup> Excessive generation of A $\beta$  leads to its oligomerization and subsequently senile plaque formation. These A $\beta$  oligomeric or fibrillar form can act as DAMPs to activate inflammasome signalling.<sup>90</sup> In experiments with AD patients, it has been observed that activation of NLRP3 inflammasome is an early-stage event rather than a late-stage event.<sup>92</sup> Another clinical study on AD has shown the release of IL-18 and IL-1 $\beta$  and co-expression of ASC, NLRP3 and caspase-1 in the monocyte.<sup>93</sup> Fibrillar A $\beta$  stimulates microglia to release IL-1 $\beta$  based on the interaction of NLRP3 and ASC, whereas soluble A $\beta$  peptides activate NLRP3 inflammasome majorly through CD36.<sup>93</sup> NLRP3 inflammasome activation in response to A $\beta$  can also be regulated by autophagy-related protein 7 (ATG7). Deficiency of cellular ATG7 causes increased cleavage of caspase 1, the formation of speck by ASC, and the release of IL-1 $\beta$  in microglia and BV2 cell (alternative model for primary microglial culture). Moreover, microglia, which are deficient in ATG7, cause a more remarkable loss of neuronal dendrites suggesting the activation of microglial inflammasome to limit neuronal destruction.<sup>94</sup>

Following uptake of A $\beta$  in the astrocytes, IL-1 $\beta$  is produced through inflammasome signalling.<sup>95</sup> According to Liu et al,<sup>90</sup> palmitate increases NLRC4 inflammasome activation in astrocytes of rat and causes maturation of IL-1 $\beta$ . In an IL-1 and MyD88 knockout rat model,

microglia were not activated. This suggests that A $\beta$  activates MYD88, which results in activation of NLRP3 inflammasome and ultimately cleavage of caspase 1.

In PD, aggregation of  $\alpha$ -syn stimulates TLR, which further contributes to the assembly of NLRP3 inflammasome and conversion of its downstream marker pro-IL-1 $\beta$  to IL-1 $\beta$ .<sup>96</sup> Fyn kinase enables the transfer of  $\alpha$ -syn to microglia via PKC-delta-dependent NF- $\kappa$ B-p65 nuclear translocation. This transfer further contributes to mitochondrial ROS generation and an increase in the level of cathepsin B, which therefore activates NLRP3 inflammasome<sup>97,98</sup>. Apart from oxidative stress, mitochondrial DNA disruption can stimulate pro-inflammatory mediators to activate NLRP3 inflammasome.<sup>99</sup> Lee et al<sup>100</sup> found that microglial NLRP3 inflammasome activation in mouse model of MPTP-induced PD is essential for the motor deficit and dopaminergic neuronal loss. Elevated levels of IL-1 $\beta$  were also found in CSF and blood of the PD patients.<sup>101</sup> In addition to this, increased NLRP3, caspase-1 and IL-1 $\beta$  were detected in transgenic  $\alpha$ -syn-A53T overexpressed mouse model of PD.<sup>12</sup> The serine-threonine kinase cyclin-dependent kinase 5 (CDK-5) is responsible for phosphorylating NLRP, ASC and POP1 ASC-2, which ultimately leads to inflammasome activation.<sup>102</sup>

### Immunotherapeutics for age-related neurodegenerative diseases

Hitherto, FDA-approved drugs for symptomatic treatment targeting A $\beta$  and Tau tangle are, donepezil, galantamine, rivastigmine and AADvac1 (a vaccine developed by Axon Neuroscience (NCT02579252), currently in clinical trial phase II) are in practice.<sup>103</sup> Now, targeting immune cells such as microglia and macrophages for modulation of neuroinflammation is of great interest. A $\beta$  plaque burden can also be reduced by injections of anti-A $\beta$  monoclonal antibodies (mAbs) into the systemic circulation.<sup>104,105,103,106</sup> Tyrosine kinase inhibitors, which are currently in phase III clinical trial, can inhibit mast cell differentiation and degranulation, exhibiting beneficial effects as an adjunct with conventional therapy (NCT01872598). Endocannabinoids inhibit the neuronal microglial activation by promoting the receptor interaction of CD200.<sup>107</sup>

### Vaccination

In April 2020, Elan/Wyeth's group is planning to launch a dose-escalation, multiple-dose, randomized and double-blind phase II clinical trial for the AN1792 vaccine (NCT00021723) against AD. It comprises QS21 and preaggregated Ab1-42 as an adjuvant.<sup>108</sup> Recently, a phase I clinical trial on active vaccine CAD106 was launched by Novartis Pharmaceuticals (NCT00411580). This vaccine

targets the small A $\beta$  fragment (A $\beta$  1-6), which is a B-cell epitope.<sup>109</sup> It showed marked improvement of cognitive behaviour in phase I trials, but the result of phase II clinical trial is yet to be disclosed (NCT02565511). Janssen and Pfizer conducted a phase II clinical trial on ACC-001 (NCT01284387). It also targets A $\beta$ (1-6) fragment, which is coupled to a carrier protein and the adjuvant QS-21, a surface-active saponin.<sup>110</sup>

Passive immunization using monoclonal antibody is the recent trend seen in immunotherapy, in which administration of exogenous anti-A $\beta$  monoclonal antibody is performed without the chance of Th1-mediated antibody production.<sup>111</sup> Janssen/Pfizer conducted phase II clinical trial on bapineuzumab AAB-001 (NCT00606476) and bapineuzumab AAB-003,<sup>112</sup> while Eli Lilly conducted phase III clinical trial on solanezumab (NCT02760602).<sup>111</sup> However, these drugs failed to show any significant clinical improvement in phase III trial. The limitation of passive immunization is the unavailability of appropriate antigen targets, repeated injections in chronic diseases, haemorrhagic risk, blood-brain barrier (BBB) penetration, high costs and generation of the immune response against injected antibodies.

In PD, immunotherapeutics such as peroxisome-proliferated receptor gamma (PPAR- $\gamma$ ) agonists such as fenofibrate help to reduce inflammation and oxidative stress, and simultaneously elevate the dopamine level.<sup>113</sup> NSAIDs such as aspirin, an irreversible COX-1 inhibitor, decrease inflammation and oxidative stress by elevation of lipoxin.<sup>114</sup> Statins inhibit TNF- $\alpha$ , IL-1 $\beta$  and IL-6 and lead to a decline in inflammation.<sup>115</sup> In an experiment by Gordon et al., it has been observed that daily oral administration of MCC950 (20 mg/kg) can inhibit NLRP3 inflammasome-mediated caspase-1 activation in striatum.<sup>101</sup> Han et al.<sup>116</sup> revealed that kaempferol inhibits the formation of the NLRP3 inflammasome by activating autophagy in microglia, which further reduced the NLRP3 protein expression. Bushen-Yizhi formula suppresses NLRP3 inflammasome activation in the SN- and MPP<sup>+</sup>-stimulated BV-2 microglia cell lines.<sup>117</sup> PMX-205, the antagonist of C5a, protects against dopaminergic neurodegeneration. Anti- $\alpha$ -synuclein immunotherapy not only can be a promising approach, but it acts by inhibiting the movement of extracellular  $\alpha$ -synuclein to other neurons.<sup>118</sup> Other vaccinations such as 9E4 (humanized mouse monoclonal antibody) and AFF-1 (short peptides-AFFITOPES) minimize the aggregation of calpain cleaved  $\alpha$ -synuclein and oligomers of  $\alpha$ -synuclein, respectively.<sup>13</sup> There are many limitations regarding the development of immunotherapy, one of them is the direct administration of  $\alpha$ -synuclein antibody to the brain, which hinders  $\alpha$ -synuclein homeostasis. Moreover, these clinical trials are costly and take a longer duration to develop new approaches for synucleinopathy<sup>119</sup> (Table 1).

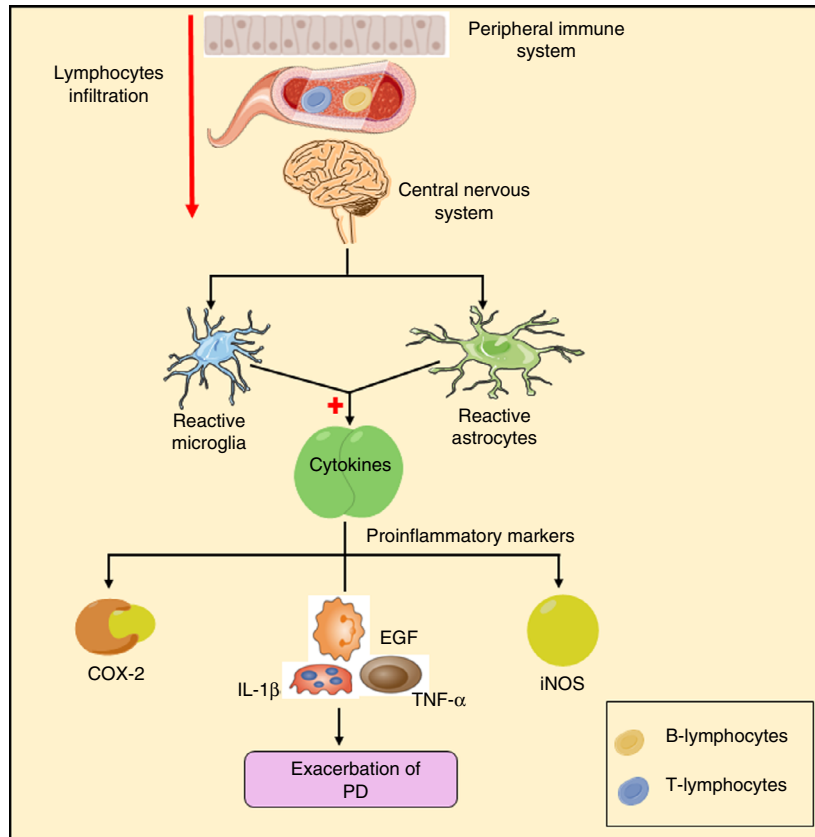
## STIMULATION OF THE IMMUNE SYSTEM IN MULTIPLE SCLEROSIS AND AMYOTROPHIC LATERAL SCLEROSIS

### Complement system

Experimental autoimmune encephalomyelitis (EAE) is the best model for studying the role of the complement system in MS.<sup>120</sup> Binding of C3d to CR3 receptor mediates phagocytosis of myelin by microglia.<sup>121</sup> Further, it leads to the activation of TNF- $\alpha$  and the generation of NO, which culminate in demyelination.<sup>122</sup> At 2 h post-formation, terminal complex C5b-9 in lytic dose in macrophages, neurons and oligodendrocyte progenitor cells induces demyelination.<sup>123</sup> In contrast, the sublytic dose of C5b-9 can prevent oligodendrocyte apoptosis via phosphatidylinositol 3-kinase/Akt pathway (PI3K/Akt).<sup>124</sup> Watkins et al.<sup>125</sup> revealed clinical data of 22 MS patients, which confirm the upregulation of C1q protein of the classical complement system and fragment Bb of the alternative complement pathway in the grey matter of cortex. To validate the role of complement system in MS, transgenic mice deficient in C3 or factor B were used in an antibody-independent model of EAE, which showed less severity of disease.<sup>126</sup> A marked decrease in the infiltration of T cells and macrophages, along with a reduced expression of P-selectin, was detected in PVG/C6-deficient rats.<sup>127</sup> Therefore, it can be observed that the complement system has a dualistic role. Hence, its modulation instead of complete inhibition can improve the quality of life in MS patients.<sup>27</sup>

In the case of ALS, the upregulation of various components of the complement system, such as C1q, C3, is reported.<sup>128</sup> Activation of its components such as MBL, MASP-1, C3, C4a and C5a leads to the destruction of BBB integrity.<sup>128</sup> One of the critical elements is C5a peptide, which binds to the C5aR receptor of neurons and glia.<sup>129</sup> It also links to another G protein-coupled receptor C5a-like receptor 2 (C5L2), which leads to the activation of mitogen-activated protein kinase (MAPK) and protein kinase B (PKB/Akt) pathways.<sup>130</sup> C5a is responsible for the entry of macrophages in the skeletal muscles of the hSOD1<sup>G93A</sup> mouse model, contributing to muscle denervation in ALS.<sup>131</sup> SOD1<sup>G93A</sup> C5aR1 knockout mouse model has shown to increase the survival rate, which indicates that C5aR1 activation exacerbates the deleterious effect of ALS.<sup>132</sup> Another mouse model, TDP-43<sup>Q331K</sup>, shows similar activation of complement C5a in the lumbar region of the spinal cord and tibialis anterior muscle.<sup>133</sup> This indicates that C5a can be a potential therapeutic target for ALS. Microarray analysis and laser-capture microdissection in the transgenic animal model revealed that the levels of C1q and C4 were elevated throughout the progression of the disease.<sup>134</sup> Moreover,





**FIGURE 3.** Microglial mediated neuroinflammation in PD. Infiltration of lymphocytes from the peripheral immune system to the central nervous system and aggregation of  $\alpha$ -syn stimulate the activation of the microglial cell, which is accompanied by the release of ROS and NO along with inflammatory markers such as IL-1 $\beta$ , IL-18, TNF- $\alpha$ , EGF and COX-2. All these inflammatory markers result in neuronal cell death (IL – interleukin, TNF- $\alpha$  – tumour necrosis factor- $\alpha$ , EGF – epidermal growth factor, COX-2 – cyclooxygenase-2, ROS – reactive oxygen species, NO – nitric oxide) (Adapted from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence (<http://smart.servier.com/>))

mRNA and protein of classical components C1q and C4 in addition to terminal complements C3 and C5b-9 were elevated in 16 ALS patients.<sup>135</sup> Farber et al. found that activated C1q is responsible for converting resting microglia into reactive microglia via  $Ca^{2+}$  signalling, which further stimulates pro-inflammatory markers such as TNF- $\alpha$  and IL-6, which are detrimental for neurons.<sup>136</sup> Thus, modulating complement system activation can be a promising approach for neuroprotection in ALS (Figure 4).

### Microglia activation in ALS

Microglia play the role of a double-edged sword. In rNLS8 mouse model, human TAR DNA binding protein 43 (hTDP-43) pathology-related ALS microglia exhibit a protective role by reducing inflammatory markers. Inhibitors of microgliosis such as PLZ3397, CSF1R and c-kit failed to recover motor function in rNLS8 mice.<sup>137</sup>

Moreover, after microglial activation, the M2 phenotype secretes neuroprotective factors such as BDNF, while M1 releases inflammatory cytokines to detrimental effect.<sup>138</sup> Fractalkine, a chemo-attractant bound to surface receptor CX3CR1 of microglia, which helps them in intercellular signalling of impaired neurons.<sup>139</sup> It acts as neuroprotective by stimulating PI3K/Akt, which leads to activation Bcl-x<sub>L</sub>(antiapoptotic protein) and quelling of BAD (proapoptotic protein).<sup>140</sup>

The SOD1<sup>G93A</sup> transgenic mouse model is extensively used for studying human ALS.<sup>141</sup> In the SOD1<sup>G93A</sup> mouse model, reactive microglia and astrocytes cause induction of nerve growth factor (NGF) expression correlated with p75 neurotrophin factor (p75NTR) expression in the area of degenerating motor neurons, which lead to apoptosis.<sup>142,143</sup> Reactive microglia causes upregulation of lymphocyte function-associated molecule-1 (LFA-1), leucocyte common antigen (LCA), complement receptor CR3 and CR4, immunoglobulin receptor Fc $\gamma$ R1 and



MHC-II complex.<sup>144</sup> These reactive microglia generate the superoxide anions ( $O^{2-}$ ) to promote oxidative stress, which worsens the ALS condition.<sup>33</sup> In addition to this, reactive microglia secretes pro-inflammatory markers such as IL-1, IL-6 and TNF- $\alpha$ . IL-1 further recruits IL-6, colony-stimulating factor (CSF), IL-8 and IFN- $\alpha/\beta$ .<sup>145</sup> Apart from these inflammatory markers, there is a three-fold elevation in the expression of COX-2 protein and mRNA in astrocytes, microglia, neurons and in the spinal cord of the transgenic mouse model during the progression of disease.<sup>146</sup>

### Microglia and T-cell interaction in MS

The induction of the immunological response against CNS antigen in MS is still paradoxical.<sup>147</sup> Activated microglia contribute to oxidative stress following oligodendrocytes, and neuronal and axonal injury-associated demyelination.<sup>148</sup> Two contrary hypotheses are involved in describing the functions of the immune system in lesions of MS. First, the pathology starts in the periphery by stimulation of innate and adaptive immunity and progress towards the CNS.<sup>149</sup> The second hypothesis states that it begins from CNS and then shifts to the periphery.<sup>150</sup> Activated microglia helps in the infiltration of T cells responsible for adaptive immunity such as Th1, Th2 and Th17. Th1 releases pro-inflammatory markers (IFN- $\gamma$  and TNF- $\alpha$ ), Th-2 secretes anti-inflammatory markers (IL-4, IL-6, and IL-13), and Th17 releases IL-17 and granulocyte-macrophage colony-stimulating factor (GM-CSF).<sup>151</sup> Both MHC-I and MHC-II are expressed by activated microglia, which later stimulate CD8<sup>+</sup> T cells and CD4<sup>+</sup> T cells, respectively.<sup>152</sup> CD4<sup>+</sup> release antibodies against myelin sheath and oligodendrocyte antigens result in demyelination.<sup>153</sup> In contrast, stimulated CD4<sup>+</sup> cells can modulate T cells into iT<sub>reg</sub> (regulatory T cells), which suppress the immune system by inhibiting the antigen-presenting cell (APC) and induce neurotrophic factors such as BDNF and GDNF, but impaired activation of iT<sub>reg</sub> leads to autoimmune disease.<sup>154,155,156</sup>

### Inflammasome activation

Dysregulation of NLRP3 inflammasome can be detrimental and eventually end up with degeneration of neurons.<sup>157</sup> In the SOD1<sup>G93A</sup> mouse model, increased expression of TLR-4 and NF- $\kappa$ B in the diseased brain suggests that NLRP3 inflammasome activation culminates in pyroptosis.<sup>158</sup> Scientists have also observed an increased expression and co-localization of NLRP3 inflammasome in the spinal cord of SOD1<sup>G93A</sup> mouse model.<sup>159</sup> Co-localization and activation of NLRP3 and upregulation of IL-18 in the serum of ALS patients were reported by Kadhim et al., which then further activates caspase-1.<sup>160</sup> Increased expression of the NLRP3

inflammasome, along with aggregation of p62 and damaged mitochondria, is indicative of diminished autophagy in ALS.<sup>161</sup> According to Meissner et al., in the SOD-1<sup>G93A</sup> mouse model, activation of microglial IL-1 $\beta$  and caspase-1 occurs without activation of NLRP3.<sup>162</sup> In contrast, protein aggregates such as TDP-43<sup>Q331K</sup>, TDP-43<sup>A315T</sup>, TDP-43<sup>WT</sup>, and SOD-1<sup>G93A</sup> showed microglial NLRP3-dependent inflammasome activation in TDP-43<sup>Q331K</sup> and a SOD-1<sup>G93A</sup> mouse model of ALS, respectively, by using Nlrp3<sup>-/-</sup> knockout and NLRP3 inhibitor MCC950.<sup>163</sup>

In MS, elevated levels of IL-1 $\beta$  and caspase-1 in peripheral blood mononuclear cells (PBMC) indicate the contribution of NLRP3 inflammasome in experimental mouse model.<sup>164</sup> NLRP3 inflammasome stimulates the migration of Th cells and APC in CNS to increase the expression of chemotactic proteins such as osteopontin, CXCR6 and CCR2.<sup>164</sup> Co-localization and activation of NLRP3 through IL-1 $\beta$  aid in demyelination, while stimulation of NLRP3 helps in neuroprotection.<sup>165</sup> Moreover, NF- $\kappa$ B facilitates pro-IL-1 $\beta$  transcription, while expression of pro-IL-18 is constituted, which increases after cellular activation.<sup>166</sup> Progression of relapse-onset MS was marked by the upregulation of IL-1 $\beta$  in CSF.<sup>167</sup> In addition to this, MS patients showed a significant increase in serum and CSF levels of IL-18 levels.<sup>168</sup> IL-18 is responsible for the stimulation of CD8<sup>+</sup> mucosal-associated invariant T (MAIT) cells along with activation of integrin, which enables the infiltration of CD8<sup>+</sup>T in CNS.<sup>169</sup> Increased rare genetic variants in NLRP1/3 and CASP1 lead to its inactivation through autophagy, mitophagy and type 1 interferons.<sup>170</sup>

### Immunotherapeutics for modulating the immune system in ALS and MS

To date, US FDA-approved drug, riluzole, can increase life expectancy for about 2-3 months.<sup>171</sup> The mechanism of action is to suppress the glutamate release at synaptic cleft.<sup>171</sup> Recently in May 2017, edaravone becomes the second FDA-approved drug. It shows functional recovery by preventing the nitration of a tyrosine residue in CSF.<sup>172</sup> Inflammatory markers such as TNF- $\alpha$  and FasL expression are suppressed by COX-2 inhibitors, thalidomide and its congener lenalidomide in the SOD-1<sup>G93A</sup> mouse model.<sup>173</sup> Another COX-2 inhibitor cyclosporin has been proven effective in the transgenic mouse model, and currently, it is in clinical trial phase IV (NCT01795872).<sup>174,175</sup> A clinical trial of glatiramer acetate at a dose of 40 mg/day failed due to inappropriate regime to modulate ALS.<sup>176</sup> Anakinra is an antagonist of IL-1, which then further inhibits activation of IL-6 and other pro-inflammatory markers in ALS.<sup>177</sup> PMX205, the antagonist of C5aR, shows extended survival and slow progression of disease.<sup>133</sup> Cyclo(His-pro) helps in the reduction of ROS generation and NF- $\kappa$ B and therefore inhibits

TABLE 1. Immunotherapies for various neurodegenerative diseases

Sr. No.	Disease	Target	Treatment	
			Approved	Clinical trials
	AD	Reduce Tau oligomer accumulation	—	AADvac1 <sup>103</sup>
		Microglial activation inhibitor	Endocannabinoids <sup>107</sup>	—
	ALS	Suppress glutamate release	Riluzole <sup>171</sup>	—
		Inhibit nitration of tyrosine residue	Edaravone <sup>172</sup>	—
		Inhibit TNF- $\alpha$ and FasL	Lenalidomide and thalidomide <sup>173</sup>	Cyclosporin <sup>174</sup>
		Inflammasome	Cyclo(His-pro) <sup>178</sup>	—
	MS	Halt humoral and cell-mediated immunity	IFN- $\beta$ , glatiramer acetate and natalizumab <sup>181</sup>	—
		Sphingosine 1 phosphate modulator	Fingolimod, teriflunomide and dimethyl fumarate <sup>184</sup>	Laquinimod, ponesimod, siponimod and ceralifimod <sup>183</sup>
	PD	PPAR- $\alpha$ agonist	Fenofibrate <sup>113</sup>	—
		Inhibit TNF- $\alpha$ , IL-6 and IL-1 $\beta$	Statins and aspirin <sup>114,115</sup>	—
		Reducing the accumulation of $\alpha$ -synuclein oligomers and calpain cleaved $\alpha$ -synuclein.	—	9E4 and AFF-1 <sup>13</sup>
	Stroke	NLRP3 inflammasome inhibitor	—	Beta-hydroxy butyrate and MCC-950 <sup>249,244</sup>
		Treg cell activator	—	Trichostatin <sup>252</sup>
	HD	Semaphorin 4D inhibitor	—	VX-15 <sup>218</sup>

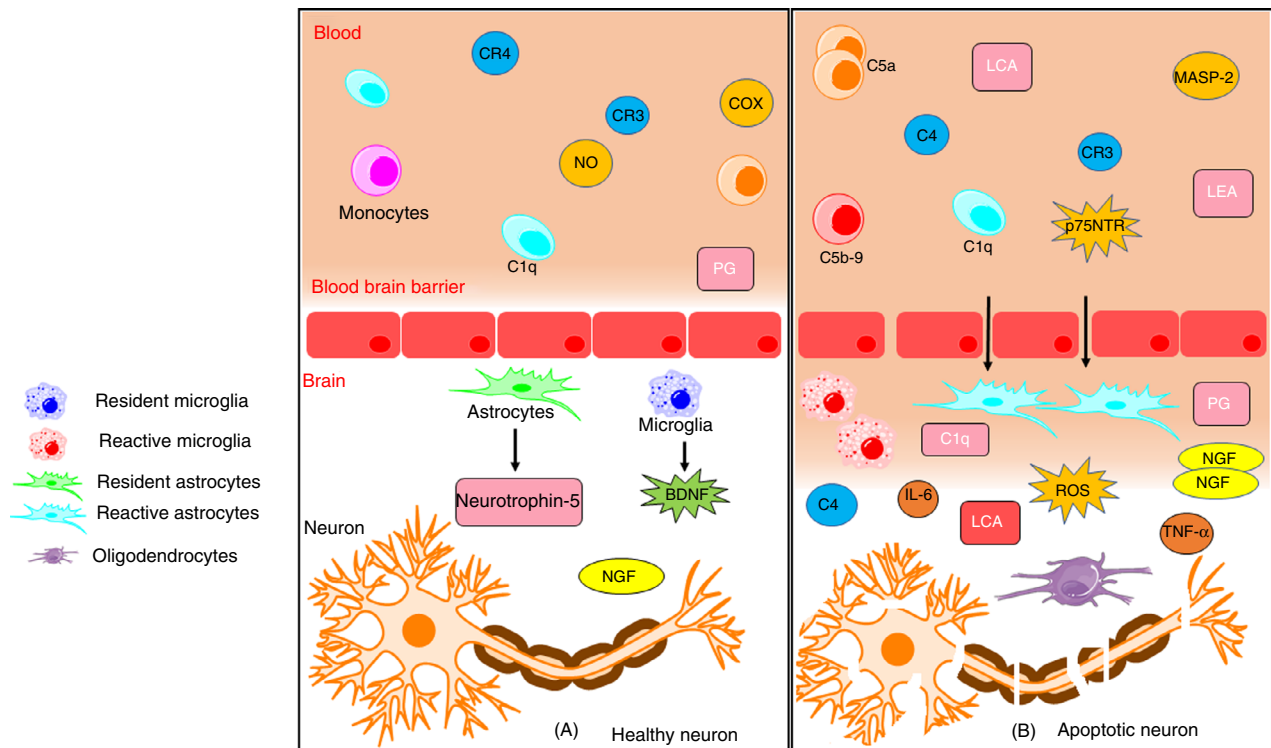
NLRP3 inflammasome in ALS.<sup>178</sup> Two vaccines, tgG-DSE2lim and tgG-DSE5b, were tested in hSOD1<sup>G37R</sup> mouse, which resulted in late-onset and increased life expectancy.<sup>179</sup>

NEDA (no evidence of disease activity) is a broadly accepted approach for early treatment of MS that starts with injectables followed by oral doses and infusions.<sup>180</sup> Injectable disease-modifying therapies include interferon- $\beta$ s (IFN- $\beta$ s), glatiramer acetate (GA) and natalizumab (NTZ).<sup>181</sup> Immunomodulating drugs such as mitoxantrone intercalate with DNA and halt humoral immunity and T-cell count.<sup>182</sup> Infusion of rituximab and ocrelizumab that are anti-CD-20 antibodies is approved for relapsing–remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS).<sup>183</sup> Sphingosine 1 phosphate (S1P) modulator, fingolimod, is the first oral approved drug that is phosphorylated by sphingosine kinase to form fingolimod phosphate, impeding with circulating immune cells.<sup>184</sup> Other orally approved drugs are teriflunomide and dimethyl fumarate for RRMS.<sup>185,186</sup> The drugs that are in clinical trials are laquinimod, ponesimod, siponimod and ceralifimod.<sup>183</sup> A combination of two antibodies trastuzumab and pertuzumab can be used for regulating complement system.<sup>187</sup> Intranasal administration of genetically engineered CAR/FoxP3 T<sub>reg</sub> cells can quell the EAE model of MS.<sup>188</sup> As myriads of treatment are emerging, these therapies are expected to improve the livelihood of MS patients (Figure 5).

## IMMUNE MODULATORS OF HUNTINGTON'S DISEASE

### Complement system

HD is an inherited, dominant and autosomal neurodegenerative disease that is triggered by an expansion of three-base-pair (CAG) repeat in exon 1 of the *HTT* gene.<sup>189</sup> This expansion repeats translate into a polyglutamine tract at the N-terminus of the protein.<sup>190,191</sup> Experimental data suggest that in HD, microglia activate the classical pathway of the complement system via pathological peptide-like mutant huntingtin (mHtt). Mutation in the gene of chromosome 4p 16.3 leads to the generation of mHtt.<sup>192,191</sup> In situ hybridization study reveals that the striatum, neurons, astrocytes and myelin sheath of the HD brain are strongly positive for C1q, C1r, C3, C4, C9-neoepitope and iC3b-neoepitope deposition.<sup>190,193</sup> In the early disease stages, negative outcome for staining of complement component suggests that early neuronal damage precedes local synthesis and activation of complement components. Microarray analysis reports of HD brain tissue indicate that in the caudate nucleus and motor cortex area, complement components C3, C4A and C4B get highly expressed.<sup>194</sup> Researchers have worked on various animal models of HD. Among them, the R6/2 transgenic mouse model was proven to be a more realistic model despite having the limitations to



**FIGURE 4.** Neuroinflammation in ALS. (A) Components of the complement system, microglia and astrocytes reside near the blood-brain barrier and help in homeostasis and protection of CNS. It promotes neurogenesis by releasing BDNF, neurotrophin-5, etc. It also helps in removing debris and suppressing inflammation and therefore leads to neuroprotection. (B) On tissue injury, activation of C4a, C5a and C3 of the complement system is responsible for the entry of microglia and astrocytes to promote its conversion from resting to its activated form. Reactive microglia and astrocytes release pro-inflammatory markers such as TNF- $\alpha$ , IL-1 $\beta$  and iNOS. These markers further lead to the generation of ROS and culminate in oxidative stress. In addition to this, reactive microglia causes upregulation of LFA-1, LCA, complement receptor CR3 and CR4, immunoglobulin receptor Fc $\gamma$ R1 and MHC-II complex. Chronic activation of C3a and C5a promotes entry of peripheral immune cells, which secretes chemokines and cytokines on endothelial cells and disrupts the integrity of BBB. It also causes induction of NGF correlated with p75NTR in an area of degenerating motor neurons, which leads to apoptosis (BDNF – brain-derived neurotrophic factor, TNF- $\alpha$  – tumour necrosis factor, IL – interleukin, iNOS – inducible nitric oxide synthase, ROS – reactive oxygen species, LFA-1 – lymphocyte function-associated molecule-1, LCA – leucocyte common antigen, NGF – nerve growth factor, p75NTR-p75 – neurotrophin factor, Fc $\gamma$ R1 – fragment crystallizable gamma receptor 1, BBB – blood-brain barrier, MHC – major histocompatibility complex) (Adapted from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence (<http://smart.servier.com/>))

demonstrate the significance of complement system in HD.<sup>195</sup>

### Microglial activation

Marked microgliosis has been found in the post-mortem human HD brains.<sup>193</sup> It was reported that medium spiny GABA neurons (MSNs) of the striatum are most vulnerable to the neurotoxicity mediated by mHtt.<sup>196</sup> mHtt mostly accumulates in nerve terminals and neuronal dendrites rather than in soma and other cells, leading to microglial activation.<sup>196</sup> Activated and proliferated microglia contributes to neurodegeneration by upregulating inflammatory cytokines.<sup>197,198</sup> There are several pathways

through which microglial activation occurs in HD, which are as follows:

### NF- $\kappa$ B pathway

Microglia mostly express TLR-2 receptors, which are accountable for IL-10 and IL-6 secretions.<sup>199,200</sup> It also expresses TLR-3 and TLR-4 receptors that are linked with the production of pro-inflammatory cytokines such as IL-6, IL-10, IL-12, TNF- $\alpha$  and CXCL-10.<sup>200</sup> A group of inhibitory proteins, I $\kappa$ Bs, sequestered NF- $\kappa$ B in the cytoplasm.<sup>199</sup> When I $\kappa$ B kinase (IKK) phosphorylates I $\kappa$ Bs, it leads to the dissociation of NF- $\kappa$ B from I $\kappa$ Bs and translocation of NF- $\kappa$ B to the nucleus.<sup>201</sup> IKK $\alpha$ , IKK $\beta$  and IKK $\gamma$

are the subunits of IKK that is activated by soluble mHtt, ultimately leading to NF- $\kappa$ B pathway activation.<sup>202</sup> Trager et al. reported that the interaction of mHtt with IKK causes transcriptional changes in the NF- $\kappa$ B signalling with an induction in the level of IL-6, IL-8, IL-1 $\beta$  and TNF- $\alpha$ . siRNA lowers the mHtt level and causes attenuation of the NF- $\kappa$ B pathway with concurrent downregulation of pro-inflammatory cytokine levels in HD.<sup>203</sup>

#### *Kynurenine pathway*

Studies on the R6/2 HD mouse model have shown that peripheral macrophages exacerbate the HD pathogenic condition through the Kynurenine mono-oxygenase pathway (KP).<sup>204</sup> KP is the major route of metabolism of L-tryptophan in mammals and the principal pathway for the formation of nicotinamide adenine dinucleotide (NAD<sup>+</sup>).<sup>205</sup> Levels of two neurotoxic metabolites of the kynurenine pathway such as 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN) are increased in neocortex and striatum in the early stage of HD.<sup>204</sup> These QUIN and 3-HK, in addition to astrocytic deficiency and altered glutamate reuptake, have a role in N-methyl D-aspartate (NMDA) receptor overstimulation (excitotoxicity), free radical formation, lipid peroxidation and decrease in dopamine release.<sup>206,207</sup> This will ultimately contribute to neurodegeneration and cognitive dysfunction.

#### *Cannabinoid pathway*

Cannabinoid receptors are GPCR and mainly consist of CB1 and CB2 types of receptor.<sup>208</sup> CB2 plays a role in cell survival, differentiation and proliferation by adenylyl cyclase, cyclic AMP-protein kinase A (PKA), extracellular signal-regulated kinase 1 (ERK1) and ERK2, p38 mitogen-activated protein kinase and JUN N-terminal kinase (JNK) pathways.<sup>209</sup> CB<sub>1</sub> receptors are mostly present in striatal MSNs in R6/2 HD mouse model.<sup>210</sup> It plays a neuroprotective role by increasing the expression of brain-derived neurotrophic factor (BDNF).<sup>211</sup> In the R6/2 mouse model, the genetic knockdown of CB2 receptors shows microglial activation along with exacerbation of behavioural abnormalities and reduction in life span.<sup>212</sup>

#### **Inflammasome activation**

The mHtt aggregates in the caudate and putamen area and acts as DAMPs to cause neostriatal atrophy.<sup>213</sup> Although recent studies have observed that in the absence of any stimuli, mHtt overexpression in the primary murine microglia induces inflammatory gene expression,<sup>214</sup> studies on the R6/2 mouse model suggest that caspase-1 and caspase-3 get activated and further aggravate neurodegeneration.<sup>215</sup> Another research shows that inhibition of ATP-sensitive P2 purinergic receptor (P2X7) leads to

the alleviation of HD through the suppression of NLRP3 inflammasome signalling.<sup>216</sup> An increase in expression, as well as activity of the major myeloid transcription factors such as CCAAT/enhancer-binding protein alpha/beta (C/EBP $\alpha/\beta$ ) and Pu.1, may cause the production of pro-inflammatory cytokines, whereas the aggregation of mHtt triggers activation of inflammasome, but the mechanism to activate Pu.1 and C/EBP activity in microglia is yet to be explored.<sup>217,214</sup>

#### **Immunotherapeutics in HD**

Immunotherapy is a promising area for the treatment of HD. Recently, Vaccinex – ‘a Rochester’ – a New York-based biotechnology company, is conducting a double-blinded clinical trial on antibody VX-15.<sup>218</sup> It inhibits Semaphorin 4D, which is a transmembrane protein causing neuroinflammation and neurodegeneration.<sup>219</sup> Apart from this, an antisense oligonucleotide (ASO) therapy is also in phase I clinical trial.<sup>220</sup> The limitation of ASO therapy is that it can be administered through lumbar puncture only.<sup>220</sup>

### **INVOLVEMENT OF THE IMMUNE SYSTEM IN EXACERBATION OF ISCHAEMIC STROKE**

#### **Complement system**

The complement system plays a significant role in the pathogenesis of ischaemic stroke.<sup>221,222</sup> After an ischaemic attack, the levels of C3a, C4d and soluble C5b-9 in plasma are increased instantly, while the elevation of C5a occurs within 7-14 days.<sup>223,222</sup> The role of C1q, initiator of the classical pathway in the pathogenesis of ischaemic stroke, is quite complex. Reports suggest that the accumulation of C1q occurs at 3 to 6 h post-ischaemic stroke.<sup>224</sup> After 24 h of ischaemic insult, biosynthesis and functional activity of C1q by microglia get drastically increased.<sup>224</sup> However, C1q-deficient transgenic mice do not show any protective role in ischaemic stroke.<sup>223</sup> Conversely, neonatal C1q-deficient mice show less functional deficit.<sup>225</sup> This discrepancy between neonatal and adult C1q is mainly due to the differences in the presence of C1q in the CNS of adult and neonatal mice.<sup>226</sup> MBL, the initiator of the lectin pathway, also exacerbates ischaemic stroke pathology in transgenic mice and exhibits less cerebral infarct with better functional outcome post-stroke.<sup>227</sup>

Compared with the above two pathways, the alternative pathway has also been reported in ischaemic stroke pathology.<sup>221,222,223</sup> Factor B-deficient mice, when treated with CR2-fH, an alternative pathway inhibitor, show better improvement 24 h post-reperfusion.<sup>228</sup> CR2-fH inhibits the complement activation site by recognizing C3 opsonin.<sup>229</sup>

## Microglial responses after ischaemic stroke

Microglial activation shows characteristic temporal and spatial patterns in the peri-infarct zone.<sup>230</sup> In the case of focal cerebral ischaemia, microgliosis is prominent in the core region, accumulation region and marginal regions.<sup>230</sup> Within the cortical region where blood flow is normal, ramified microglia are majorly observed, whereas microglia with few stout and short processes are observed in the marginal zone. Finally, the hypertrophic cell body containing amoeboid microglia is found in the accumulation region and in the core region.<sup>231</sup> The distribution pattern signifies the transformation of morphology microglia that reflects the changes of its function and also a different pathological state of the tissue.<sup>51</sup> After global transient ischaemia, the hippocampal CA1 region has an extensive microglial expansion.<sup>232</sup> Immediately after an ischaemic episode, the release of IFN- $\gamma$  shifts the microglial polarization towards pro-inflammatory M1 phenotype, whereas at a later stage, CXCL-16 and IL-4 lead to anti-inflammatory M2 polarization.<sup>233,234</sup> In the early stage, activation of pro-inflammatory M1 microglia leads to the production of cytokine, TNF- $\alpha$ , IL-1, ROS, RNS and protease, while at the reparative phase, anti-inflammatory M2 microglia helps in attenuation of inflammation by producing IL-10 and TGF- $\beta$ .<sup>235,39</sup> Prolonged overexpression of microglia further leads to peripheral immunosuppression that may predispose to bacterial infection, pneumonia and urinary tract infection (UTI).<sup>236</sup> Hence, microglial activation following ischaemic stroke leads to exacerbation of pathology, whereas at the late stage, microglia contribute to neuronal protection.<sup>51</sup>

## Role of inflammasome signalling

The activation of inflammasome signalling is involved in atherogenesis, a major risk factor for stroke.<sup>237,238</sup> Macrophages are transformed into foam cells, and these can activate NLRP3 inflammasome. Atherogenesis causes the formation of plaque that leads to lysosomal rupturing of foam cells.<sup>238</sup> It further causes the release of cathepsin, various proenzyme and ROS, which ultimately activate NLRP1 and NLRP3.<sup>239</sup> TLR-4 and TLR-12 identify minimally oxidized LDL and FFA, and increase myeloid differentiation primary response protein MyD88 following activation of TIR-domain-containing adaptor-inducing interferon- $\beta$  (TRIF) to induce the expression of NF- $\kappa$ B.<sup>240</sup> Further, an increase in the expression of NLRP-3, ASC and pro-caspase-1 contributes to inflammasome assembly.<sup>241,242</sup> Inflammatory cytokines such as IL-1 $\beta$  and IL-18 activation also induce neutrophil, macrophage and lymphocyte infiltration, followed by their activation.<sup>243</sup> Release of MMPs 1, 2, 3, 9 and 12 is triggered by the inflammatory cytokines.<sup>244</sup> These MMPs play an important role in extracellular matrix remodelling and also

trigger plaque stability.<sup>245</sup> This cyclic mechanism activates NLRP3 and aggravates atherosclerosis, which therefore contributes to the development and exacerbation of stroke pathology.

## Post-stroke activation of inflammasome signalling

After ischaemic stroke, damaged cells release DAMPs, which leads to activation of PRRs such as TLR-2, TLR-4, IL-1 $\beta$  and RAGE, which may further activate NLRP1 and NLRP3 inflammasome via MAPK and NF- $\kappa$ B pathways.<sup>45,246</sup> In the core area, depletion of ATP leads to activation of NLRP1 by conversion of ATP-bound inactive inflammasome to ADP-bound active inflammasome.<sup>247</sup> Increased expression of NLRP3 or NLRP1, along with ASC and pro-caspase-1, leads to inflammasome assembly, and thus maturation of pro-inflammatory cytokines into inflammatory cytokines that further leads to neuronal cell death via pyroptosis.<sup>248</sup>

## Immunotherapy in ischaemic stroke

Recent studies reported that  $\beta$ -hydroxybutyrate and MCC950 could inhibit the NLRP3 inflammasome by reducing the secretion of pro-inflammatory cytokine (IL-1b) by macrophage.<sup>244,249,250</sup> Treg cells are suppressors of neuroinflammation.<sup>251</sup> Forkhead box transcription factor (FOXP3) is a marker of Treg cells, and FoxP3+ Treg cells are reported to attenuate inflammation.<sup>251</sup> Trichostatin A activates FoxP3 and reduces the proliferation of Th1 cell, which suppress the production of IFN- $\gamma$  by promoting the Treg cells.<sup>252</sup>

## MICROGLIAL MODULATION VIA GUT MICROFLORA AFFECTING CNS DISORDERS

As discussed previously, microglial activation leads to generation of NO. Aberrant NO generation has been linked with various neurodegenerative diseases, specifically AD and PD.<sup>253</sup> Studies have reported that gut commensal bacteria produce short-chain fatty acids (SCFA) to a certain extent, which are particularly responsible for microglial maturation and functional regulation.<sup>254</sup> Disruption of gut microflora has been observed to contribute to different CNS disorders via microglial dysfunction.<sup>254,255</sup> Hence, targeting the link between microglia and host gut microflora is a promising therapeutic approach. The Kallyope company is conducting a study for investigating the communication pathways of the gut/brain axis for developing novel therapies for various CNS disorders. However, this study is still in its infancy, which requires further research to determine how probiotics can be utilized to improve microglial function and finally be beneficial in CNS disorders.<sup>256</sup>

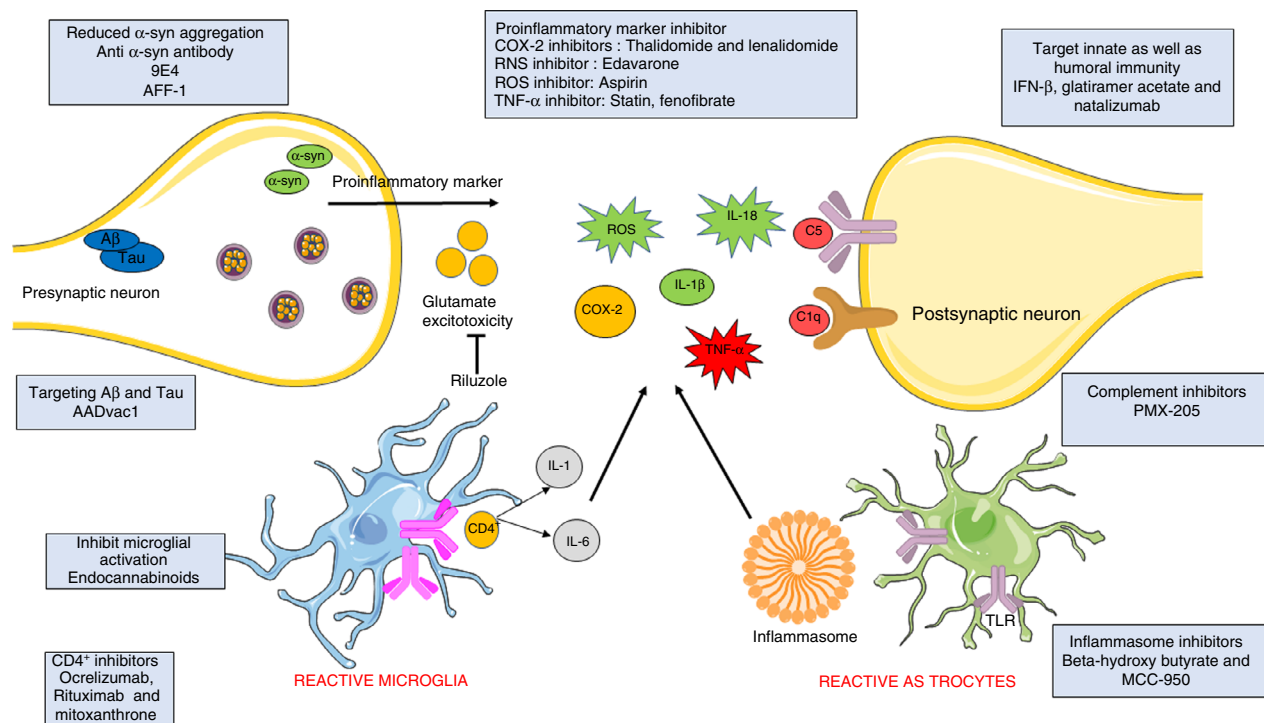


FIGURE 5. Different therapeutic targets of neurodegenerative diseases. Various therapeutic approaches targeting glutamate excitotoxicity, humoral and cell-mediated immunity and aggregation of Tau and  $\alpha$ -synuclein. Other components of the immune system such as the complement system, inflammasome, reactive microglia and astrocytes, and pro-inflammatory markers are modulated by different immunotherapies (Adapted from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence (<http://smart.servier.com/>))

## CHALLENGES TO TREAT NEURODEGENERATIVE DISORDERS VIA IMMUNE SYSTEM MANIPULATION

Manipulation of immune system as a novel therapeutic approach for neurodegenerative disorders possesses few challenges. Studies have shown that there are major gaps in understanding the disease mechanism, which often restricts bedside translation of promising in vivo results.<sup>257</sup> In vivo studies for neurodegenerative diseases are extensively based on genetic models, which reflect the familial forms of the disease. Hence, development of effective therapies is limited with the use of such models.<sup>257</sup> Along with this, age-related factors and effect of lifestyle are not considered extensively in preclinical studies. As discussed in the previous section, host gut microflora can affect both brain function and immune response.<sup>257</sup> It has been recently found that heterogeneity among individuals can also be a result of latent CNS infections causing neurodegenerative disease such as AD.<sup>258</sup> This appears consistent with ageing-related IFN-1 expression at the choroid plexus.<sup>259,260</sup> Therefore, common immunological factors contributing to different neurodegenerative diseases can be modified by systemic

immunomodulation and microglial phenotype modulation.

## CONCLUSION

This review summarizes the neuroimmune crosstalk with fundamental mechanisms and potential therapeutic approaches. As discussed in the article, the innate immune reaction can be detrimental to neurons and oligodendrocytes, and at the same time, it can also be beneficial for recovery. This response depends upon the sources of cytokines and on their cognate receptor's nature. The production of innate immune protein, as well as the presence of adaptive immune cells in the brain environment, is an important feature of neurodegeneration. Dysregulation of components of the immune systems such as microglia, T cells, complement system and inflammasome signalling plays a vital role in degenerating neurons, but the genetic background, gender and environment also contribute towards progression of the pathology. Singlet therapeutic approaches, in addition to the present choices of therapy, can suffice to reduce neuroinflammation and toxicity, thus preventing the induction and exacerbation of

neurodegenerative diseases such as AD, PD, ALS, MS, HD and ischaemic stroke.

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## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

## AUTHOR CONTRIBUTIONS

FB, MB, PB, XW, KR and DRY conceived and designed the study. FB, MB, AD, DS and PB outlined the performed rigorous literature search. FB, MB, BS, PJ, SR, AS and US conceived and designed the figures and images. FB, MB, AD, AB, KK, PB, KR and DRY wrote the manuscript.

## DATA AVAILABILITY STATEMENT

Not applicable.

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