

Review

Targeting complement in neurodegeneration: challenges, risks, and strategies

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Evidence implicating complement in neuroinflammatory and neurodegenerative diseases (NDDs) has accumulated over the past decade, revealing complement as a driver of pathology across these diverse diseases. Over the same period, there has been an explosion of interest in the development of complement-modulating drugs, first for a few rare complement dysregulation diseases but recently also for more common diseases where complement contributes to the disease process. To date, there has been little attention paid to the potential role of anticomplement drugs in neurodegeneration and the current landscape does not feature drugs that can enter the central nervous system (CNS), a prerequisite in most NDDs. Here we summarise the evidence implicating complement in neurodegeneration, build the case for testing anticomplement drugs, and discuss how drugs may be modified or designed *de novo* to inhibit complement in neurodegeneration.

Complement, neuroinflammation, and neurodegeneration

Neurodegeneration, the progressive loss of neurons, is a core feature of many neurological diseases, including not only the ‘classical’ NDDs (see [Glossary](#)), **Alzheimer’s disease (AD)**, **Parkinson’s disease (PD)**, **Huntington’s disease (HD)**, and **amyotrophic lateral sclerosis (ALS)**, but also neuroinflammatory diseases like **multiple sclerosis (MS)** and neuromyelitis optica (NMO) where the initial inflammatory component is succeeded by neurodegeneration. In some respects, labelling diseases as ‘neurodegenerative’ is unhelpful as it implies inevitable progression refractory to interventions. Indeed, AD and other **dementias** were long considered untreatable; even today, most drugs used in dementias treat symptoms rather than underlying disease.

Research over the past 20 years has provided a better understanding of disease triggers in dementias, challenging these long-held views and implicating other, more tractable targets. Genetics has led the progress; large **genome-wide association studies (GWASs)** have identified risk genes for various dementias that implicate unexpected pathways, notably inflammatory pathways. AD GWASs strongly implicated microglia, the brain-resident phagocytes, and **complement** where the genes encoding **complement receptor 1 (CR1)** and clusterin were top GWAS-significant hits [1,2]. Genetic evidence was supported by biomarker studies in brain, **cerebrospinal fluid (CSF)**, and plasma; markers of inflammation and complement dysregulation implicated these pathways in disease pathogenesis [3–6]. A final pillar of evidence was provided by animal models of dementia where targeting of inflammation, either via microglial or complement suppression, ameliorated disease [7–10].

Complement activation drives inflammation; the activation fragments C5a and C3a are potent proinflammatory effectors, while the lytic **membrane attack complex (MAC)** initiates

Highlights

For most neurodegenerative diseases (NDDs), therapeutic options are limited, providing symptomatic benefit but not impacting disease progression; new treatments addressing critical effectors in the disease process are needed.

Evidence implicating complement in NDDs has accumulated over the past two decades, establishing complement dysregulation as a driver of pathology and a novel target for therapy in these diseases.

Over the same period, highly effective anticomplement drugs have been developed for therapy of complement dysregulation; however, their use to date has been restricted to rare systemic diseases.

Current anticomplement drugs are not fit for purpose in most NDDs because they do not adequately access the central nervous system (CNS).

Blood–brain barrier-penetrant anticomplement drugs, created either by modifying current drugs or by designing new drugs, could suppress complement dysregulation, neuroinflammation, and neurodegeneration to halt or slow disease progression.

Inhibition of complement is not without risk; this might be particularly the case in the CNS and requires close attention.

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inflammatory pathways in many cell types [8,11,12]. These physiological processes, important in immune defence, require strict regulation to limit ‘friendly fire’ damage to self; when regulation fails, complement contributes to self-damage and disease, evident in many systemic complement dysregulation diseases [13–15]. Recognition of the critical roles of complement as an initiator and/or propagator of disease catalysed major efforts from pharma to deliver safe, effective anticomplement drugs. Missing so far has been the enthusiasm to produce drugs that access the brain, essential for treatment of NDDs where the **blood–brain barrier (BBB)** restricts entry of molecules. This brief review makes the case for targeting complement dysregulation in NDDs, explores ways in which current anticomplement drugs could be modified and new drugs designed to access brain, and discusses potential benefits and risks of manipulating complement in the brain. We hope that, by highlighting unmet need, this review will encourage effort from pharma to prioritise NDDs in anticomplement drug pipelines.

Neurodegeneration: a consequence of complement dysregulation?

In the brain, as in other organs, complement contributes to both immune defence and house-keeping tasks such as efficient elimination of dead cells and other debris. Sources of complement may include local production and influx from the periphery, the latter severely restricted by the BBB in health [16–18]. Given the evidence that peripheral, as well as central, inflammation contributes to neurodegeneration [19,20], peripheral complement dysregulation is likely to also play a role in some NDDs.

The tightly regulated nature of complement enables its switching on when needed and off when not; complement dysregulation, in the brain as in other organs, occurs when this rigid control is lost. The result is excessive inflammation, damage to self-cells, and propagation of injury, of particular relevance in brain where inflammation is poorly tolerated and brain cells are uniquely vulnerable to complement damage (Figure 1) [8,21,22]. For some NDDs there is compelling evidence implicating complement while for others evidence is sparse, reflecting a paucity of research.

Two lines of inquiry have built the case for complement as a guilty party in NDDs; the first is evidence that it is produced at the scene of the crime and the second is that it directly inflicts damage to brain cells. Complement synthesis by isolated primary brain cells and brain cell lines was demonstrated over 30 years ago, with microglia, astrocytes, and neurons all shown to produce complement proteins when appropriately triggered [16,23]. More recently, complement protein biosynthesis by glia and neurons has been confirmed *in situ* in NDD brains, confirming that a functional complement system exists in the brain even when the BBB is intact (reviewed in [24]). Evidence from animal models and human NDDs has comprehensively demonstrated that complement mediates synaptic loss, the crucial injury underpinning neurodegeneration [25,26]. The recognition molecule C1q binds the synapse and triggers local complement activation, opsonising the synapse for phagocytic elimination. Presence at the scene and capacity to commit the crime make complement a likely suspect.

Complement in MS and NMO

MS is an autoimmune inflammatory disease of the **CNS** characterised by demyelination and neurodegeneration, the latter responsible for progressive disability and cognitive decline. Complement has been recognised as a driver of demyelination in MS for many years, abundant in demyelinating plaques and decorating axons in and around plaques [27–31]. Triggers for activation include damaged myelin and autoantibodies, the latter poorly defined in MS (Figure 1). Biomarker studies in MS CSF and plasma demonstrate complement dysregulation, and complement deficiency or blockade inhibits myelin loss in MS models [32–34]. The contribution of

Glossary

α -Synuclein: protein that accumulates in PD and related diseases; aggregates in the brain to form Lewy bodies, the hallmark of the disease.

Alzheimer’s disease (AD): a progressive neurological disorder; the most common cause of dementia.

Amyloid: pathological deposits in the AD brain comprising amyloid- β (A β) aggregates, hallmarks of AD.

Amyotrophic lateral sclerosis (ALS): a rare neurological disease primarily affecting nerves responsible for controlling muscle movement.

Blood–brain barrier (BBB): a sealed barrier isolating the brain from the rest of the body that maintains brain haemostasis by regulating the entry of molecules into the brain.

Blood–spinal cord barrier (BSCB): the equivalent of the BBB protecting the spinal cord.

C3b/iC3b: C3 activation fragment involved in opsonisation.

Central nervous system (CNS): the brain and spinal cord.

Cerebrospinal fluid (CSF): a fluid that surrounds the brain and spinal cord; collected for testing via lumbar puncture.

Complement: an immune system that enhances the capacity of antibodies and phagocytic cells to clear microbes and damaged cells, promote inflammation, and directly attack pathogens;

comprises a network of >30 proteins in blood and on cells. Activation involves an enzymatic cascade triggered by three pathways: classical (CP), lectin (LP), and amplification loop (AL).

Complement receptor 1 (CR1): receptor for fragments of C3 and C4; found on erythrocytes and immune cells, including microglia. GWASs showed an association of CR1 variants with AD.

Dementia: a progressive decline in thinking, behavioural, and social skills.

Genome-wide association study (GWAS): approach used in genetics research to associate specific genetic variations with diseases.

Huntington’s disease (HD): a progressive brain disorder affecting movement, mood, and thinking skills, caused by a defective gene that encodes an abnormal huntingtin protein.

Membrane attack complex (MAC): a cytotoxic and proinflammatory product of complement activation; a complex of proteins (C5b, C6, C7, C8, C9_n) that forms a lytic pore.

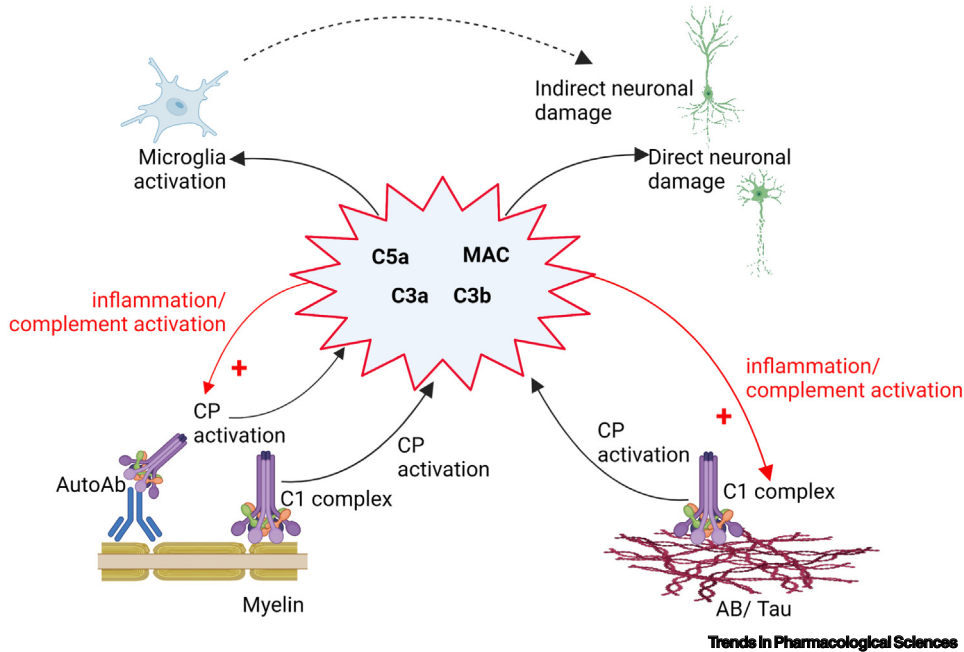


Figure 1. Complement activation and its effects in neurodegeneration.

For a Figure360 author presentation of Figure 1, see the figure legend at <https://doi.org/10.1016/j.tips.2022.02.006>.

Multiple sclerosis (MS) and Alzheimer's disease (AD) are used as examples of mechanisms. In MS, damaged myelin directly binds and activates C1, the initiating component of the classical pathway; autoantibodies against myelin/oligodendrocyte antigens can also bind C1. Once bound, C1 activates the classical pathway with the resultant local production of complement activation products. In AD, aggregated amyloid (and possibly tau aggregates) bind and activate C1 to trigger complement activation. Complement activation products attract and activate microglia to drive more inflammation and damage that in turn enhances complement activation – a vicious cycle. Complement activation products injure neurons, particularly synapses, indirectly by labelling with C3 fragments that engage and activate microglia and directly through membrane attack complex (MAC) formation. The figure was made using BioRender (<https://app.biorender.com>).

complement to axonal loss and neuronal dysfunction/death is less clear; however, complement activation products on denuded axons imply a role in their destruction – either indirectly through recruitment of microglia or directly through MAC-induced injury [8,13,21,35]. BBB impairment, secondary to local inflammation, is a key feature of MS lesions, providing a route for the influx of complement proteins to exacerbate local damage. NMO has many features in common with MS, usually presenting with visual disturbances and limb weakness; cognitive impairment is a common feature [36]. It is distinguished from MS by the restricted distribution of demyelination (spinal cord, optic nerve) and the presence in most cases of autoantibodies against aquaporin-4 (Aqp4), an astrocyte channel protein [37,38]. Neurodegeneration is present in areas of pathology and complement deposition abundant in lesions, CSF, and plasma. BBB breakdown is an obvious feature of lesions, likely to be mediated by anti-Aqp4 autoantibodies [39].

Current MS therapy is dominated by **monoclonal antibodies (mAbs)** targeting peripheral immune cells, either directly ablating specific cell types or preventing entry into CNS. These are effective in most MS cases but ineffective in **primary progressive MS**, an unmet need [35]. Despite the abundance of evidence implicating complement dysregulation in MS, and particularly in primary progressive MS, to date there have been no trials of anticomplement drugs. Because the BBB is impaired in areas of pathology in MS, even the current crop of anticomplement drugs, including mAbs, might prove effective in therapy. Indeed, anticomplement mAbs and recombinant complement regulators were efficacious in rodent MS models [40,41]. Experience in NMO

Monoclonal antibody (mAb): a single-target-specific immunoglobulin made by the cloning and expansion of a unique single-antibody-producing white blood cell.

Multiple sclerosis (MS): commonest demyelinating disease. Loss of myelin disrupts signal transmission, causing muscle weakness and coordination, mental, and psychiatric problems.

Neurodegenerative diseases

(NDDs): an umbrella term to describe a group of neurological diseases characterised by progressive loss of neurons.

Neuromyelitis optica (NMO): a rare demyelinating disease involving spinal cord and optic nerves.

Parkinson's disease (PD): a NDD presenting with movement disorder, caused by the loss of a specific set of brain nerve cells.

Primary progressive multiple sclerosis (PPMS): a type of MS characterised by progressing decline of neurological function (accumulation of disability) from the onset of symptoms.

Tau: a group of protein isoforms hyperphosphorylated in AD to form insoluble aggregates called neurofibrillary tangles.

clearly supports the testing of current anticomplement drugs in MS; eculizumab (C5-blocking mAb) was FDA approved for NMO therapy in 2019, and this drug and its variants are now considered first-line therapy. A cyclic peptide C5 inhibitor, zilucoplan was FDA approved for NMO in 2021 and a procession of other anticomplement drugs are in trials [14,42] (Table 1). It is frustrating that, despite evidence of efficacy in this rare disease, there is a lack of enthusiasm for trials in MS, a much more common disease and large health burden.

Complement in dementias

Dementia is by far the largest health challenge in many societies and is a huge economic burden through lost productivity and care costs. Western nations are gripped by a dementia epidemic, fuelled by longer lifespans. The prevalence of dementia in the UK, Western Europe, and the USA is approximately 2% of the adult population and rising, over 850 000 cases in the UK alone. For most forms of dementia there is a lack of effective therapies.

AD

AD is the commonest form of dementia, responsible for 60–70% of cases in Western societies. Patients present with cognitive impairment, particularly impacting recent event memory, progressing through more severe cognitive deficit, confusion, and emotional lability, to immobility and complete dependence in late disease. A small proportion of cases are monogenic familial, presenting in relatively young adults; the large majority are spontaneous and polygenic and present later, usually in individuals over 65 years and often much older. The disease is slowly progressive with an average life expectancy post-presentation of 6–7 years. Imaging shows brain atrophy and pathology shows signature lesions, **amyloid** plaques, and **tau** tangles, accompanied by neuronal dysfunction, lost interneuronal connections and reduced neuron numbers.

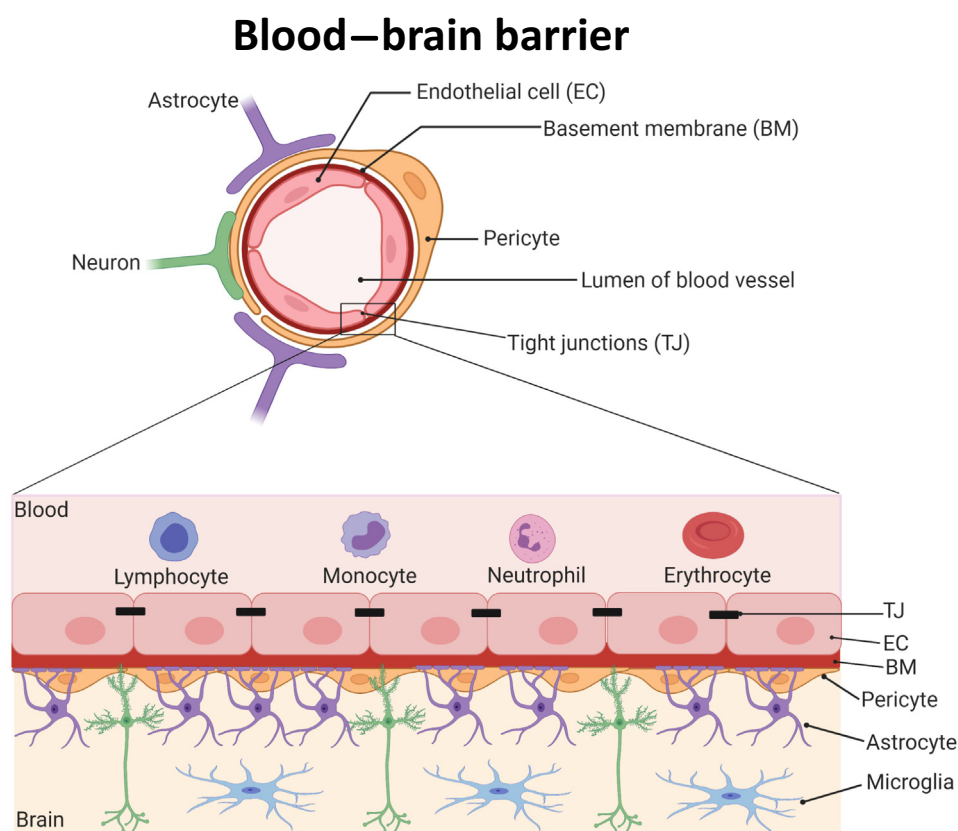
The first evidence linking complement to AD came from immunohistology; plaques and periplaque areas stained positive for complement proteins and activation products [43,44]. CSF and plasma biomarker studies provided evidence of ongoing complement dysregulation in the AD brain [3,4]. GWAS evidence of complement gene association with AD risk supported a causal role [1,2,45]. Precisely how complement is activated in AD remains unclear; however, amyloid fibrils bind complement classical pathway activation complex C1 and trigger the classical pathway (Figure 1) [46]. Compelling mechanistic evidence was provided by the demonstration in

Table 1. Complement therapeutics in NDDs

Disease	Drug	Target	Type	Stage	Company
NMO	Eculizumab	C5 cleavage	mAb	In clinic 2019	Alexion/AZ
	Ravulizumab	C5 cleavage	mAb	Phase III trial	Alexion/AZ
	Zilucoplan	C5 cleavage	Cyclic peptide	Pre-trial	UCB
ALS	ANX-005	C1q blocker	mAb	Phase II trial	Annexon
	Pegcetacoplan Ravulizumab	C3 cleavage C5 cleavage	Linear peptide mAb	Phase II trial Phase III failed 2021	Apellis Alexion/AZ
	Zilucoplan CPO10 (anti-C6)	C5 cleavage C6 blocker	Cyclic peptide mAb	In platform trial Preclinical	UCB Complement Pharma
HD	ANX-005	C1q blocker	mAb	Phase II trial	Annexon
MS	No tested anticomplement drugs	Many tested in models	n/a	All preclinical	n/a
AD	No tested anticomplement drugs	Some data from models	n/a	All preclinical	n/a
PD	No tested anticomplement drugs	Minimal model data	n/a	All preclinical	n/a

AD models that synaptic loss, an early component of neurodegeneration, was mediated by complement activation [25,47]. Other AD animal model findings are confusing; deficiency of complement component C3 or brain expression of a C3 inhibitor increase amyloid pathology in an amyloidosis model, but more recent studies, while confirming increased amyloid load, found that C3 deficiency protects against neurodegeneration and cognitive decline [48,49].

The BBB comprises an interacting unit of endothelial cells, pericytes, and astrocytes enmeshing the brain vasculature to restrict the passage of cells and molecules into and out of the brain (Figure 2). In preclinical and early AD, the BBB is grossly intact, although some studies suggest subtle damage even at these earlier stages [50,51]. Whether intact or subtly damaged, the BBB represents a challenge for AD therapy; for example, brain levels of peripherally delivered mAb drugs are typically 1000-fold lower than in plasma or other organs [52]. Nevertheless, several mAb therapies have been tested in AD, particularly to remove amyloid; the FDA recently approved the anti-amyloid mAb aducanumab for AD, albeit on tenuous evidence of efficacy [53]. Although first proposed 20 years ago [54], no anticomplement drugs have yet been tested in AD. The mAb-based anticomplement drugs administered peripherally are unlikely to achieve sufficient brain levels to have an impact and current small molecule agents were not designed



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Figure 2. Architecture of the blood–brain barrier. The brain vasculature has evolved an efficient barrier to restrict the passage of cells and molecules into and out of the brain; this, combined with numerous transport systems, protects brain health and homeostasis. Brain microvascular endothelial cells, fastened together by tight junctions and sitting on a basement membrane, line the luminal side of the vessel, while pericytes and foot processes of astrocytes coat the abluminal surface. The figure was made using BioRender (<https://app.biorender.com>).

for BBB penetrance. It is likely that new and/or modified anticomplement drugs will be needed for AD therapy; strategies to address this are discussed later.

The synucleinopathies: PD, dementia with Lewy bodies, and multisystem atrophy

The synucleinopathies are NDDs characterised by intraneuronal aggregates of **α -synuclein**, a neuronal synaptic transport protein; aggregates grow to form dense Lewy bodies [55]. Precisely how the production/presence of these aggregates causes neuronal loss remains unclear. PD, the commonest of the synucleinopathies (UK prevalence 1:450), presents with movement disorders, typically tremor, slowing of movement, stiffness, and gait problems. Subtle changes, notably loss of smell and disrupted sleep, may precede more obvious symptoms by up to 10 years. Mild cognitive impairment is common but progression to clinical dementia unusual. The cornerstone of drug therapy for 60 years has been levodopa. By increasing brain dopamine levels, levodopa has a remarkable effect on movement disorder symptoms in most patients; however, the efficacy wanes with long-term treatment. Other available drugs also target dopamine signalling either acting as agonists or reducing dopamine breakdown in the brain.

Complement activation products were first reported in PD brain over 40 years ago [56,57]. A comprehensive study of complement activation in PD reported that neurons and Lewy bodies in the substantia nigra were strongly positive for the complement markers **iC3b** and C9, indicative of ongoing complement dysregulation [58]. A recent *in vitro* study showed that α -synuclein aggregates bound C1 and directly activated complement; when overexpressed in a neuronal cell line, α -synuclein triggered complement activation and cell killing [47]. Evidence that complement is a primary driver of neurodegeneration in PD is lacking; nevertheless, parallels with AD suggest a role for anticomplement therapies. As with AD, the BBB in PD is grossly intact, although a recent imaging study showed significant BBB disruption in later-stage PD patients [59]. It is therefore likely that constraints described above for anticomplement drugs in AD also apply to PD and other synucleinopathies, requiring new agents that cross the BBB.

HD

HD is an autosomal dominant NDD disease caused by triplet (CAG) expansions in the gene encoding huntingtin; mutant huntingtin protein interferes with multiple signalling pathways to cause neuronal damage and death [60]. Inflammation in the brain or the periphery has been demonstrated as an exacerbating factor and flagged as a target for therapy [61]. Evidence from animal models also implicated inflammation in HD pathology [62] and genetic analyses identified disease-associated inflammatory pathways [63]. One study described C1q, C4, C3, iC3b, and MAC deposition on neurons, myelin, and astrocytes in HD striatum, evidence of complement dysregulation in the HD brain [64]. Annexon recently initiated a Phase II trial of their anti-C1q mAb ANX005 in at-risk or early-HD patients, due to report mid-2022. Further work is merited to establish whether and when complement contributes to inflammation and cell damage in HD, essential to support a case for future treatment strategies.

ALS

ALS is a rare NDD specifically affecting motor neurons, the most common of a group of NDDs termed motor neuron diseases. The UK prevalence is between 6.2 and 8.6/100 000 [65]. Individuals present, usually in middle age, with muscle weakness or stiffness that gradually progresses to affect all voluntary muscles; most die of respiratory failure within ~5 years of diagnosis. A proportion of cases develop cognitive impairment; there is significant overlap with frontotemporal dementia [66]. A small minority of cases are monogenic, familial while the large majority (95%) are spontaneous and polygenic. Although several genes have been implicated in both familial and spontaneous

ALS, the precise mechanisms leading to selective loss of motor neurons remain unclear. Current therapies are symptomatic and none affects the relentless disease progression.

Inflammation has long been recognised as a component of ALS pathology; anti-inflammatory drugs have been suggested for the treatment of ALS but none has progressed to the clinic [67]. Evidence implicating complement was provided by ALS mouse models; C1q and C3 were upregulated in the spinal cord, neurons and endplates were decorated with C1q and C3 fragments, and an anticomplement drug prolonged survival [68,69]. In human ALS tissue, complement activation products localised in areas of pathology, implicating complement dysregulation in the disease process [70,71]. This has in turn focussed attention on the use of anticomplement drugs. BBB and **blood–spinal cord barrier (BSCB)** disruption occurs early in ALS, likely preceding neuronal loss [72]. This raises the prospect of using current BBB impermeant anticomplement drugs in ALS; four have already advanced to clinical trials in ALS: Annexon's anti-C1q mAb ANX-005, Appellis's C3-blocking peptide empaveli, Alexion's anti-C5 mAb ravulizumab, and UCB's C5-blocking peptide zilucoplan (Table 1). Disappointingly, ravulizumab failed to achieve endpoints in Phase III leading to termination of the trial in August 2021. Perhaps BBB/BSCB-penetrant anticomplement drugs, as mooted above for AD/PD, would be more effective in ALS, particularly in early disease.

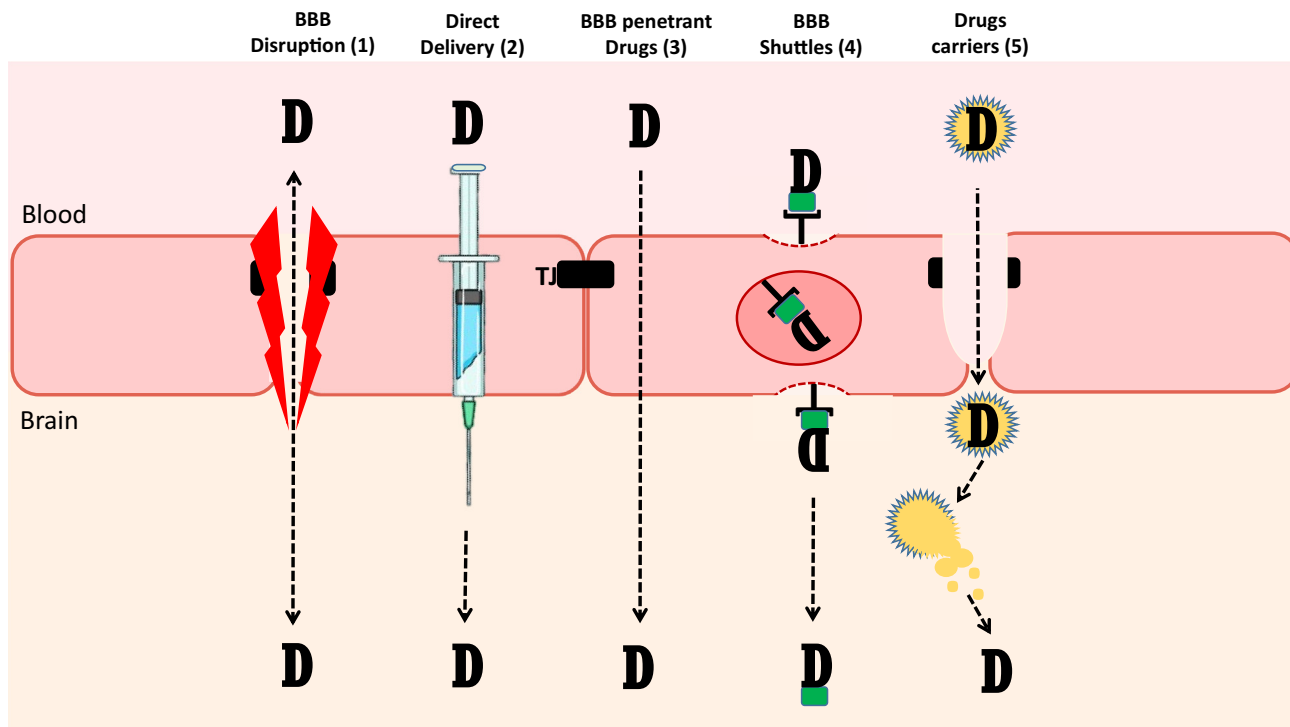
Getting anticomplement drugs into the brain

Although peripheral complement dysregulation may contribute to neuroinflammation in some NDDs, most of the action is in the brain; treatment thus requires anticomplement drugs that can access the brain. The BBB is a highly selective diffusion barrier formed by brain microvascular endothelial cell tight junctions, pericytes, astrocytes, and associated basement membranes (Figure 2). This barrier plays a fundamental role in maintaining brain homeostasis, essential for the healthy function of neurons. It protects the brain from the entry of pathogens, toxins, blood proteins, and immune cells, but also prevents the entry of most systemically administered drugs. Ions and salts pass between barrier cells (paracellular); small lipophilic molecules pass through the cells (transcellular). The entry of other molecules requires active processes, specific endothelial cell transporters that shuttle cargo from luminal to abluminal endothelial surfaces. These include the protein/peptide transporters transferrin receptor and insulin receptor.

Because current anticomplement drugs do not cross the BBB/BSCB, systemic delivery of these agents is unsuitable for targeting complement dysregulation in most NDDs. The problem of obtaining efficient CNS drug delivery has received enormous attention over recent years, particularly in pain therapy and cancer treatment; strategies developed to date include: (1) temporary disruption of the BBB to let drug in using physical methods (osmotic shock, ultrasound) or chemical agents including bradykinin analogues; (2) delivering the drug directly into the CNS to circumvent the barrier, either into the CSF or directly into the brain parenchyma; (3) the development of drugs with appropriate chemical properties to efficiently cross the barrier; (4) the use of 'shuttles' to smuggle drug into the brain; and (5) loading of drugs (including siRNA drugs) in nanovesicles or nanoparticles that cross the barrier (Figure 3). These approaches are reviewed elsewhere [73,74]; here we specifically address those relevant to complement therapies.

Direct delivery of current anticomplement drugs into the CNS

Direct delivery of drug into the CNS requires the insertion of a needle (in some form) into the CSF space or CNS parenchyma. These are complex and potentially dangerous approaches, justified for one-off delivery of an imaging agent or acute treatment of, for example, CNS infections, but hard to contemplate for chronic NDDs. To target specific brain areas, convection-enhanced drug delivery has proved effective; a catheter is placed into the relevant brain area and fluid



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Figure 3. Routes of drug delivery across the blood–brain barrier (BBB). The BBB represents a significant challenge for drug delivery to the brain in neurodegenerative diseases (NDDs). Most drugs do not cross from the blood in significant amounts. The exceptions are small lipophilic drugs that cross by transmembrane diffusion (Route 3 in the figure); none of the current anticomplement drugs has this capacity. The simplest (and crudest) way to deliver a drug is to breach the barrier using physical or chemical agents; for example, localised ultrasound or enzymes (Route 1). The barrier can also be subverted by injecting the drug directly into the cerebrospinal fluid (CSF) or the central nervous system (CNS) (Route 2); numerous devices have been developed to do this in other disease contexts. Increasingly, drugs are modified to hitch lifts on transporter systems (e.g., TfR) in the BBB – so-called ‘Trojan horse’ methods. These shuttle the drug across the barrier and (with good design) release it in the CNS (Route 4). Drugs can also be packaged in vesicles [extracellular vesicles (EVs) or nanovesicles] or on nanoparticles that can cross the barrier and deliver the drug, an area of major interest currently (Route 5).

pressure gradients and bulk flow in the interstitial fluid distribute the drug widely in the brain [75]. Ingenious devices have been developed for sustained CNS drug delivery; for example, drug pumps delivering intrathecally over long periods have been widely used in pain relief for decades, although not without complications [74]. Apellis recently reported preclinical testing of intrathecal pump delivery of a C3 blocker (<https://investors.apellis.com/events-and-presentations>). Remarkable as they are, it seems unlikely that these interventional approaches would be broadly appropriate for anticomplement drugs in common NDDs.

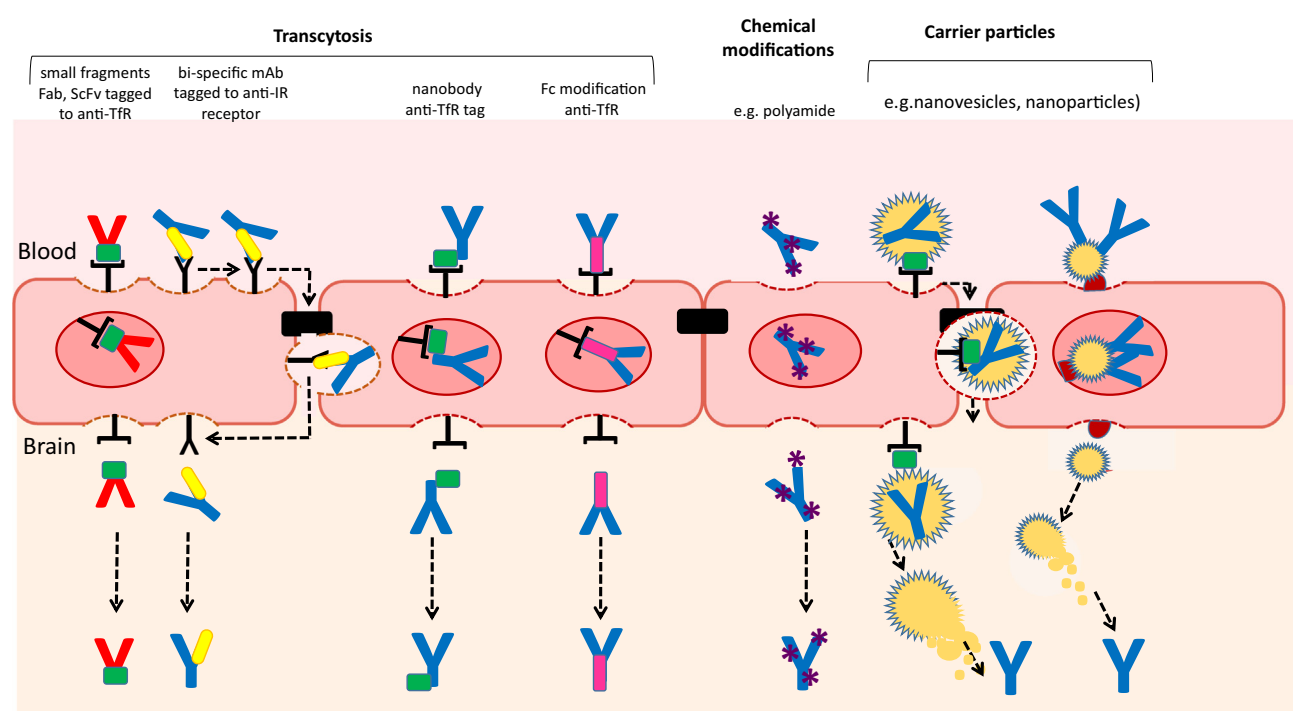
Opening the BBB to let the anticomplement drug in

Numerous methods are described to transiently disrupt the BBB to allow drugs to enter the brain. In AD, focused ultrasound was shown to facilitate brain drug delivery by transient barrier disruption without worsening cognitive symptoms. Osmotic opening of the BBB by intracarotid infusion of hypertonic sugar solutions allowed the entry of peptides, antibodies, and other large molecules [76]. More prolonged, reversible BBB opening can be achieved by the use of bradykinin analogues such as RMP-7 [77]. While they are promising for one-off delivery of long-acting agents such as RNA-based drugs, the need for frequent dosing makes these approaches unviable for other anticomplement drugs.

Modifying current anticomplement drugs to enhance brain penetrance

Given the preponderance of mAbs among current anti-complement therapeutics, modifications enabling mAbs to cross the BBB are relevant (Figure 4). Chemical modification is the simplest way of increasing mAb BBB penetrance [78,79]. Polyamine modification using natural polyamines such as putrescin or cationisation by carbodiimide modification increases BBB penetrance by altering the mAb charge. Chemical modifications may in some instances markedly reduce drug activity or introduce nonspecific associations with plasma proteins, but the major limitation is that conferred increases in BBB penetrance are modest, making it difficult to reach therapeutic levels in the brain.

'Trojan horse' methods for smuggling protein drugs across the BBB involve hijacking receptor-mediated transport; for example, utilising brain endothelial cell receptors [80–82]. Therapeutic mAb or antibody fragments conjugated with receptor-binding antibody fragments to generate bispecific agents, or tagged with recently described receptor ligand peptides, are efficiently delivered into the brain, as shown over a decade ago for a bispecific mAb targeting BACE1 and the transferrin receptor [83]. mAb Fc engineered to generate a transferrin receptor binding site showed enhanced CNS uptake and pharmacodynamics [84]. Receptor affinity in these constructs is critical to efficient delivery, requiring the identification of the affinity 'sweet spot' to



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Figure 4. Delivering anticomplement antibodies across the blood–brain barrier (BBB). The majority of current anticomplement drugs are antibodies: large proteins with minimal BBB penetrance (typically attaining ~1/1000th of systemic levels). If such agents are to be used in neurodegenerative diseases (NDDs), efficient delivery methods are needed. Hijacking of brain endothelial shuttle systems is a proven method for other antibody therapeutics. Anticomplement monoclonal antibodies (mAbs), either intact or active fragments, can be tagged with shuttling receptor-binding peptides or antibody fragments (1; TfR as example), generated as a bispecific mAb with one 'arm' anticomplement and the other antireceptor [2; insulin receptor (IR) as example], or linked recombinantly to an antireceptor nanobody (3; TfR as example). Specific amino acid modifications in the anticomplement mAb Fc can confer TfR binding (4). For all of these methods, receptor binding affinity is crucial to ensure that the agent is released from the receptor in the central nervous system (CNS). Simple chemical modifications (5) can enhance delivery to a minor degree, likely to be insufficient for anticomplement mAb in most contexts. Packaging in vesicles or on particles to shuttle across the BBB (6) is a rapidly evolving area and potential direction of travel for anticomplement mAb drugs.

maximise delivery; for example, bispecific mAbs with reduced transferrin receptor affinity showed efficient transport into mouse brain while high-affinity mAbs were trapped in the BBB [85]. Other potential transporters include the receptor for melanotransferrin [86]; melanotransferrin has a very low abundance in plasma and relatively low affinity for its receptor, implying that it may not compete with drugs utilising its receptor. New peptide delivery systems are emerging; for example, the 19-residue peptide angiopep-2 binds the receptor LRP1 and efficiently delivers mAb fragments, currently progressing for therapy in glioblastoma [87].

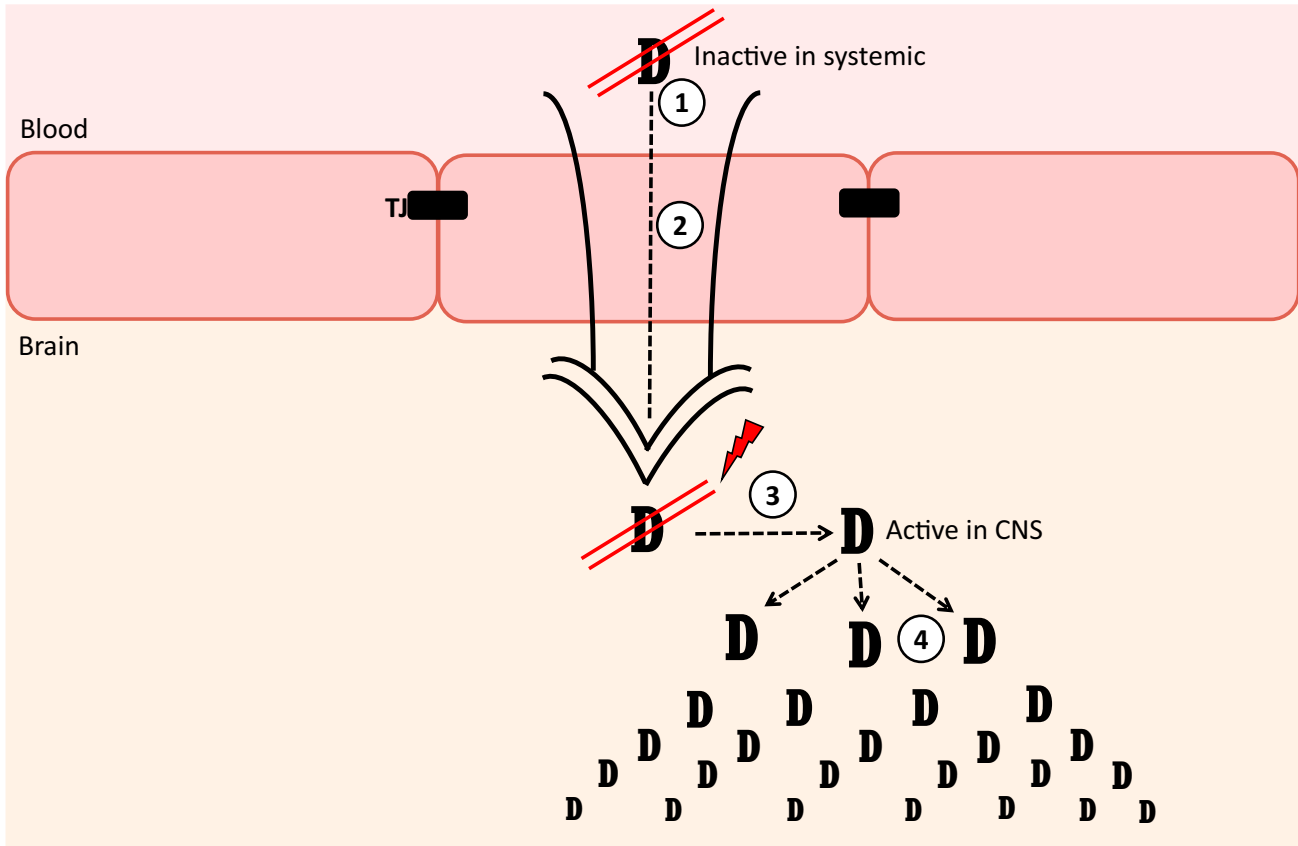
For any anticomplement drug given systemically for brain delivery, consideration needs to be given to the 'sink effect'; abundant plasma complement proteins will bind the drug before it can be delivered to brain. For example, a brain-targeted anti-C5 mAb will become saturated with C5 in the periphery, neutralising its function before brain entry. Strategies such as delivering unmodified anticomplement mAbs to pre-saturate the systemic target prior to administration of the BBB-modified mAb might help, but better would be to have anticomplement prodrugs that are active only after crossing the barrier – a challenge for future drug design. One possibility, achievable with current anticomplement drugs, is to package them for release once in the CNS. Therapeutic mAbs and mAb fragments can be encapsulated in CNS-targeted vesicles – for example, extracellular vesicles – for efficient delivery [88]. Extracellular vesicles are made by all cell types and coordinate cell–cell communication; they can cross the BBB in both directions. Exosomes show particular promise for drug delivery because of their stability and biocompatibility. Challenges around efficient targeting to the brain and the timely release of drug cargo in the brain remain to be resolved.

Designing new anticomplement drugs for therapy in neurodegeneration

From the discussion above, the properties of an ideal anticomplement drug for the treatment of NDDs can be readily listed. The drug should, when delivered systemically: (1) have little or no systemic activity; (2) efficiently enter the CNS across the intact BBB/BSCB and achieve levels sufficient to block complement activation; (3) activate to bind its target only after delivery into the CNS; (4) distribute widely across the CNS parenchyma; and (5) be retained in the CNS in an active form for prolonged periods (Figure 5). These represent considerable hurdles in drug design and it is likely that progress will be incremental.

Current small molecule inhibitors offer the simplest opportunity for rapid progress through redesign, incorporating features that increase BBB penetrance, guided by computational tools that predict drug penetrance [89]. Peptide-based anticomplement drugs could simply be linked to BBB-penetrating peptides of the sort described earlier for delivery or redesigned to capture features that enhance BBB penetrance. For mAbs and other protein anticomplement drugs, conjugation with shuttling antibodies or peptides is likely to be a first option, although the incorporation of shuttling receptor binding properties within the mAb itself is a compelling strategy [82]. New drugs not subject to the 'sump effect' described earlier would be game changing for CNS delivery; here, agents that target complement enzymes and activation complexes rather than native components are an attractive approach [90].

We have deliberately omitted discussion of RNA-based anticomplement drugs and gene therapy approaches from the earlier text; however, in discussing new agents for NDDs they are hard to ignore. Knocking down the production of complement components or increasing the production of complement regulators in the CNS might prove an effective approach. There has been a considerable pharma effort to design such drugs, particularly for use in age-related macular degeneration [91]; lessons learned in this ocular NDD may inform future strategies in NDDs in general.



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Figure 5. Properties of an ideal anticomplement drug for neurodegenerative disease (NDD) therapy. The ideal anticomplement drug for therapy in NDDs would: (1) have little or no anticomplement activity in the systemic environment, both to avoid the 'sump effect' of plasma complement proteins and to reduce the risks of systemic complement inhibition; (2) efficiently traverse the blood–brain barrier (BBB) by either diffusion or the engagement of shuttles as described; (3) become activated once in the environment of the central nervous system (CNS); and (4) diffuse widely in the brain parenchyma to suppress complement activation over a broad area.

How to do it: selecting the right target, treating at the right stage of disease, and minimising risks associated with anticomplement drug therapy in NDDs

Although to date the anticomplement drug arena has been dominated by agents targeting C5, complement presents numerous drug targets [14,15]. Drugs targeting individual activation pathways (CP, LP, AP), the lynchpin molecule C3, or the MAC downstream of C5 are all in development or the clinic. Optimal therapy for a specific NDD requires the identification of the right target for that disease, which is likely to differ for different NDDs. Knowledge of when pathological complement dysregulation occurs during the disease course is also essential for effective treatment; for example, inflammation and complement dysregulation are early events in AD so treatment of late disease is unlikely to be effective [92]. Both of these requirements can be addressed using biomarkers to identify in a specific NDD which complement pathways are activated and when in the disease course. In AD, considerable effort has been invested in identifying plasma complement biomarkers that aid diagnosis and/or predict the disease course to inform the selection of patients with clear evidence of complement dysregulation for inclusion in trials [93,94]. Optimised marker sets would identify complement dysregulation early, pinpoint targets for intervention, and provide a measure of the efficacy of the drug.

As in other settings, the major risk of blocking complement activation in the CNS is infection; the infection risk depends on the stage of inhibition, with early inhibition posing the highest risk. This is likely to be an even bigger concern in the CNS where infections are life-threatening, rapidly progressive and often present with nonspecific symptoms [95]. In other contexts, the infection risk of anticomplement therapies is managed using prophylactic antibiotics and immunisation [96]; similar precautions will be needed with CNS-targeted complement inhibition, using appropriate brain-penetrant antibiotics [97]. A second risk, specific to drugs acting at or before C3 cleavage, is loss of the opsonic activity essential for clearance of debris; this may be particularly important in the CNS, where local elimination systems are crucial because of its isolation. Garbage accumulation may trigger more inflammation and damage that, in the context of NDDs, could cause disease exacerbation with long-term treatment; in AD-model mice, brain expression of a C3 convertase inhibitor caused accelerated amyloid pathology [25,48]. The risks, while significant, are likely to be manageable with appropriate selection of the drug target and attention to prophylaxis and monitoring.

Concluding remarks and future perspectives

There is now a compelling body of evidence implicating complement dysregulation in NDDs. With the notable exception of NMO, where anticomplement drugs have rapidly become the standard of care, and ongoing trials in ALS, another rare disease, efforts to test complement blockade in NDDs are lacking. There is an understandable reluctance to progress to testing in AD and other common NDDs where trials are difficult, expensive, and lengthy, but given the unmet need, the potential for targeting complement cannot be ignored. By contrast, it is hard to understand the lack of enthusiasm to test anticomplement drugs in MS, where there is unmet need in primary progressive disease, the role of complement is clear, and the example of NMO shows the potential impact.

Regardless of the target, anticomplement drug use in NDDs will require new or modified drugs that enter the CNS efficiently (see [Outstanding questions](#)). This is a well-trodden path in other therapeutic areas such as pain management and cancer therapy; innovations used in these areas can readily be recycled for anticomplement drug design. Other inhibitors of progress include cost, difficulty of administration, and perceived risk of iatrogenic harm; ongoing developments in anticomplement drugs for systemic diseases will soon address many of these issues.

Declaration of interests

No interests are declared.

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Outstanding questions

Is complement dysregulation a feature of the early/preclinical stages of NDDs, and can this be identified in screening?

Can current anticomplement drugs be modified to efficiently cross the intact BBB?

Can new anticomplement drugs be tailored for BBB penetration?

Can BBB-penetrant anticomplement prodrugs, inactive in the systemic circulation, be designed to minimise systemic effects, eliminate the 'sump effect', and maximise activity in the brain?

Can BBB-penetrant anticomplement drugs be produced at the scale and cost that is required for use in a common, chronic disease?

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