BRAIN
REVIEW ARTICLE

# Next-generation antibody-based therapies in neurology

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Antibody-based therapeutics are now standard in the treatment of neuroinflammatory diseases, and the spectrum of neurological diseases targeted by those approaches continues to grow. The efficacy of antibody-based drug platforms is largely determined by the specificity-conferring antigen-binding fragment (Fab) and the crystallizable fragment (Fc) driving antibody function. The latter provides specific instructions to the immune system by interacting with cellular Fc receptors and complement components. Extensive engineering efforts have enabled tuning of Fc functions to modulate effector functions and to prolong or reduce antibody serum half-lives. Technologies that improve bioavailability of antibody-based treatment platforms within the CNS parenchyma are being developed and could invigorate drug discovery for a number of brain diseases for which current therapeutic options are limited. These powerful approaches are currently being tested in clinical trials or have been successfully translated into the clinic. Here, we review recent developments in the design and implementation of antibody-based treatment modalities in neurological diseases.

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**Abbreviations:** ADAs = antidrug-antibodies; Abdegs = antibodies that enhance IgG degradation; ADCC = antibody-dependent cell-mediated cytotoxicity; Fc = crystallizable fragment; IR = insulin receptor; ITP = immune thrombocytopenia; FcγR = Fc receptor; FcRn = neonatal Fc receptor; IVIg = intravenous immunoglobulins; (m)Abs = (monoclonal) antibodies; NMOSD = neuromyelitis optica spectrum disorder

## Introduction

Therapeutic antibodies can be separated into two broad categories. The first category comprises intravenous immunoglobulins (IVIg), a preparation of polyclonal serum IgG pooled from thousands of blood donors; recombinantly produced monoclonal antibodies (mAbs) represent a second category.[1] While IVIg products have been used to treat neurological disease conditions such as epilepsy or neuromuscular diseases since the 1980s,[2] it was not before 2004 that mAbs received regulatory approval for a neurological indication. Natalizumab, marketed as Tysabri®, was the first mAb to be approved in the USA and Europe for the treatment of multiple sclerosis.[3] The distinction between both categories started to blur with the technological development of recombinant replacement products for IVIg, based on progress in our understanding of IVIg's mechanisms of action and the subsequent use of these technologies to additionally improve mAbs. So far, mAbs and IVIg are used for treating a wide and

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growing spectrum of neurological diseases (Table 1), and neurological disease conditions are among the most frequent non-cancer indications for testing the safety and efficacy of new Ab-based treatment platforms.[4,5] All of the compounds discussed in our article are designed based on the structure and function of Abs. Since there is no specific term to encompass all the newly developed Ab-based drugs, we chose the term 'Ab-based therapeutics' for simplicity reasons to cover all Ab- and recombinant Ig-domain-based molecules. Here, we illustrate the biology of Ab-based therapeutics and highlight new technologies that could reinvigorate drug discovery for a number of brain diseases for which current therapeutic options are limited.

## Harnessing IgG-Fc biology to improve therapeutic antibodies

The design and clinical implementation of therapeutic antibodies are principally based on the biological functions of IgG molecules that confer protection against infectious diseases. Immunoglobulins evolved to specifically recognize target structures (antigens) mediated by the fragment antigen-binding (Fab) domains, while the fragment crystallizable (Fc) domain contains the binding sites for immune effector molecules such as the C1q component of the complement system and through binding to Fc receptors. (Fig. 1).[6] In the context of infectious diseases, the Fab domain may directly prevent infection by neutralizing pathogens.[7] The Fc domain triggers immune effector functions by interacting with Fc receptors, c-type lectins or the complement system to ensure that antibody-opsonized material can additionally be visualized and appropriately eliminated by the immune system.[8] The same principles apply to monoclonal and polyclonal therapeutic antibodies. Their simplest mode of action is to bind to target molecules and thereby interfere with their activity and interaction with binding partners. However, even those mAbs specifically produced to block soluble or membrane-bound target molecules elicit Fc-mediated effector functions as long as they contain a

**Table 1 Antibody-based treatments in neurological diseases**

| Indications | Antibody/FDA approval | Molecular target | IgG subclass; Fc variant; Fc function | Key references |
|---|---|---|---|---|
| Alzheimer's disease | Aducanumab/2021 | Aggregated amyloid-β | Human IgG1; n/a; binds aggregated amyloid-β forms | Sabbagh *et al.*[112] |
| CIDP/on-label<br>GBS/off-label<br>MMN/on-label<br>MG/off-label<br>LEMS/off-label<br>Myositis/off-label | Intravenous Immunoglobulins/ off-label | Immune modulation | All subclasses; n/a; pleiotropic effects | Chen *et al.*[2] Lünemann *et al.*[115] |
| Glioblastoma | Bevacizumab/2017 (not approved by EMA) | VEGF | Humanized IgG1k; n/a; binds VEGF | Wick *et al.*[116] Friedman *et al.*[117] |
| Migraine | Erenumab/2018 | CGRP receptor | Human IgG2; n/a; competes for binding to CGRP receptor | Dodick *et al.*[118] Goadsby *et al.*[119] Reuter *et al.*[120] |
| Migraine | Fremanezumab/2018 | CGRP | Humanized IgG2; n/a; binds CGRP | Ferrari *et al.*[121] Silberstein *et al.*[122] Dodick *et al.*[123] |
| Migraine/cluster headache | Galcanezumab 2018 and 2019 | CGRP | Humanized IgG4; S228P, F234A, L235A; binds CGRP | Detke *et al.*[124] Skljarevski *et al.*[125] Stauffer *et al.*[126] Goadsby *et al.*[127] Dodick *et al.*[128] |
| Migraine | Eptinezumab/2020 (not yet approved by EMA) | CGRP | Humanized IgG1; N297A; binds CGRP | Lipton *et al.*[129] Silberstein *et al.*[130,131] |
| NMOSD<br>MG | Eculizumab/2019 and 2017 | Complement factor 5 (C5) | Humanized IgG2/4; IgG2 until T260, then IgG4; binds and inhibits cleavage of C5 | Pittock *et al.*[132] Howard *et al.*[133] Muppidi *et al.*[134] |
| NMOSD | Inebilizumab/2020 | CD19 | Humanized IgG1k; afucosylated; ADCC | Cree *et al.*[135] |
| NMOSD | Satralizumab/2020 | IL-6 receptor | Humanized IgG2; SMART-Ig®; binds membrane-bound and soluble IL-6 receptors | Traboulsee *et al.*[27] Yamamura *et al.*[29] |
| RRMS | Natalizumab/2004 | Integrin α4β1 | Humanized IgG4k; n/a; binds α4β1 | Yednock *et al.*[136] Rudick *et al.*[137] Polman *et al.*[138] |
| RRMS | Alemtuzumab/2013 | CD52 | Humanized IgG1κ mAb; n/a; ADCC > CDC | Ruck *et al.*[139] Cohen *et al.*[140] Coles *et al.*[141] |
| RRMSPPMS | Ocrelizumab/2017 and 2017 | CD20 | Humanized IgG1; n/a; ADCC | Hauser *et al.*[9] Bittner *et al.*[142] Montalban *et al.*[143] |
| RRMS/off-label<br>NMOSD/off-label<br>MG/off-label<br>Myositis/off-label | Rituximab/off-label | CD20 | Chimeric IgG1k; n/a; ADCC + CDC | Yamout *et al.*[144] De Flon *et al.*[145] Hauser *et al.*[146] Cabre *et al.*[147] Nikoo *et al.*[148] Nowak *et al.*[149] Díaz-Manera *et al.*[150] Stieglbauer *et al.*[151] Oddis *et al.*[152] |

CDC = complement-dependent cytotoxicity; CGRP = calcitonin-gene related peptide; CIDP = chronic inflammatory demyelinating polyneuropathy; EMA = European Medicines Agency; FDA = Food and Drug Administration; GBS = Guillain–Barré syndrome; IL = interleukin; LEMS = Lambert–Eaton myasthenic syndrome; MMF = multifocal motor neuropathy; MG = myasthenia gravis; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis. A fucosylation of the Fc glycan increases the FcγRIIIA binding affinity and enhances ADCC.[59] The S228P Fc mutation increases stability by abolishing formation of half antibody molecules. F234A/L235A/N297A mutations and IgG2/4 fusion lead to reduced FcγR and C1q (complement) binding.[95,153] SMART-Ig® increases FcRn binding at pH 6.0 and increases half-life.

functional Fc domain.[8] Other mAbs, for example, CD20-targeting antibodies, are specifically designed to recruit immune effectors through their Fc domain after binding to their target epitopes.[9] Cell-depleting therapeutic IgG antibodies such as those targeting B lineage cells lyse target cells through at least three mechanisms: antibody-dependent cell-mediated cytotoxicity (ADCC) triggered by signalling through activating Fc receptors (FcγRs) expressed by cytotoxic innate immune effector cells, including natural killer cells or myeloid cells; complement-dependent cytotoxicity through binding of C1q, which initiates activation of the classical complement pathway and antibody-dependent cellular phagocytosis mediated by phagocytes recognizing opsonized target cells.[10] *In vitro* assays provided evidence that all of the described Fc-mediated effector mechanisms may contribute to the depleting efficacy of a single mAb.[11] To what extent these different effector mechanisms contribute to cell-depleting or, in general, therapeutic Ab activity *in vivo* is less well understood and might depend on the disease condition treated and on the organ environment in which the antibody mediates its activity. It has become clear across many preclinical animal model systems that cytotoxic antibody binding to cellular FcγRs is critical for their therapeutic activity *in vivo*.[12,13] New developments in Fc-engineering technologies are now being used to specifically address and improve particular effector functions and to create entirely new Ab-based therapies. Improving access to the CNS by mAb modifications is another important target for Ab- and Ig-domain-based therapies (see section 'Evolving strategies to overcome the blood–brain barrier').

## IgG-Fc engineering generates a growing repertoire of antibody-based therapeutics

The costs of producing entire multimeric therapeutic antibodies and the supply shortages for IVIg generated an urgent need for alternatives. The most promising developments are: first, recombinant antibody preparations that degrade IgG; second, multimeric IgG-Fc preparations that block binding to activating Fcγ receptors and finally, IVIg preparations with enhanced levels of anti-inflammatory sialic acid-rich IgG glycovariants (sIVIg). Similar Fc-engineering technologies have been applied to modify therapeutic mAbs. These developments will be outlined next.

### Targeting degradation

The neonatal Fc receptor (FcRn) is a major histocompatibility class I-related receptor responsible for the transfer of humoral immunity from the mother to the newborn. Throughout life, FcRn contributes to effective humoral immunity by recycling IgG and extending its half-life in the circulation (Fig. 2). The receptor, mainly expressed by endothelial and myeloid cells, binds tightly to the Fc portion of IgG at acidic pH (pH 6.0) but not at physiological pH (pH 7.4). The cells internalize serum IgG, which binds to FcRn in an acidic endosomal compartment. FcRn then recycles IgG back to the cell surface where it releases IgG at physiological pH, thus extending its serum half-life, which ranges between 3 and 4 weeks, the longest of any plasma protein.[14] The rate of FcRn-mediated IgG recycling has been estimated to be 40% greater than the rate of IgG production, indicating that recycling of IgG, and not its production, is the dominant process for maintaining the IgG plasma concentration in humans.[15] Serum proteins that do not bind to a recycling receptor are destined for lysosomal degradation.[14] FcRn-mediated recycling can be blocked therapeutically by Abdegs (Abs that enhance IgG degradation). Abdegs are engineered to have Fc regions that bind to FcRn with an unusually high affinity at both near neutral and acidic pH, thereby out-competing endogenous antibody binding to FcRn and forcing the rapid catabolism of pathogenic antibodies.[16] One

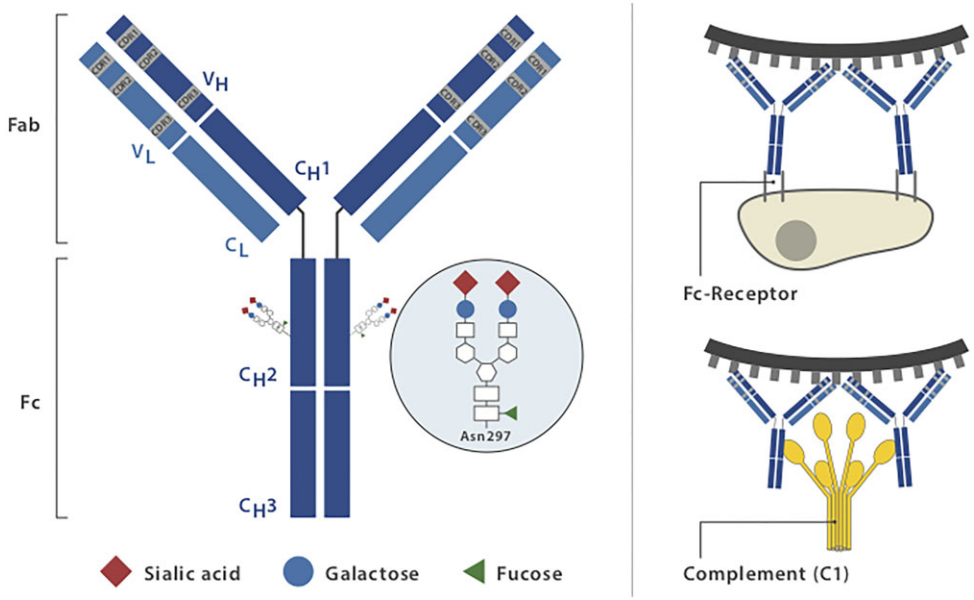


**Figure 1 Structure and effector functions of immunoglobulin G (IgG).** IgG is composed of two heavy and two light chains linked by disulphide bonds. The antigen-binding fragment (Fab) consists of two moieties with identical structures, which define the antigen-specificity through their complementarity-determining regions CDR), highlighted in grey. The crystallizable fragment (Fc) mediates antibody effector functions through binding to Fc receptors and interaction with the C1q component of the complement system. A highly conserved IgG-Fc *N*-glycan (Fc glycan) is attached to each of the asparagine 297 (N297) residues in the CH2-domains of the two Fc fragments. The Fc glycan has an essential role on Ab structure and function. Its common core-structure consists of an N-acetylglucosamine (GlcNAc) attached to the asparagine, to which a second GlcNAc and three mannoses are attached. This core can be further extended by a bisecting GlcNAc attached to the core mannose (not shown) as well as by galactose (blue circle), sialic acid (red diamond) and fucose (green triangle) residues.

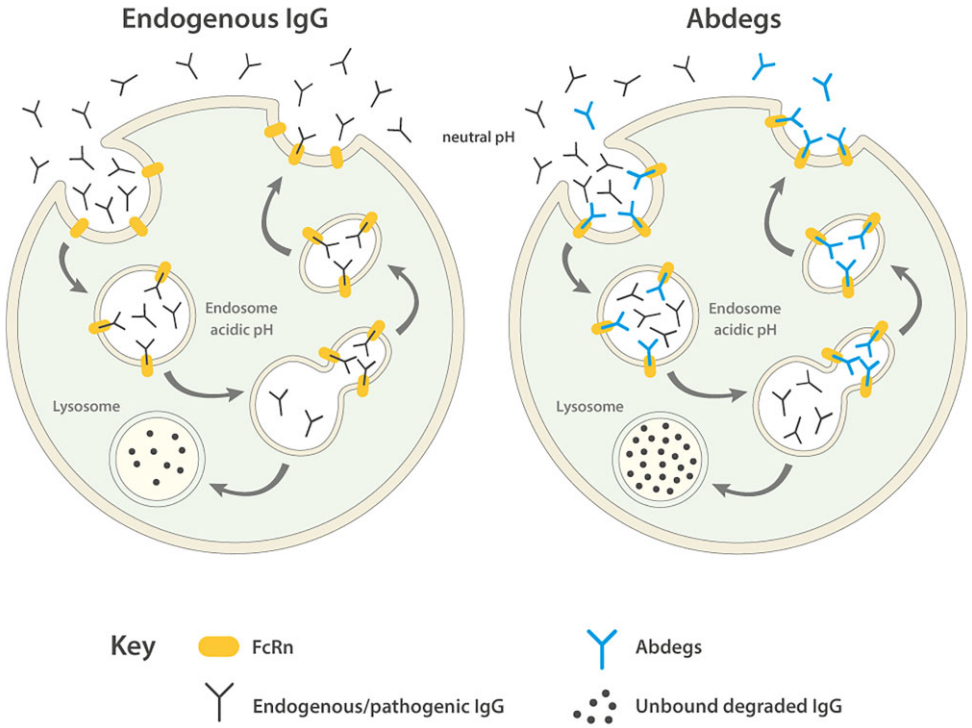


**Figure 2 Harnessing FcRn function through Abdegs.** IgG enters cells by fluid-phase pinocytosis in small tubulovesicular transport carriers that fuse with larger, FcRn-positive early acidic endosomes in which binding to FcRn can occur. Bound IgG molecules are recycled and released by exocytosis, involving the fusion of recycling compartments with the plasma membrane. By contrast, IgG that does not bind to FcRn in sorting endosomes enters lysosomes and is degraded. Abdegs bind to FcRn with an increased affinity at both near neutral and acidic pH and compete with endogenous IgGs for FcRn binding in acidic endosomes. Consequently, more endogenous IgG molecules are driven into lysosomes and are degraded.

example of an Abdeg is efgartigimod, a recombinant IgG1 Fc portion mutated at five residues to increase FcRn affinity. A single administration of efgartigimod in humans reduced total IgGs by about 50%, while repeated administration at a saturating dose of 10 mg/kg further lowered IgG levels by ~75%.[17] Enhancing the degradation of endogenous IgG might also contribute to the anti-inflammatory efficacy of high doses of IVIg, which oversaturate FcRn.[18] Alternative strategies to interfere with IgG-FcRn interactions are mAbs or antibody variable fragments that block the FcRn binding to IgG, for example, rozanolixizumab or nipocalimab, humanized high-affinity anti-human FcRn monoclonal antibodies or small molecules inhibiting FcRn function.[19,20] To date, the results from studies in non-human primates and clinical trials for several FcRn-based inhibitors indicate that they induce significant and sustained decreases in endogenous IgG levels in healthy volunteers while being safe and well-tolerated, and also have beneficial clinical efficacy in patients with myasthenia gravis, as outlined next (NCT03457649, NCT03971422, NCT03052751).[17,19]

Seldegs (selective degradation of antigen-specific antibodies) have been designed to selectively deplete antibodies of a particular antigen (Ag)-specificity while avoiding global reduction in IgG levels. Seldegs consist of an Ag molecule combined with an Fc domain with increased affinity to FcRn at both near neutral and acidic pH. Consequently, circulating Abs that bind to Ag-Fc fusion proteins are delivered to lysosomes for enhanced degradation. Due to their Ag-specificity, seldegs can be applied at lower doses as compared to the other FcRn-targeting approaches and are, therefore, less prone to lower total IgG levels.[21] While seldegs have been shown to capture Ag-specific antibodies, such as myelin oligodendrocyte glycoprotein (MOG)-targeting antibodies, and direct them into degradative lysosomal compartments *in vitro*,[21] their therapeutic efficacy *in vivo* has yet to be shown.

In principle, those Fc domain modifications promoting FcRn interaction can also be harnessed to increase serum persistence of Ab-based therapeutics resulting in reduced dose and administration frequencies.[22] A strategy that might be of special interest in the treatment of chronic diseases, where—despite their long half-lives—mAb must be administered repetitively. However, Fc domain modifications might also interfere with biological function and clinical efficacy of the mAb. Of note, Fc variants [e.g. YD (M252Y/T256D) DQ (T256D/T307Q) and DW (T256D/T307W)] that improve serum half-life while retaining effector functions *in vitro* by enhanced FcRn binding have already been identified,[23,24] whereas their efficacy *in vivo* awaits evaluation in preclinical disease models.

Lysosomal degradation can also be used to enhance Ab-mediated clearance of antigens. So-called acid-switched antibodies are designed to bind their target antigen with a higher affinity at near-neutral pH than at acidic pH. Ag–Ab complexes enter acidic sorting endosomes in which Ag dissociates from Abs and enters the lysosomal pathway for degradation while the FcRn-bound antibody is recycled.[16] Most acid-switched antibodies have been generated to support degradation antigens that exist in soluble forms, such as the complement factor C5 or interleukin-6 (IL-6), but are also feasible for IL-6R, which can be membrane-bound or soluble.[25,26] One example is satralizumab, an anti-IL-6 receptor monoclonal antibody optimized for FcRn binding and recently approved for the treatment of aquaporin 4

water channel autoantibody (AQP4-IgG) seropositive neuromyelitis optica spectrum disorder (NMOSD).[27,28] In the acidic environment of the late endosomal compartment, satralizumab bound to FcRn dissociates from the IL-6 receptor, is transported back to the plasma membrane and released from FcRn, ready to bind another IL-6 receptor.[25] The two phase 3 trials SakuraSky (satralizumab as add-on therapy to immunosuppressants) and SakuraStar (satralizumab monotherapy) demonstrated significant reduction of relapse rates in NMOSD for satralizumab treatment compared to placebo. In contrast to other trials, also seronegative NMOSD patients were included, however, SakuraSky did not detect significant reduction of relapse rate in this subgroup.[27,29,30]

## Targeting FcγR signalling

The family of FcγRs consists of several activating members (FcγRIA, IIA, IIC, IIIA and IIIB in humans) and one inhibitory member (FcγRIIB) (Fig. 3). Both activating and the inhibitory receptors are co-expressed on many innate immune effector cells residing in lymphoid organs such as macrophages.[31–33] Thus, Abs and immune complexes (IC) trigger both activating and inhibitory signalling pathways. FcγRIIB is the only FcγR expressed on B cells, in which it transduces an inhibitory signal on colligation with the B cell receptor; among circulating blood cells, FcγRIIB expression levels are highest on B cells and basophils.[31,32,34] The observation that the IgG-Fc fragment is the predominant mediator of the anti-inflammatory activity of IVIg spurred interest in FγR-dependent anti-inflammatory signalling.[35,36] Notably, aged IVIg preparations were found to be more potent in suppressing autoantibody activity in an immune thrombocytopenia (ITP) animal model due to an increase in IgG dimers within the IVIg preparation.[37] Furthermore, the critical role of activating FcγRs in mediating autoantibody activity in humans was demonstrated by a clinical trial using FcγR-specific blocking antibodies to ameliorate autoimmune pathology in ITP patients.[38] On the basis of the aforementioned findings, several groups started to develop recombinant IgG multimers. These synthetic small immune complex (IC-)like molecules bind to cellular FcγRs without triggering cell activation and competitively block the binding of autoantibodies to these receptors.[39] IgG multimers show therapeutic efficacy in experimental animal models of autoimmune neuritis and myasthenia gravis as well as in preclinical models of ITP, inflammatory arthritis and skin blistering diseases.[40–44] Recombinant human IgG-Fc multimers have been developed, and preclinical data support the potential of Fc multimers as a synthetic alternative to IVIg.[45] The mechanisms by which Fc multimers confer their anti-inflammatory activity might well go beyond simply shielding activating FcγR from auto-Abs or pathogenic ICs. Immunomodulatory effects similar to those reported for IVIg have been described in preclinical models, including FcRn blockade, stimulation and upregulation of the inhibitory FcγRIIB, and expansion of regulatory T cells.[44]

Alternative therapeutic strategies to modulate FcγR signalling that are currently being tested in the context of autoimmunity include mAbs directed against activating FcγRs (FcγRI, FcγRIIIA) or the inhibitory FcγRIIB with anti-inflammatory agonistic function. For example, the mAb SM201 recognizes an epitope outside the IgG-binding site of FcγRIIB and mediates IC dependent inhibition of B cells *in vitro*, whereas the antagonistic FcγRI mAb 197 induced clinical improvement and specific down-modulation of FcγRI expression on monocytes in an ITP patient [38,46–48] In contrast, to support anti-tumour immunity, FcγRIIB antagonistic mAb are being developed. For example, a fully human FcγRIIB antagonistic antibody was shown to overcome resistance to and to functionally augment anti-tumour activity of rituximab in chronic lymphocytic leukaemia.[49]

Tyrosine-kinase inhibitors harness effector functions similar to Abs even though they cannot be defined as Ab-based therapeutics. Tyrosine-kinase inhibitors target signalling molecules downstream of Ab-induced crosslinking of activating FcγRs, such as the common FcRγ-chain, the spleen tyrosine kinase (Syk) and the Bruton's tyrosine kinase (BTK). These play a critical role in activating innate immune effector cells and initiating the release of pro-inflammatory cytokines, chemokines and other pro-inflammatory events.[50,51] Therefore, small inhibitory molecules directed to TK have been identified as a potential pathway to block autoimmune inflammation. Spleen tyrosine-kinase inhibitors, for example, fostamatinib, have shown potent activity in blocking ITP in mice and humans (NCT00706342) and have been approved by the FDA for chronic ITP.[52] Along the same lines, BTK inhibitors such as rilzabrutinib have shown promising results in investigational studies in patients with ITP and a phase 3 trial is ongoing (NCT04562766).[53] Other BTK inhibitors showed promising results in patients with relapse-onset multiple sclerosis,[54] resulting in three ongoing phase 3 studies (NCT04338022, NCT04338061 and NCT04586023).

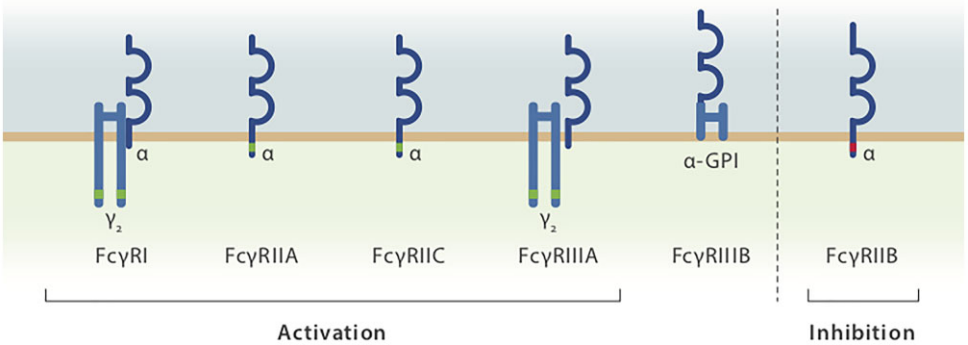


**Figure 3 The human FcγR family.** FcγRIA, FcγRIIA/IIC and FcγRIIIA initiate activating signalling pathways via immune tyrosine-based activation motifs (ITAMs, highlighted in green), whereas FcγRIIB is an inhibitory FcγR carrying an immune tyrosine-based activation motif (ITIM, highlighted in red). FcγRIII lacks a signalling domain. The strength of the signal mediated through both activating and inhibitory FcγRs, which are often co-expressed on inflammatory immune cells, sets the threshold for the initiation of FcγR-dependent effector responses.

### Targeting Fc glycosylation

Glycosylation of IgG-Fc domains contributes to both the stability and biological activity of antibody molecules and is essential for effector functions.[55] The *N*-linked glycosylation at asparagine 297 in the Fc domain of IgG1 is composed of a heptameric core sugar structure with variable amounts of branching and terminal sugar residues such as galactose, sialic acid (SA), *N*-acetylglucosamine and fucose [56] (Fig. 1). Fc glycosylation changes have been exploited in the monoclonal therapeutics field. Removal of fucose from the core biantennary structure of the IgG1 glycan enhances FcγRIIIA binding and ADCC.[57,58] These observations led to the development of so-called glycoengineered, i.e. afucosylated, therapeutic cell-depleting mAbs such as the CD20-targeting antibodies obinutuzumab or ublituximab.[59] Afucosylation has become a clinically approved strategy to improve the efficacy of anti-cancer antibodies through enhanced ADCC.[60,61] Whether enhanced ADCC translates into increased clinical efficacy in neurological diseases as compared to fucosylated CD20-targeting mAbs remains to be shown. Ublituximab is currently being tested in phase 3 clinical trials in patients with relapse-onset multiple sclerosis and has also been investigated in a pilot safety study in patients with aquaporin-4 $IgG^+$ NMOSD (NCT02276963).[62] A potential benefit is that its increased biological efficacy may allow lower doses and shorter infusion times versus other anti-CD20 mAbs.[63]

The addition of terminal sialic acid to the Fc glycan is thought to improve Fc domain binding to non-classical Fc receptors such as lectins and to confer anti-inflammatory activities to IgG molecules.[64,65] In animal models of autoantibody-mediated tissue inflammation, IVIg preparations and isolated Fc fragments enriched for terminal sialic acid residues have a >10-fold higher anti-inflammatory activity than non-enriched preparations, while the removal of sialic acid residues results in reduced immunoprotective activity.[66–68] Despite strong evidence from studies in various model system for an important role of sialylation in the *in vivo* therapeutic activity of IVIg,[69] desialylation of IgG has shown no clinical effect in some animal models of autoimmunity, for example, experimental autoimmune encephalomyelitis (model for multiple sclerosis).[70,71] Recently, highly tetrasialylated IVIg, in which both sugar domains contained the maximal level of two sialic acid residues, were tested for clinical efficacy in comparison to IVIg in a small ITP patient cohort and showed superior clinical efficacy (NCT03866577).[72] To date, no studies have been performed using tetrasialylated IVIg in IVIg-responsive neurological disease.

## Evolving strategies to overcome the blood–brain barrier

Currently, neurological diseases susceptible to Ab-based therapies such as multiple sclerosis or neuromuscular disorders are driven, at least in part, by immune factors accessible outside of the CNS, whereas diseases largely confined to the CNS parenchyma, such as neurodegenerative disease conditions, are less accessible to Ab-based therapies.[73]

Among the largest obstacles to effective CNS delivery is the blood–brain barrier, formed by tight junctions between brain endothelial and epithelial cells that limit the transfer of therapeutic molecules between the blood and the interstitial fluid of the CNS.[73] Large molecules such as Abs can only traverse the blood–brain barrier by receptor-mediated transport through endothelial cells. The transferrin receptor (TfR) and the insulin receptor (IR) expressed by endothelial cells are natural brain portals, and mAbs specific for either one of these receptors could improve the ability of Abs to penetrate the CNS parenchyma.[74–76] Indeed, bi-specific Ab platforms targeting the TfR or IR on the one hand and CNS disease-associated targets such as BACE1 (β-site amyloid precursor protein-cleaving enzyme 1), an enzyme that cleaves the amyloid precursor protein to generate the pathogenic form of amyloid-β in Alzheimer disease, on the other hand, have been developed with promising results in preclinical models.[76–78] The drawbacks of this strategy are that both the TfR and IR are not specific for brain endothelial cells and have essential physiological functions that have raised important safety concerns.[79]

Alternative attempts to use receptor-mediated transcytosis to increase brain uptake of therapeutic Abs with binding sites distant from the natural ligands of TfR or IR are currently being developed and could reinvigorate drug discovery for a number of brain diseases for which current therapeutic options are limited.[80,81]

## Engineering antibody therapeutics to improve treatment safety

mAb side-effects are the result from the interaction with the target protein and/or its function, off-target effects due to antibody polyspecificity or reactions to the foreign proteins by the host immune system.[82]

A prominent example for a target-mediated side-effect of mAb is the cytokine release syndrome, which is often found for cell-depleting mAb such as rituximab and alemtuzumab.[83] The release of cytokines including interferon gamma (IFNγ), tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6) leads to systemic inflammation and corresponding symptoms such as fever, chills and malaise, and might proceed to multi-organ failure.[83] Another prominent target-mediated side-effect in neurology is progressive multifocal leukoencephalopathy (PML) in the context of natalizumab. Natalizumab (Tysabri®) is a recombinant, humanized mAb to integrin α-4 and inhibits the interaction with VCAM-1 (vascular cell adhesion molecule-1) on endothelial cells of the blood–brain barrier. Thereby, natalizumab prevents the transmigration of activated lymphocytes and monocytes into the CNS. The reduced immunosurveillance of the CNS is assumed to be the cause for opportunistic JC-virus infections that cause PML.[84]

Polyspecificity of mAbs describes the binding of multiple epitopes on different antigens by one antibody. The identified main mechanism of polyspecificity are rigid adaptation, conformational flexibility and differential ligand positioning.[82] For rituximab, a nonimmune off-target effect has been reported in recurrent focal segmental glomerulosclerosis after renal transplantation, where it was shown to bind SMPDL-3b (sphingomyelinase-like phosphodiesterase 3b protein) improving podocyte survival.[85] However, whether off-target effects are also associated with clinical relevant adverse events is understudied and has not been investigated in detail so far.

As a reaction to foreign proteins are generated antidrug-antibodies (ADAs) by T cell dependent and independent mechanism. ADAs can bind to the therapeutic antibody, diminish its effect and lead to the formation of ICs. ICs can induce type III hypersensitivities such as serum sickness with fever and lymphadenopathy occurring 6–21 days after drug

administration.[86] Particularly antibodies of rodent origin cause intense ADA responses, however also humanized and fully human mAb can induce ADA responses. For example, around 30% of patients with multiple sclerosis treated with the chimeric rituximab developed ADAs,[87] whereas humanized natalizumab induced ADAs in around 6%.[88] However, the humanized alemtuzumab induced ADAs in 85% of treated multiple sclerosis patients.[89] Therefore, sequence homology is not the only determinant of ADA generation. Additional factors might include the biopharmaceutical parameters, patient's background and specific treatment factors (administration route and duration).[82] Further posttranslational modifications such as glycosylation occurring after protein synthesis or while manufacturing and storage can influence immunogenicity and ADA generation of mAbs.[90]

Also, specific Fc modifications might influence adverse event risk. For example, afucosylated mAbs might increase infusion-related reactions due to enhanced affinities to FcγRIII.[61]

Different engineering strategies have been developed to counteract those undesired mAb effects. Chimerization and humanization are used to reduce immunogenicity of mAb.[82] Further, unwanted immunogenic reactions through FcγR and C1q binding can be ameliorated by Fc isotype selection or Fc modification. IgG2 and IgG4 are used when strong effector (ADCC or complement-dependent cytotoxicity, respectively) functions are undesired and ADCC is suppressed by specific Fc mutations (e.g. L234A/L235A, L234A/L235A/P329G).[91,92] Moreover, different computational models have been developed to detect immunogenic T cell epitopes, which might be used to engineer mAbs with less ADA induction.[93] ADA induction through posttranslational modifications can be avoided by optimization of production and storage processes as well as by stabilizing sequence mutations.[82,94]

## Next-generation antibody therapeutics in neurology: evidence from clinical trials

Currently approved mAbs in neurology are already very diverse in terms of IgG subclasses, Fc variants and Fc functions (Table 1). The next generation of mAb will implement sophisticated Fc engineering to provide superior characteristics compared to earlier mAb. Those characteristics might comprise optimized serum half-lives, enhanced or reduced effector functions such as target cell depletion, or Fc functions in selected targets. Many of those new concepts are currently subject to clinical investigation in several neurological disorders, and are outlined in the following as well as in Table 2.

Increased serum half-live reduces application frequency and thereby reduces the therapeutic burden imposed on patients. An example of optimizing half-live by Fc engineering is ravulizumab (Ultomiris®). Ravulizumab is a humanized monoclonal antibody directed to complement component C5 and was engineered from eculizumab permitting longer dosing intervals (8 weeks compared to 2 weeks for eculizumab). A targeted substitution of four amino acids in the complementary binding and neonatal Fc regions in the eculizumab backbone results in enhanced endosomal dissociation of the ravulizumab–C5 complex, lysosomal degradation of C5 and recycling of ravulizumab to the extracellular space.[30] Moreover, the fusion of IgG2 and 4 molecules (IgG2 until T260, then IgG4) reduces binding of FcγR and C1q.[95] Ravulizumab has already been approved for paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome.[96] For neurological indications, ravulizumab is currently investigated in phase 3 trials in NMOSD (NCT04201262), anti-acetylcholine receptor positive myasthenia gravis (NCT03920293) patients and a trial in amyotrophic lateral sclerosis is active, but not yet recruiting (NCT04248465). For the

**Table 2 Engineered next-generation antibody therapeutics in neurology: clinical trials**

| Next-gen mechanism | Exemplary mAb or Ab biologics | Target | Neurological indications | Clinical trials[a] |
|---|---|---|---|---|
| Optimized half-life | Ravulizumab | Complement factor 5 | MG | Phase 3, NCT03920293 |
| | | | NMOSD | Phase 3, NCT04201262 |
| | Satralizumab | IL-6 receptor | NMOSD | Phase 3, NCT02073279, NCT02028884 |
| Enhanced Fc effector function/IgG stability | Ublituximab | CD20 | RRMS | Phase 3, NCT03277248 |
| | | | | Phase 2, NCT02738775 |
| | | | NMOSD | Phase 1, NCT02276963 |
| | Inebilizumab | CD19 | NMOSD | Phase 2/3, NCT02200770 |
| | Rozanolixizumab | FcRn | MG, | Phase 3, NCT03971422 |
| | | | | Phase 2, NCT03052751 |
| | | | CIDP | Phase 2, NCT03861481 |
| Reduced Fc effector function | Aquaporumab | AQP4 | NMOSD | Preclinical studies |
| | Crenezumab | Monomeric + aggregated amyloid-β | Alzheimer's disease | Phase 2, NCT 01343966 |
| | | | | Phase 3, NCT02670083, NCT03114657 |
| | Eculizumab | Complement factor 5 | MG, | Phase 3, NCT01997229 |
| | | | NMOSD | Phase 3, NCT01892345 |
| | Eptinezumab | CGRP | Migraine | Phase 3 NCT02559895, NCT02974153 |
| | Galcanezumab | CGRP | Migraine/cluster Headache | Phase 3, NCT02614261, NCT02614183, NCT02614196, NCT02397473 |
| Superselective targets | Aducanumab | Aggregated amyloid-β | Alzheimer's disease | Phase 3, NCT02484547, NCT02477800 |

CIDP = chronic inflammatory demyelinating polyneuropathy; MG = myasthenia gravis; RRMS = relapsing-remitting multiple sclerosis.
[a]ClinicalTrials.gov.

myasthenia gravis trial, first results were announced in July 2021 in an interim analysis.[97] The trial met the primary end point reduction of the Myasthenia Gravis-Activities of Daily Living Profile (MG-ADL) (ravulizumab: −3.1, placebo: −1.4, treatment difference: −1.6, $P <$ 0.001). In addition, the proportion of patients experiencing an improvement of Quantitative Myasthenia Gravis total score of at least five points was higher in the ravulizumab group (30.0 versus 11.3%). The benefits were detected as early as of Week 1 and throughout the study period of 52 weeks. The trial showed no new safety signals; headache, diarrhoea and nausea were the most common adverse events. No cases of meningococcal infection have been observed so far.[97]

With ublituximab (TG-1101) another mAb was designed to improve applicability compared to previous mAb generations by enhancing Fc receptor functions. Ublituximab is a glycoengineered anti-CD20 IgG1 mAb. The Fab domain of ublituximab targets a unique CD20 epitope, and its Fc region with low fucose content enhances affinity for all variants of FcγRIIIA receptors and thereby ADCC (100× facilitated ADCC compared to rituximab, the prototypic CD20-targeting Ab, *in vitro*).[98] The results of the two twin phase 3 trials (NCT03277248 and NCT03277261) of ublituximab in relapse-onset multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis have been recently presented at the yearly European Academy of Neurology congress.[99] Ublituximab was infused on the first day over 4 h followed by 1-h infusions at Day 15 and then every 6 weeks. Teriflunomide was used as an active comparator. In comparison to teriflunomide, ublituximab reduced the mean annual relapse rate in both trials (0.188 versus 0.076 relapses per year in ULTIMATE I, and 0.178 versus 0.091 relapses per year in ULTIMATE II) and no evidence of disease activity rates were significantly higher (44.6 versus 15% in ULTIMATE I, and 43 versus 11.4% in ULTIMATE II), whereas confirmed disability progression was similar for ublituximab and teriflunomide at 12 weeks and at 24 weeks. The most common adverse events associated with ublituximab comprised infusion-related reactions, nasopharyngitis and headaches.[99] In a previous phase 2 trial, ublituximab was tested in RRMS patients against placebo (NCT02738775). Ublituximab depleted >99% of B cells: a depletion that was maintained over 48 weeks.[63] The higher efficacy for ADCC allows for substantially shorter infusion times as compared to non-defucosylated glycovariants of CD20-targeting antibodies. However, afucosylated mAbs might increase infusion-related reactions due to enhanced affinities for FcγRIII, which might interfere with the desired engineering effect.[61] Consistent with this, 43% of patients with multiple sclerosis experienced an infusion-related reactions treated with ublituximab, whereas several cohort studies report significantly lower infusion-related reactions rates, e.g. with 16.7 or 25.7%.[99–101]

In addition, stabilization of the antibody molecule might also improve durability and efficacy of monoclonal antibodies. An example is the S228P mutation in the hinge region of rozanolixizumab, a human IgG4 anti-FcRn mAb.[95] In accordance with increased blocking function of IgG recycling, a phase 2 study (NCT03052751) in myasthenia gravis demonstrated a 68% decrease in IgG and acetylcholine receptor (AChR)-Ab levels as well as a dose-dependent improvement in the myasthenia gravis clinical disease activity.[102] A consecutive phase 3 trial is ongoing (NCT03971422). The success of FcRn modulation led to an expansion to further neurological indications. Consequently, rozanolixizumab (NCT03861481) is currently tested in phase 2 studies for chronic inflammatory demyelinating polyneuropathy.

To prevent side-effects, Fc engineering can also be used to reduce unfavourable Fc functions and one example is aquaporumab, a non-pathogenic human IgG1 mAb against AQP4. Antibodies to AQP4 water channels play a fundamental role in the pathogenic processes in NMOSD.[103] It was generated from clonally expanded plasmablasts from the CSF of NMOSD patients and the Fc domain was mutated (L234A/L235A) to neutralize effector functions such as complement activation.[104] Animal and mechanistic studies with human materials showed that aquaporumab blocks autoantibody binding to aquaporin-4 and prevents complement and cellular cytotoxicity. Those data are promising and support further clinical development.[104,105] Similar strategies of Fc engineering have been used in amyloid-β targeted therapy in Alzheimer's disease. In Alzheimer's disease, protein misfolding and increased production and deposition of neurotoxic amyloid-β leads to progressive neuroaxonal degeneration.[106] Several mAbs were designed to interrupt this self-perpetuating pathology reducing amyloid-β deposition. To reduce vascular side-effects such as vasogenic oedema and micro-haemorrhages, IgG4 (crenezumab) instead of IgG1 or Fc mutations (AAB-003, three mutations in CH3; GSK933776, L235A/G237A) have been used to reduce FcγR and C1q binding by mAb.[95] However, in a phase 2 trial (NCT01343966) crenezumab failed to reach the predefined primary end points of improved cognition, as the anti-amyloid-β mAb bapineuzumab (IgG1) and solanezumab (IgG1) did in corresponding phase 3 studies (NCT00575055, NCT00574132; NCT00905372, NCT00904683).[107,108] All three antibodies bind monomers and aggregated forms of amyloid-β.[109] Thus suboptimal efficacy might, at least in part, be related to the saturation of antibodies by soluble amyloid-β monomers, which thus cannot engage the deposited Aβ. Aducanumab (BIIB037), a fully human anti-amyloid-β (N terminus of amyloid-β3-6) IgG1 mAb, is able to circumvent this problem by selective binding of aggregated amyloid-β forms (both the insoluble fibrils and the soluble oligomers). Moreover, IgG1 related FcγR binding induces effective antibody-dependent cellular phagocytosis.[109,110] Correspondingly, in a phase 3 clinical trial (NCT02484547), high-dose aducanumab met the primary end point (change in Clinical Dementia Rating Sum of Boxes) at Week 78 (23% reduction of decline versus placebo, $P = 0.01$). Consistent with this, these patients also showed a reduction of clinical decline in the Mini-Mental State Examination (15% versus placebo, $P = 0.06$), the AD Assessment Scale-Cognitive Subscale 13 Items (27% versus placebo, $P = 0.01$) and the AD Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version (40% versus placebo, $P = 0.001$). Amyloid plaques were reduced with low- and high-dose aducanumab compared to placebo at 26 and 78 weeks ($P < 0.001$).[111] However, in interpreting those data it has to be considered that the second phase 3 trial (NCT02477800) did not show any clinical benefits, whereas amyloid plaque burden was reduced in a dose-dependent fashion.[112] Those contradictory findings might be related to several factors such as different durations of exposure to high-dose aducanumab, variation in the performance of placebo groups or prove missing efficacy.[112] Nevertheless, in June 2021 the FDA granted accelerated approval of aducanumab for Alzheimer's disease.[113] Further antibody-engineering approaches are currently used to improve immunotherapy in Alzheimer's disease (e.g. to cross the blood–brain barrier) and are reviewed elsewhere in detail.[114] Overall, Fc engineering is instrumental in improving efficacy, safety and applicability of mAb in the treatment of several neurological disorders, which is supported by first clinical trials.

### Future of antibody-based therapies

Improved concepts of Ab biology, the increasing research and development investments and the adoption of collaborative research strategies by pharmaceutical companies, increasing prevalence rates for chronic diseases, and the growing clinical experience based on both clinical trials as well as community use of approved drugs will foster the development of Ab-based therapies in the future. As of 2020, >80 Ab-based therapeutics have been approved in the USA or EU, and a growing number of Abs are in regulatory review.[111] The global market for the use of recombinant mAbs alone is currently valued at US $140 billion and is estimated to grow to US $370 billion by the end of 2027.

Many neurological diseases are among the most recently identified new and approved indications for Ab-based therapies. However, despite the significant progress, there remain central outstanding questions or problems that need to be addressed in the future:

(i) Despite the rapid development in broadening and improving therapeutic applications of antibodies in neurological diseases, gaps in our armamentarium, including strategies that deliver Ab biologics into the CNS, remain to be addressed. Further, it is not known whether strategies that allow Ab-based platforms to cross the blood–brain barrier, such as receptor-mediated transport through transferrin and insulin receptors, are safe and efficient in humans.

(ii) It is not clear whether improving pharmacodynamics and bioavailability of Ab-based treatment platforms within the CNS parenchyma, combined with efficient target validation processes, reinvigorate drug discovery for neurological diseases currently not amenable to immunotherapy.

(iii) It remains to be explained whether technologies and processes that decrease production and processing costs of Ab-based treatments together with validated biomarker development programs bring more efficient and affordable Ab-based treatments to the clinic.

## Conclusions

Substantial progress has been made over the past decades and has led to improved engineering technologies, safety and efficacy of the first generation of therapeutic Abs in neurology. These developments, along with a greater understanding of the immunomodulatory properties of Abs, have paved the way for the next generation of new and improved Ab-based treatment platforms. Fc-engineering technologies are now being used to specifically address and improve particular effector functions and safety issues to create entirely new Ab-based therapies for immune-mediated neurological diseases. Effector functions of therapeutic Abs can further be improved by regulating FcγR binding and signalling. It remains to be demonstrated, however, that enhanced effector functions indeed translate into higher clinical efficacy. Improving access to the CNS is another important target for Ab- and Ig-domain-based therapies. With dedicated attention to basic, translational and clinical research, we shall soon build even better, more effective and safe Ab-based treatment platforms able to target CNS diseases currently not amenable to immunotherapy.

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