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REVIEW

Therapeutic Antibodies in Neurological Diseases: Witnessing the Continuation of the Impressive Success in Neuro-Immunotherapies

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This is the second time in the past 6 years that both of us have been involved as Guest Editor or contributors to a special issue of *Neurotherapeutics* dedicated to immunotherapies in autoimmune neurological disorders [1, 2]. The present issue on *"Antibody Therapies"* [3] is a confirmation of the explosive progress we have been witnessing in the field of autoimmune neurology and neurological immune-therapy. Since the previous issue 6 years ago [1, 2], the evolving progress has not only been impressive but has also been occurring at a remarkably fast pace, as highlighted in the present issue by five newly approved anti-B cell or anti-IL6 receptor therapeutic antibodies in multiple sclerosis (MS) and neuromyelitis optical spectrum disorders (NMOSD), three anti-complement agents approved for NMOSD and myasthenia gravis (MG) and the first approved anti-FcRn inhibitor for MG [3]. The magnitude of this progress, as we have both been experiencing in our practice, can be much easily appreciated when looking back at two previous special issues on Neuroimmunotherapies for *Seminars in Neurology*, one in 1994 when we had nothing approved for any neurological autoimmunity but only hoped for a better future [4], and the second in 2003 when we celebrated the first 3–4 Disease Modifying Therapies (DMTs) in MS and the approval of IVIg in Guillain-Barré Syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), but we were projecting a brighter future for all neuroimmunotherapeutics [5]. The present issue, which also highlights the first drugs ever approved for NMOSD and MG [3], is a testimony of how such an overwhelming success is steadily changing the therapeutic algorithm of autoimmune neurological disorders. Furthermore, the development of several of the novel treatments is an elegant example of how informed knowledge about pathophysiology leads to targeted treatment approaches. In addition, selective and specific antibody interventions instruct about pathogenesis via therapeutic interventions (i.e. https://pubmed.ncbi.nlm.nih.gov/34050331/). Considering the large number of ongoing trials with targeted therapeutic monoclonal antibodies or similar agents across all the neuroimmunology field, we may predict that yet another special issue of Neurotherapeutics covering newly approved neuro-immunotherapies might be forthcoming not in 6 years as the present one, but in a much shorter time period. Importantly, the field of monoclonal therapeutic antibodies is expanding to non-immune disorders as well, with the remarkable progress made in migraine, while the very challenging trials in Alzheimer's disease with anti-beta-amyloid agents, although with controversial results, have stimulated interest to apply antibody therapies to target other neurodegenerative diseases.

The present issue starts with translational science on B cell therapies by Stathopoulos and Dalakas who discuss the B cell biology in autoimmune neurological diseases, how B cells regulate T cell activation processes, participate in antigen presentation, cytokine production and ectopic intermeningeal lymphoid aggregate formation [6]. They then describe the unprecedented success of anti-B cell agents in MS and NMOSD, highlight the efficacy data of these agents in other neurological autoimmunities and summarize the new agents currently in the offing. McCombe and Pittock discuss the basic elements of the complement cascade, the role of complement in all autoimmune neurological disorders and the complement targeted immunotherapies based on approved indications or ongoing trials [7]. The advent of treatments modulating the complement system re-classifies distinct diseases even as "complementopathies" (e.g. https://pubmed.ncbi.nlm.nih.gov/34569094/). Continuing on the

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translational science, Nelke et al. explain how the neonatal Fc Receptor (FcRn) facilitates IgG recycling extending the half-life of IgG and how FcRn blockade leads to antibody degradation pointing out the emerging anti-FcRn inhibitors as promising therapeutics in antibody-mediated autoimmune neurologic diseases [8]. The fourth article in the first subsection is by Dalakas who discusses the newly recognized as distinct group, the IgG4 antibody–mediated neurological disorders and their immunopathogenesis [9]. The article highlights the uniqueness of IgG4-antibody subclass which, in contrast to IgG1-3, does not exert pathogenic effects on targeted antigens by triggering inflammatory processes or complement-mediated immune responses, but by blocking enzymatic activity or disrupting protein–protein interactions affecting signal transduction pathways. It further explains why the common IgG4-mediated neurological disorders, such as MuSK-myasthenia, autoimmune nodopathies and the anti-LGI1-associated syndromes, do not respond to IVIg but effectively respond to anti-B cell agents [9].

Proceeding to specific diseases, Krajnc et al. provide an overview of the monoclonal antibody therapies as currently applied in Relapsing Remitting MS (RRMS), describing their mechanism of action while stressing safety profile and risk management in relation to pregnancy, vaccination and family planning [10]. Havla and Hohlfeld elaborate on the inadequacy and challenges of the antibody therapies currently used in Primary Progressive MS (PPMS), stressing the need for promising approaches with the newer therapies utilizing agents that have a combined anti-inflammatory, neuroprotective and re-myelinating actions [11]. Krämer and Wiendl importantly highlight what the antibody therapies that were tried but failed in MS have taught us about pathophysiological disease mechanisms. Furthermore, they help in understanding crucial pharmacokinetic—and dynamic parameters, such as crossing the blood–brain barrier, or appreciating the fundamental factors essential for optimizing future trial designs [12]. Redenbaugh and Flanagan then discuss the NMO/SD groups stressing the distinction between AQP4-IgG seropositive NMOSD from the Myelin oligodendrocyte glycoprotein (MOG)–IgG-associated disease (MOGAD), outlining the benefits and challenges of the current immunotherapies based on observational rather than controlled studies, and pointing out the need for large-scale systematic studies [13].

Smets and Titulaer then describe the current treatment options for Autoimmune Encephalitis based on step-by step therapeutic approaches highlighting the need for future therapies with monoclonal antibodies against B cells (rituximab, ocrelizumab, inebulizumab, daratumumab), IL-6 (tocilizumab, satralizumab), FcRn and complement [14]. Subsequently, Dalakas provides a detailed description of the Glutamic Acid Decarboxylase (GAD)-spectrum disorders with a specific focus on stiff person syndrome, the biologic basis of autoimmune neuronal excitability, the significance of GAD antibody titers in the context of their association with reduced GABA level in the brain and CSF, and summarizes the current step-by-step immunotherapies and future prospects of antibody therapies in these disorders [15]. Duong and Prüss complete the CNS autoimmunities discussing the paraneoplastic Autoimmune Neurological Syndromes, the role of Immune Checkpoint Inhibitors, the complex immunopathological interplay of cancer immunity and cross-reactive neurological autoimmune phenomena, stressing the potential benefit and evolving concepts of therapeutic monoclonal antibodies as future treatment options [16].

Proceeding neuroanatomically to the autoimmunity of the peripheral nervous system, Querol et al. explain the role of complement in CIDP based on preclinical and clinical evidence, stress how complement appears to play a role in promoting macrophage-mediated demyelination and outline the strong rationale for using anti-complement therapeutic antibodies in the treatment of CIDP [17]. Briani and Vinsentin follow with the present immunotherapies in all chronic autoimmune neuropathies including CIDP and anti-MAG, emphasizing the need for targeted therapies, either individually or combined, with various monoclonal antibodies targeting B cells, complement and FcRn [18]. Rajabally then follows with the acute autoimmune neuropathies, best represented by GBS, summarizing the effectiveness of IVIg, clarifying key IVIg kinetics and the failure of the second IVIg dose, while addressing the merits of the ongoing anti-complement trials [19].

The major progress on the use of antibody therapy is best highlighted in myasthenia gravis, as discussed by Vanoli and Mantegazza, who describe the first drugs approved in the disease targeting complement and FcRn which, along with the success of anti-B cell agents, offer an exciting promise for better outcomes, even setting the basis for a precision medicine approach [20]. Myasthenia gravis, one of the “ancestor disease” in neuroimmunology, always characterized by a very detailed understanding of the pathological immune response, impresses by various novel therapeutic approaches and thus the possibilities to control the disease with immunological interventions at the level of (1) effector cascades or (2) basal immune regulatory networks. Zeng et al. then discuss the autoimmune inflammatory myopathies, stressing the effectiveness of IVIg in certain disease subsets including the now approved indication for Dermatomyositis, the promising results with some anti-B cell agents and the disappointing effects of various antibodies in IBM, pointing out the need for further research [21]. Finally, the progress of monoclonal antibodies (mAbs) in migraine, probably the first non-immune disease where monoclonal antibodies are effective by targeting calcitonin gene-related peptide

(CGRP), is discussed by Cohen et al. who specifically point out that the anti CGRP-targeted mAbs represent a radical shift in migraine therapy because they are not only effective in preventing chronic and episodic migraines, but they also offer numerous advantages over oral migraine therapies [22].

Neuroimmunotherapy, as pointed out 30 years ago [5], remains an unfinished business but probably the most impressive area of therapeutic progress in neurology. We are continuously discovering new target molecules utilizing the latest in immunobiology applying targeted therapeutics, while concurrently focusing on uncovering safer and longer-acting agents that improve patients' satisfaction, tolerance and compliance. This is now best exemplified in MS where we are seeing a gradual shift from injectable to oral agents and from weekly or monthly administrations to longer intervals that further ensure improvements in quality of life. Novel treatment aims cannot only be postulated, but also achieved (e.g. https://pubmed.ncbi.nlm.nih.gov/34422112/). While we are improving tremendously on all the above, we still lag behind on neuroprotection (https://pubmed.ncbi.nlm.nih.gov/25773662/), especially with agents exerting both immunomodulation and neuroprotection, in a single or combination therapy, as proposed in the *Neurotherapeutics* issue 6 years ago [2]. On the safety side, we are all witnessing—albeit not as often as before—some rare adverse events necessitating customized choices for drugs best suited for individual patients or a specific stage of the disease, while still waiting on progress in precision medicine. The goal of our therapies ideally is the "best possible disease control" and "the best possible QoL for the patient". While newer treatments partially provide very high efficacy (of effectiveness), derisking immune therapy and monitor patients for safety and adverse events remains one of the most important challenges of modern neuroimmunology (e.g. https://pubmed.ncbi.nlm.nih.gov/30967901/; https://pubmed.ncbi.nlm.nih.gov/34422112/).

Putting this issue together required considerable effort. The editorial assistance of Linda Powel chasing all of us to be on schedule was, one more time, essential not only in keeping strict timing guidelines but also in admirably advising us on how best to handle the reviewing process. Finally, the conception of this topic by the editor-in-chief Dr. M. Maral Mouradian was both timely and insightful. Most of all, however, our thanks and gratitude go to all our long-time friends and esteemed colleagues who contributed such outstanding reviews during this difficult period of the COVID-19 pandemic. We truly believe that their contribution to this issue will serve as a reference text on immunotherapies for the autoimmune neurological disorders until the next issue in a few years when we all hope we will get together again to celebrate another landmark issue attesting to the progress in the field.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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