frontiers in Immunology

TYPE Mini Review
PUBLISHED 15 September 2026
DOI 10.3389/fimmu.2026.1955727

Check for updates

OPEN ACCESS

EDITED BY
Wenbin Liu,
Capital Medical University, China

REVIEWED BY
Li Wang,
Southwest Medical University, China

*CORRESPONDENCE
Xiaomeng Lin
2024n105@zcmu.edu.cn
Xudong Cai
xudongcai1979@hotmail.com
Guanghui Zhong
zgh20040712@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 01 August 2026
REVISED 18 August 2026
ACCEPTED 31 August 2026
PUBLISHED 15 September 2026

CITATION
Yu K, Xu X, Gao J, Xing J, Yin X, Song Q, Wen K, Lin X, Cai X and Zhong G (2026) Immunotherapy of membranous nephropathy: strategic evolution from CD20 monoclonal antibodies to future vaccines. *Front. Immunol.* 17:1955727. doi: 10.3389/fimmu.2026.1955727

COPYRIGHT
© 2026 Yu, Xu, Gao, Xing, Yin, Song, Wen, Lin, Cai and Zhong. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Immunotherapy of membranous nephropathy: strategic evolution from CD20 monoclonal antibodies to future vaccines

Kena Yu[1,2†], Xin Xu[1†], Junwei Gao[1†], Jie Xing[1], Xiaofan Yin[2], Qin Song[2], Kaizhi Wen[2], Xiaomeng Lin[3*], Xudong Cai[1*] and Guanghui Zhong[1*]

[1]Department of Nephrology, Ningbo Municipal Hospital of Traditional Chinese Medicine (TCM), Affiliated Hospital of Zhejiang Chinese Medical University, Ningbo, China, [2]Department of Nephrology, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China, [3]Ningbo Research Institute of Chinese Medicine, Ningbo Municipal Hospital of Traditional Chinese Medicine (TCM), Affiliated Hospital of Zhejiang Chinese Medical University, Ningbo, China

Membranous nephropathy (MN) arises from autoantibody-mediated attack on podocyte antigens, with immune deposits forming subepithelially at the glomerular basement membrane to trigger complement activation and subsequent podocyte damage, eventually manifesting as proteinuria. Traditional therapy hinges on nonspecific immunosuppression, which is characterized by modest effectiveness and a substantial side-effect profile. In recent years, CD20-targeting monoclonal antibodies, most notably rituximab (RTX), have curtailed autoantibody production through peripheral B-cell depletion and consequently emerged as a first-line treatment option for patients at intermediate-to-high risk. However, a considerable proportion of patients still show no initial response or later relapse. Resistance mechanisms are heterogeneous, encompassing Fc receptor polymorphisms, plasma cell longevity, and anti-RTX antibody formation. To address these hurdles, novel biologics that target the BAFF/APRIL signaling axis, CD38-positive plasma cells, and the complement cascade have entered the clinical arena, further broadening the immunotherapeutic landscape for MN. In parallel, as our understanding of immune memory and autoantibody-generating cells continues to expand, a so-called "immune reset" approach is gaining traction, with its core rationale being the restoration of a robust yet self-tolerant immune system. This review charts the progression of MN therapies, from CD20 monoclonal antibodies and their optimized use, through novel biologics, to vaccine-based strategies that target autoantibody-specific B or T cells (including CAAR-T, Treg therapies, B-cell epitope vaccines, and T-cell vaccines). We further consider their theoretical promise for inducing antigen-specific immune tolerance and the barriers to clinical implementation.

KEYWORDS
anti-CD20 antibody, B cells, CAAR-T, immune tolerance, immunotherapy, membranous nephropathy, regulatory T cells, vaccine

1 Introduction

Membranous nephropathy (MN), a leading cause of adult nephrotic syndrome, is driven by circulating autoantibodies that target podocyte antigens and deposit as immune complexes *in situ* along the glomerular basement membrane. This event triggers the complement cascade, which in turn damages podocytes and ultimately manifests as proteinuria (1). In idiopathic MN, anti-PLA2R autoantibodies occur in about 70-80% of patients, correlate with clinical activity, and have become standard for both diagnosis and longitudinal surveillance (1, 2). High-throughput techniques like laser microdissection with mass spectrometry have expanded the MN antigen spectrum, identifying new podocyte targets—THSD7A (3), NELL1 (4), HTRA1, and CNTN1—that underpin precision diagnosis and targeted therapy (5).

For moderate-to-high-risk MN, standard therapy combines glucocorticoids with either cyclophosphamide or CNIs (e.g., cyclosporine A, tacrolimus), but these regimens carry risks of drug dependence, myelosuppression, infection, and nephrotoxicity (6–8). Thus, there exists a pressing clinical gap for immunomodulatory therapies that are both more targeted and less toxic. Given that B cells serve as key drivers of autoantibody formation (9, 10), RTX—a CD20-targeting chimeric monoclonal antibody—eliminates circulating B cells, thereby effecting a significant decline in anti-PLA2R antibody levels and inducing remission. This agent has accordingly become a first-line therapeutic choice, offering better tolerability than conventional therapies (9, 11, 12). Yet these CD20-negative long-lived plasma cells, which are not depleted by RTX, continue to reside in patients and are responsible for both initial treatment failure and subsequent recurrences (9, 13). Other nodes in the MN pathogenic cascade are also druggable. Anti-CD38 antibodies (daratumumab, felzartamab) eliminate RTX-resistant long-lived plasma cells (14, 15); complement blockers against C5, C5aR, or C1s interrupt effector steps at podocytes (9, 16). Belimumab or telitacicept adds another layer by limiting autoreactive B-cell renewal via BAFF/APRIL (17, 18). Yet none is antigen-specific—each broadly dampens immune pathways, carries infection risks, and fails to restore tolerance.

Growing insights into immune memory and the cells that generate autoantibodies are now paving the way for a more forward-looking therapeutic strategy—one that has come to be known as "immune conditioning (19)." The essence of the proposal is to re-establish a stable, self-tolerant immune system—an "immune reset" (20) in short—and this marks a decisive turn in MN therapy: from passive immunosuppression to proactive immune regulation. From this vantage, MN immunotherapy evolves across three escalating tiers. At the base, passive immune clearance—via CD20 antibodies such as rituximab—depletes circulating B cells and curtails autoantibody output, though rebound of the B-cell compartment often reignites disease. One tier up, immune modulation deploys inhibitors of BAFF/APRIL signaling, CD38-positive plasma cells, or the complement cascade not to ablate but to recalibrate immune effector pathways, trading antigen specificity for broader, more sustained control. At the apex, antigen-specific tolerance—the strategic endpoint of MN therapy—is pursued through CAAR-T cells, regulatory T-cell approaches, and B-cell epitope vaccines that restore durable tolerance toward defined autoantigens. Along this logic, the present review traces the full arc of MN immunotherapy: from the clinical deployment and mechanistic refinement of anti-CD20 agents, through biologics targeting plasma cells, survival signals, and complement, to cell- and vaccine-based strategies against autoantibody-specific B or T cells (Figures 1, 2). We critically examine their theoretical rationale, summarize existing preclinical findings, and identify the key challenges that stand in the way of translational application.

2 Immunopathological mechanisms and therapeutic targets in membranous nephropathy

2.1 B-cell differentiation, antibody generation, and the limits of anti-CD20 therapy

The immunopathology of MN hinges on the transition of autoreactive B cells into antibody-secreting plasma cells. Along the B-cell developmental trajectory, CD20 is expressed from the pre-B stage through the memory stage, and is absent at the plasma-cell endpoint. This feature defines the practical ceiling for RTX and other anti-CD20 monoclonal antibodies (21, 22). In MN, autoreactive B cells specific for podocyte antigens like PLA2R undergo somatic hypermutation and affinity maturation, then become long-lived plasma cells that settle in bone marrow, spleen, and other secondary lymphoid tissues, where they sustain ongoing production of high-affinity autoantibodies (9, 23). These long-lived plasma cells, however, express no CD20, so they can evade elimination by RTX—a feature that constitutes a principal source of disease recurrence (13). Beyond their role in antibody production, B cells also function as antigen-presenting cells, shuttling podocyte antigens to $CD4^+$ T cells and jointly promoting the propagation and maintenance of autoimmune responses (24). This finding places renewed emphasis on the diverse pathogenic roles that B cells play in MN.

2.2 The BAFF/APRIL signaling axis: sustaining plasma cell survival and persistence

Multiple cytokines and signaling cascades cooperate to regulate B-cell survival, differentiation, and isotype switching. B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL)—key TNF-superfamily ligands—bind to receptors on B cells,

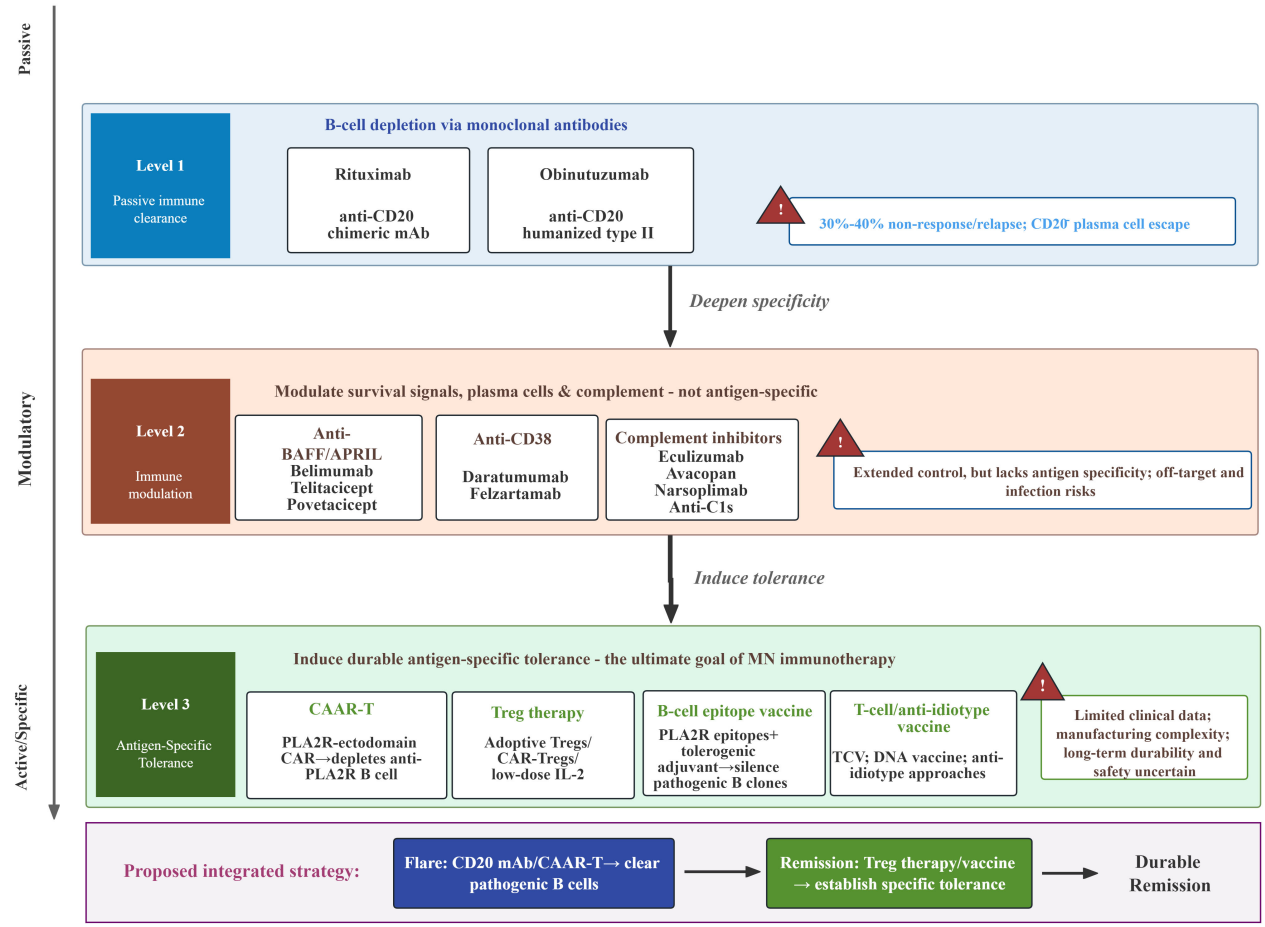


FIGURE 1
Strategic evolution of membranous nephropathy immunotherapy: from passive immune clearance to antigen-specific tolerance. Level 1: Passive immune clearance. Anti-CD20 mAbs deplete B cells; Level 2: Immune modulation. Non-specific control via BAFF/APRIL blockade, anti-CD38, and complement inhibitors; Level 3: Antigen-specific tolerance. CAAR-T, Treg therapy, epitope vaccines, and T-cell/anti-idiotype vaccines to induce durable tolerance.

thereby promoting cellular viability, facilitating plasma-cell generation, and maintaining their long-term persistence (25). MN patients exhibit significantly higher serum BAFF and APRIL levels, which correlate positively with anti-PLA2R titers and disease activity (18), thereby highlighting the BAFF/APRIL signaling pathway as a key therapeutic target in this setting.

2.3 Complement cascade activation and podocyte injury

Complement activation, a central effector event in MN-induced podocyte injury, is initiated by immune complexes formed after autoantibody engagement with podocyte antigens. These complexes activate the classical and lectin cascades, culminating in the generation of C3b, C5b-9, and other active complement fragments (26). Podocyte injury in MN is mediated in part by the membrane attack complex (MAC) C5b-9, which integrates into the cell membrane (26, 27), and is further compounded by C3a- and C5a-driven inflammatory cell recruitment and local immune amplification through receptor engagement (27). Thus, complement inhibition stands out as a principal strategy for MN (28).

3.Anti-CD20 monoclonal antibodies as first-line immunotherapy: achievements and constraints

3.1 Comparative efficacy and clinical evidence for CD20-targeting agents

Rituximab (RTX), the first chimeric monoclonal antibody targeting CD20, has secured its position in MN therapy through multiple high-quality clinical trials. The GEMRITUX study was the first RCT to demonstrate a significantly higher 6-month remission rate with RTX than with conservative management (11). The MENTOR trial subsequently established RTX as first-line for intermediate-to-high-risk IMN, demonstrating superior 12-month

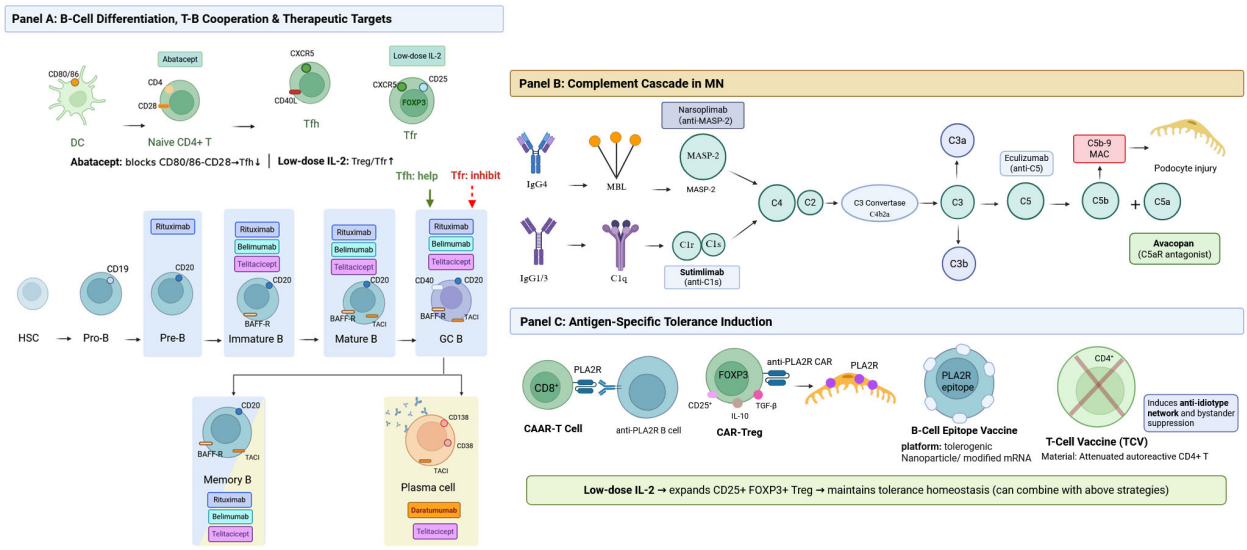


FIGURE 2
Cellular and molecular mechanisms of immunotherapy in membranous nephropathy. **(A)** DC-primed Tfh activate B cells via CD40L–CD40; Tfr suppress this axis. Therapeutics mapped along B-cell differentiation: abatacept (CD80/86–CD28), low-dose IL-2 (Tregs), rituximab ($CD20^+$ B cells), belimumab/telitacicept (BAFF/APRIL), daratumumab ($CD38^+$ plasma cells); **(B)** IgG4 triggers the lectin pathway (MBL) and IgG1/3 the classical pathway (C1q), converging on C3/C5 to generate MAC and C5a. Blocked by narsoplimab, sutimlimab, eculizumab, and avacopan (C5aR); **(C)** PLA2R-specific tolerance strategies: CAAR-T (B-cell elimination), CAR-Treg (local suppression), epitope vaccines (nanoparticle/mRNA), T-cell vaccines (anti-idiotype). Low-dose IL-2 expands Tregs to maintain tolerance homeostasis and may combine with the above strategies.

remission over cyclosporine and a widened benefit at 24 months (12). RI-CYCLO showed no significant remission difference between RTX and alternating cyclophosphamide, yet RTX was safer (29). Meta-analysis (30) confirmed a 58% overall remission rate for RTX in MN, with complete remission increasing over longer follow-up.

Obinutuzumab, a humanized type II anti-CD20 mAb, features optimized Fc glycoengineering that enhances antibody-dependent cell-mediated cytotoxicity (ADCC) and direct cell death induction (31). A phase III RCT confirmed obinutuzumab's superiority over tacrolimus in complete remission, faster response, and durability in primary MN (32), and further showed efficacy in patients resistant to RTX, implying that its strengthened effector functions could circumvent some resistance (33).

3.2 Limitations, resistance mechanisms, and strategies to overcome Anti-CD20 resistance

Despite their efficacy in MN, CD20 mAbs face real-world challenges. First, about 30-40% of patients are non-responders or relapse after initial RTX therapy (9, 13). Additionally, residual CD20-negative plasma cells in tissues continue producing autoantibodies after B-cell depletion, resulting in slow anti-PLA2R titer decline or persistent positivity, which correlates with relapse (13).

Anti-rituximab antibodies (ARA) constitute another mechanism of RTX failure. In Allinovi et al. (34), 47% of patients were ARA-positive post-RTX, with a 1-year remission rate of 54% versus 87% in ARA-negative patients, and a significantly higher relapse risk. ARA neutralizes RTX's antigen-binding site, accelerating drug clearance and weakening B-cell depletion, thereby causing treatment failure (34). Precursors in sanctuary sites (spleen, bone marrow) drive rapid B-cell reconstitution after depletion, and some repopulated cells may adopt a more pathogenic memory phenotype, contributing to relapse (9). To counter these resistance mechanisms, options include switching to obinutuzumab or adding a proteasome or complement inhibitor, which may overcome RTX resistance and improve long-term remission (33, 35).

4 In-depth intervention on the B-cell lineage: plasma cell depletion and survival signal modulation

4.1 Targeting the BAFF/APRIL signaling pathway

As noted in Section 2.2, BAFF and APRIL are elevated in MN and track with disease severity; pharmacologic blockade of this axis targets the survival signals that keep autoreactive B cells alive. Belimumab, a human IgG1 mAb, binds soluble BAFF, blocks its receptor engagement, and suppresses B-cell survival and differentiation (18). While belimumab alone has modest effects in MN, it synergizes with RTX (SLE-derived evidence) by inhibiting BAFF-mediated B-cell repopulation after RTX depletion, thus prolonging depletion and cutting relapse risk—a strategy based on the BAFF surge post-RTX that would otherwise drive pathogenic B-cell recovery (36). Therefore, the above treatment paradigms in SLE may offer new insights for the management of MN. Unlike single-target belimumab, telitacicept should inhibit a wider range of B-cell activities, notably more potent against APRIL-driven plasma cell viability and antibody production (37). Currently, clinical trials of telitacicept for MN are ongoing, with early results indicating

favorable efficacy and safety. Povetacicept (ALPN-303), a next-generation dual BAFF/APRIL inhibitor, was shown in the RUBY-3 trial to reduce proteinuria and preserve renal function in both IgA nephropathy and primary membranous nephropathy. At 48 weeks, proteinuria in primary MN fell by 82% from baseline, supporting this agent as a novel option for targeted immunotherapy in MN (38).

4.2 Anti-CD38 monoclonal antibodies: mechanisms and applications in targeting plasma cells

CD38, a type II transmembrane glycoprotein on plasma cells, is preferentially overexpressed on long-lived plasma cells, making it a rational target for their selective ablation (9, 39). Daratumumab is a human IgG1/κ anti-CD38 monoclonal antibody whose application in autoimmune disorders has gradually broadened. It eliminates $CD38^+$ plasma cells through ADCC and complement-dependent cytotoxicity (CDC), enhances their phagocytic elimination by macrophages via antibody-dependent cellular phagocytosis (ADCP), and regulates CD38 enzyme activity to affect calcium signaling and NAD^+ metabolism (40).

In MN therapy, daratumumab confers a theoretical benefit by clearing $CD20^-$ long-lived plasma cells that RTX spares, thereby curbing sustained autoantibody output (41). Daratumumab use in RTX-unresponsive MN has been documented only in individual instances, lacking systematic study. However, CD38 expression on multiple lineages (erythrocytes, T/B/NK cells) raises off-target concerns for daratumumab (40). Ongoing MN trials have yet to establish long-term efficacy and safety.

Felzartamab, another human anti-CD38 mAb, eliminates $CD38^+$ plasma cells via ADCC and ADCP. Rovin et al. (15) in a phase Ib/IIa study on anti-PLA2R+ MN: 76.9% immunologic responders, 34.6% partial proteinuria remission, no durable hypogammaglobulinemia, and low infection—indicating a safety edge over daratumumab. In contrast, Trillini et al. (42) found good safety in a prospective RTX-resistant cohort, yet without appreciable clinical remission, underscoring the need for larger RCTs to validate efficacy in this subgroup.

4.3 Complement-targeted therapy

Complement activation is a key effector of podocyte injury in MN, and inhibitors targeting distinct components of the cascade offer an additional therapeutic dimension (43). Eculizumab, a humanized anti-C5 antibody, blocks C5 cleavage into C5a and C5b, thus preventing membrane attack complex (C5b-9) formation. Eculizumab shows mixed efficacy in MN—some refractory patients derive benefit, but overall responses are low, owing to complement activation variability and sustained upstream classical signaling (44). Avacopan (CCX168) is an oral C5aR antagonist that attenuates complement-induced injury via C5a-directed chemotaxis and leukocyte activation; it has demonstrated steroid-sparing promise in ANCA-associated vasculitis (45), though the phase 3 data supporting this have since been retracted (46); its application in MN is still being investigated. Targeting MASP-2, narsoplimab (OMS721) suppresses lectin-pathway complement and has shown proteinuria reduction in IgA nephropathy, with investigation in MN ongoing (9, 47).

Anti-C1s antibody (e.g., sutimlimab), by blocking C1s to abort immune-complex-driven complement activation upstream, offers a theoretical rationale for MN and similar conditions (16, 48); its optimal use in MN remains to be established (49).

5 Antigen-specific interventions: paving the way to immune tolerance

5.1 Chimeric autoantibody receptor T-cell therapy

As a CAR-T extension into autoimmunity, CAAR-T therapy links an autoantigen (e.g., PLA2R) ectodomain to T-cell signaling moieties, enabling targeted elimination of B cells bearing cognate autoantibodies. Distinct from tumor-directed CAR-T, CAAR-T relies on autoantigen–antibody pairing to achieve selective removal of pathogenic clones without compromising normal B-cell immunity (50). Antigen recognition requires an ectodomain that retains native conformational epitopes. The full-length PLA2R ectodomain fulfills this requirement; adapting the approach to NELL1, CNTN1, or EXT1/2 depends on whether each ectodomain folds correctly on the T-cell surface (51). Inducible caspase-9 suicide switches allow pharmacologic elimination of CAAR-T cells if on-target, off-tissue toxicity occurs, while prophylactic tocilizumab or anakinra can mitigate CRS/ICANS (50). Costimulatory domain choice governs T-cell persistence and effector function. 4-1BB promotes sustained survival with lower tonic signaling, whereas CD28 drives stronger but short-lived cytotoxicity (52). Current CAAR-T constructs use 4-1BB-CD3ζ (53), though head-to-head comparisons in autoimmunity are lacking. Using PLA2R ectodomain as the antigen-recognition domain, CAAR-T cells selectively eliminate anti-PLA2R B cells *in vitro* and *in vivo*, lowering antibody titers and proteinuria in PLA2R-MN mice, with high specificity and no effect on non-target B cells. A recent study extended the platform to Graves' disease, showing that CAAR-T bearing the thyrotropin receptor ectodomain specifically eliminated autoreactive B cells, supporting cross-disease adaptability (54). Yet CAAR-T's clinical advance in MN is constrained by challenges in: tailoring constructs to other antigens (NELL1, CNTN1, etc.) (51), handling patients with unknown targets, mitigating CRS/ICANS, and enabling tunable and reversible T-cell control (50). CAAR-T also carries logistical burdens: autologous production spans 2–3 weeks of leukapheresis, lentiviral transduction, and GMP-grade expansion. CAAR-T for MN is unlikely to cost less than oncology CAR-T therapies, given the smaller patient pool and fewer economies of scale.

5.2 Co-stimulatory blockade and cytokine-directed T-cell modulation

In MN, T cells play helper and regulatory roles in immunopathogenesis; co-stimulatory blockade is a key approach to antigen-specific

tolerance. Abatacept (CTLA-4-Ig) interrupts T-cell co-stimulation by competing for CD80/CD86, thereby dampening T-cell-dependent B-cell response (55). Abatacept's efficacy in MN varies, with some studies reporting decreased proteinuria and antibodies, others not, likely attributable to heterogeneous T-cell-dependent/independent autoantibody mechanisms (56, 57). Additionally, abatacept may act directly on podocytes: by binding B7-1 (CD80) on injured podocytes, it stabilizes β1-integrin and preserves slit diaphragm integrity, as shown in B7-1-positive FSGS (58). Upstream immune inhibition also poses infection and cancer surveillance risks. Given that MN also engages innate immunity and complement (16, 56), sole co-stimulatory targeting may be insufficient.

T-cell differentiation is another target under investigation. In MN, Th17/Treg dysregulation plays a pivotal role—IL-6/IL-23-axis promotes Th17 differentiation and inflammation, whereas Treg deficiency undermines tolerance (59). IL-6 contributes to Th17-mediated inflammation in MN, and IL-6 receptor blockade with tocilizumab—though primarily validated in iMCD-associated nephropathy (60)—represents a mechanistically rational strategy for Th17-high primary MN that awaits clinical validation (61). The complexity of MN pathogenesis calls for caution in T-cell targeting—mono-targeting may not suffice for sustained tolerance, and combinatorial approaches that coordinate innate and adaptive immunity will probably be required (16, 56, 62).

5.3 Regulatory T-cell therapy

Tregs are key to peripheral tolerance, restraining effector T-cell and autoreactive B-cell activation/expansion via inhibitory cytokines (IL-10, TGF-β) and cell-contact mechanisms (63). Reduced Treg counts and dysfunction in MN, linked to activity and antibody levels (64), argue for restoring tolerance via adoptive autologous Tregs (ex vivo-expanded) or endogenous expansion to limit disease progression.

CAR-Tregs, engineered to display antigen-specific CARs, deliver precise immunosuppression to target tissues or cells. They can localize to autoantigen-presenting cells or inflamed areas in autoimmunity, providing regional control with fewer systemic adverse effects (65). HLA matching or CRISPR editing improves Treg stability and persistence, reducing MHC-related restrictions and rejection (66). Low-dose IL-2 expands Tregs to rebalance tolerance, with preliminary efficacy in SLE and other autoimmune diseases—suggesting a promising outlook for MN (67–69). Yet key obstacles to Treg therapy include the technical difficulty of expanding and sustaining Tregs ex vivo, their instability in inflamed settings (risking effector T-cell conversion), and limited homing/persistence after adoptive transfer (64).

6 Outlook: from passive elimination to active immunization

6.1 B-cell epitope-based immunotherapy vaccine

Designed to induce antigen-specific tolerance, B-cell epitope vaccines use epitopes from autoantigens (e.g., PLA2R) with suitable delivery and adjuvants to promote tolerance over activation, thereby achieving durable elimination or silencing of pathogenic B-cell clones. Epitope vaccines offer theoretical benefits over traditional B-cell depletion, including greater specificity, reduced off-target effects, and durable tolerance induction (70, 71). In the HN rat model (72), immune interventions targeting the anti-gp330 (rat Megalin) autoimmune response—such as depleting antibody-producing cells or suppressing autoantibody production—prevented the development of HN and reduced proteinuria (73), supporting the rationale for MN epitope vaccine development. Fine-mapping of human PLA2R B-cell epitopes (74) further enables patient-specific vaccine design based on individual epitope profiles. B-cell epitope vaccines face clinical barriers: epitope diversity in MN antigens may limit a one-size-fits-all approach, demanding patient-tailored design by epitope profile (51, 75); moreover, self-antigen vaccines carry the risk of tolerance breakdown and enhanced autoimmunity, requiring refined dosing and immune surveillance (76, 77). Choosing adjuvants and delivery systems that promote tolerance rather than immunogenicity remains a central hurdle in epitope vaccine design; future work may leverage nanoparticle, DNA, or mRNA platforms with refined antigen presentation and co-stimulation to safely achieve antigen-specific tolerance (78).

6.2 Vaccines: T-cell-based and anti-idiotype approaches

T cell vaccination (TCV) uses attenuated or inactivated autologous T cells to elicit immune responses against pathogenic clones, thereby eliminating autoreactive T cells and inducing immune tolerance. Initially validated by Cohen et al. (79) across multiple autoimmune models, this strategy also curbs proteinuria and attenuates glomerular injury in the HN model (80). Wang et al. (81) found that TCV induces $CD8^+$ regulatory T cells, which suppress pathogenic T and B cell responses via contact-dependent mechanisms and protect rats from HN challenge. By delivering antigens via CD40 to dendritic cells and evoking tolerogenic responses locally, DNA vaccines have been shown to avert HN (73), providing a proof-of-concept for TCV in MN—yet transitioning to clinical practice hinges on clonotype identification, standardized production, and surveillance of immune status.

Anti-idiotype vaccine strategies are grounded in the characterization of pathogenic autoantibody idiotypes, as demonstrated for anti-gp330 in HN (82). Also, DNA vaccination with a pathogenic TCR-encoding construct triggers specific anti-TCR humoral responses, attenuating proteinuria in active HN (83). Clinical translation of these strategies must account for inter-individual variability in autoantibody and TCR repertoires, likely requiring high-throughput sequencing for personalized vaccine design. Single-cell sequencing and bioinformatics now enable precise identification of pathogenic B-cell clones and TCR sequences, laying the groundwork for individualized anti-idiotype and TCV vaccines (84).

6.3 Novel vaccine platforms and technological innovations

Recent vaccine technology advances offer a major opportunity for MN vaccine translation. mRNA-based platforms, characterized

by rapid design, scalability, and multi-antigen coding, have proven effective in preventing infectious diseases and are promising for autoimmune tolerance (78, 85, 86). Optimized design and delivery allow efficient autoantigen expression and tolerogenic presentation in APCs, addressing the key drawback of conventional protein vaccines—excessive immunogenicity.

Nanoparticle delivery systems provide a tunable platform for precise antigen delivery and immune modulation. Modulating size, surface chemistry, and composition enables targeted delivery to specific immune subsets, while co-delivering immunomodulators like IL-10 and TGF-β steers responses toward tolerance (87, 88). Moreover, delivering nanoparticles to tolerogenic organs such as the liver and intestinal mucosa could harness their natural tolerogenic milieu to promote antigen-specific Treg induction and expansion.

6.4 Challenges and translational prospects

Despite the theoretical promise of MN-based vaccines, clinical translation remains challenging. Target heterogeneity is a major obstacle. Although the antigen repertoire in MN is relatively well established (5), antibody targets vary considerably across patients, and some individuals carry multiple autoantibodies simultaneously, rendering a single-antigen vaccine inadequate for covering the entire patient spectrum. Furthermore, epitope spreading may occur over the disease course, where an initial response against one epitope gradually extends to other epitopes on the same antigen or to distinct antigens, further complicating vaccine design (89).

Moreover, how long tolerance lasts determines the overall efficacy of vaccine strategies. Long-term maintenance after discontinuation is governed by Treg stability, memory response regulation, and immune microenvironment remodeling (64, 80). While $CD8^+$ Tregs are key mediators of peptide vaccine–driven tolerance (81, 90), their long-term stability and functional maintenance are poorly understood. On the safety front, self-antigen vaccines pose inherent risks of tolerance disruption and exacerbated autoimmune responses, underscoring the need for rigorous surveillance and control mechanisms (71, 76, 77).

The translational outlook for MN vaccine strategies could be advanced through several avenues: precisely identifying pathogenic B-cell clones and TCR sequences via high-throughput sequencing and bioinformatics to enable personalized vaccines (84, 91); exploring novel platforms such as nanoparticle delivery systems and mRNA vaccines to refine antigen presentation and guide immune responses (92); combining multiple immune interventions—for instance, CAAR-T with Treg therapy, or epitope vaccines with low-dose IL-2—to synergistically foster antigen-specific tolerance (50, 54, 93); and establishing comprehensive biomarker panels for early efficacy prediction and real-time monitoring (94). With rapid advances in immunology and biotechnology, vaccine strategies for MN are poised to move from proof-of-concept to clinical application, offering a new route toward long-term remission and potentially even cure.

Several rational therapies have underperformed in MN: eculizumab, limited by persistent upstream activation; felzartamab, immunologically active yet clinically ineffective in RTX-resistant disease; abatacept, with inconsistent results; and avacopan, whose phase 3 data were retracted. These results underscore that mechanistic rationale alone does not guarantee clinical benefit, and that biomarker-guided patient selection will be essential for future antigen-specific therapies. Personalized vaccines meet comparable obstacles: individualized epitope mapping and per-patient manufacturing restrict widespread use. Pre-formulated multi-epitope mRNA vaccines against prevalent PLA2R epitopes may cut costs, albeit with reduced personalization. Demonstrating cost-effectiveness will be essential for reimbursement.

7 Discussion

Here we provide a systematic overview of MN immunotherapy's development, revealing a clear transition from nonspecific immunosuppression toward antigen-specific immune tolerance that unfolds across three escalating levels.

Vaccinology offers a useful vantage on this tiered progression. The three tiers of MN immunotherapy and the established vaccine paradigm pursue opposite ends—tolerance induction versus protective immunity—yet converge on shared technological platforms. mRNA, nanoparticle carriers, and adjuvant systems, all originally refined for prophylactic vaccines, can be repurposed to build tolerogenic vaccines against MN. The correspondence runs deeper still: passive B-cell depletion mirrors passive antibody transfer; immune modulation recalls the action of immunomodulatory vaccines; and antigen-specific tolerance echoes the defining principle of prophylactic vaccination—antigen-specific protection—while inverting its purpose from immunity to tolerance.

Nevertheless, MN vaccine strategies are still at an early translational stage, and the gap with infectious disease vaccines is substantial. The reasons: the tolerogenic machinery for self-antigens is intrinsically more intricate than anti-foreign immunity, involving both central and peripheral checkpoints; the MN population is small, limiting market pull and making patient enrollment challenging; and safety margins are extremely narrow, as any sign of flare-up could halt further development.

Priorities for future studies include, first, refining self-antigen delivery via nanoparticles or peptide–MHC complexes to enhance tolerogenic vaccine precision, and testing multi-epitope regimens to address MN subtype diversity. Another priority is to develop standardized clinical endpoints and biomarker systems for evaluating MN tolerogenic vaccines. A clearance-to-tolerance sequential regimen merits testing. For clearance, rituximab is first-line; if refractory, obinutuzumab, felzartamab, or CAAR-T (most antigen-specific) can be substituted, with choice guided by anti-PLA2R titer, prior therapy, and ARA status. We propose that the transition to tolerance induction could be guided by: anti-PLA2R titers declining approximately ≥ 50% or reaching seronegativity (13, 94); $CD19^+$ B-cell recovery (~6–9 months post-rituximab, extrapolated from SLE experience) (36); and partial remission per KDIGO criteria (proteinuria <3.5 g/24h) (95). These proposed thresholds require prospective validation. Such cutoffs remain provisional pending prospective confirmation. Tolerance induction would ideally rely on PLA2R epitope vaccines carried by tolerogenic

nanoparticles or mRNA constructs, pairing them with tolerogenic rather than inflammatory adjuvants. Low-dose IL-2 could additionally support Treg expansion.

8 Conclusion

The treatment of MN has shifted from nonspecific immunosuppression toward B-cell depletion and, more recently, antigen-specific modulation. Rituximab, a CD20 antibody, clears circulating B cells and remains first-line, but resistance involving Fc receptor variants, long-lived plasma cells, and ARA production has prompted efforts to target deeper disease mechanisms. New biologics directed against BAFF/APRIL signaling, $CD38^{+}$ plasma cells, or complement provide alternatives for RTX non-responders, though each carries limitations. Strategies such as CAAR-T, Treg therapy, and B-cell epitope vaccines may enable durable remission and represent a shift toward antigen-specific therapy. Their clinical adoption, however, faces challenges including target heterogeneity, durability of tolerance, and safety concerns.

A sequential "clearance-then-tolerance" approach could combine B-cell depletion (CD20 mAbs or CAAR-T) during active disease with Treg therapy or tolerogenic vaccination in remission to sustain antigen-specific tolerance. mRNA and nanoparticle platforms may facilitate clinical translation of these vaccine strategies toward more personalized MN care.

Author contributions

KY: Methodology, Writing – original draft, Project administration. XX: Writing – original draft. JG: Software, Writing – original draft. JX: Writing – original draft. XY: Writing – original draft. QS: Writing – original draft, Validation. KW: Validation, Writing – review & editing. XL: Project administration, Resources, Writing – original draft. XC: Project administration, Funding acquisition, Writing – review & editing, Resources. GZ: Resources, Project administration, Funding acquisition, Writing – review & editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. Ningbo Clinical Research Center for Traditional Chinese medicine nephropathy: 2023L001; Traditional Chinese Medicine Science and Technology Plan Project of Zhejiang Province: 2025ZL111, 2023ZL147; Zhejiang Key Discipline Construction Plan of Traditional Chinese Medicine: 2024-XK-63.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Yin L, Tian F, Li Z, Chen W, Liu C, Zhang Y, et al. Benzo[b]fluoranthene is involved in idiopathic membranous nephropathy by inducing podocyte injury. *J Trans Internal Med.* (2025) 13:118–27. doi: 10.1515/jtim-2025-0022

2. Bi J, Guo W, Ji P, Wang X, Xie Y. Diagnosis and treatment of membranous nephropathy in integrative medicine. *Integr Med Nephrol Andrology*. (2024) 11. doi: 10.1097/IMNA-D-23-00014

3. Tomas NM, Hoxha E, Reinicke AT, Fester L, Helmchen U, Gerth J, et al. Autoantibodies against thrombospondin type 1 domain-containing 7A induce membranous nephropathy. *J Clin Invest*. (2016) 126:2519–32. doi: 10.1172/jci85265

4. Sethi S, Debiec H, Madden B, Charlesworth MC, Morelle J, Gross L. Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. *Kidney Int*. (2020) 97:163–74. doi: 10.1016/j.kint.2019.09.014

5. Ronco P, Debiec H. Pathophysiological advances in membranous nephropathy: time for a shift in patient's care. *Lancet*. (2015) 385:1983–92. doi: 10.1016/s0140-6736(15)60731-0

6. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl M A, Hoy WE, et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney Int*. (2001) 59:1484–90. doi: 10.1046/j.1523-1755.2001.0590041484.x

7. Li M, Chen X, Li Q. Advances in the treatment of refractory membranous nephropathy with integrative medicine. *Integr Med Nephrol and Andrology*. (2025) 12(2). doi: 10.1097/IMNA-D-24-00045

8. Zhao X, Liu Z, Wu C. Gut microbiota and membranous nephropathy: novel molecular mechanisms and natural product therapeutic strategies. *Integr Med Nephrol Andrology*. (2025) 12. doi: 10.1097/IMNA-D-25-00007

9. Tomas NM. Therapeutic targets in membranous nephropathy: plasma cells and complement. *Clin Kidney J*. (2024) 17:sfae243. doi: 10.1093/ckj/sfae243

10. Jin Q, Zhan Y. Traditional Chinese medicine as a promising therapy for patients with membranous nephropathy. *Integr Med Nephrol Andrology*. (2025) 12. doi: 10.1097/IMNA-D-25-00020

11. Dahan K, Debiec H, Plaisier E, Cachanado M, Rousseau A, Wakselman L, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. *J Am Soc Nephrol*. (2017) 28:348–58. doi: 10.1681/asn.2016040449

12. Fervenza FC, Appel GB, Barbour SJ, Rovin BH, Lafayette RA, Aslam N, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med*. (2019) 381:36–46. doi: 10.1056/NEJMoa1814427

13. Beck LH Jr., Fervenza FC, Beck DM, Bonegio RG, Malik FA, Erickson SB, et al. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. *J Am Soc Nephrol*. (2011) 22:1543–50. doi: 10.1681/asn.2010111125

14. Vink CH, van Cranenbroek B, van der Heijden JW, Koenen H, Wetzels JFM. Daratumumab for multidrug-resistant phospholipase-A2 receptor-related membranous nephropathy. *Kidney Int*. (2022) 101:646–7. doi: 10.1016/j.kint.2021.12.019

15. Rovin BH, Ronco PM, Wetzels JFM, Adler SG, Ayoub I, Zaoui P, et al. Phase 1b/2a study assessing the safety and efficacy of felzartamab in anti-phospholipase A2 receptor autoantibody-positive primary membranous nephropathy. *Kidney Int Rep*. (2024) 9:2635–47. doi: 10.1016/j.ekir.2024.06.018

16. Seifert L, Zahner G, Meyer-Schwesinger C, Hickstein N, Dehde S, Wulf S, et al. The classical pathway triggers pathogenic complement activation in membranous nephropathy. *Nat Commun*. (2023) 14:473. doi: 10.1038/s41467-023-36068-0

17. Barrett C, Willcocks LC, Jones RB, Tarzi RM, Henderson RB, Cai G, et al. Effect of belimumab on proteinuria and anti-phospholipase A2 receptor autoantibody in primary membranous nephropathy. *Nephrol Dial Transplant*. (2020) 35:599–606. doi: 10.1093/ndt/gfz086

18. Netti GS, Infante B, Spadaccino F, Godeas G, Corallo MG, Prisciandaro C, et al. Serum levels of BAFF and APRIL predict clinical response in anti-PLA2R-positive primary membranous nephropathy. *J Immunol Res*. (2019) 2019:8483650. doi: 10.1155/2019/8483650

19. Zhu H, Sun J, Yan Y, Liu P, Huang Y. Immune podocyte injury in autoimmune glomerular diseases. *Front Immunol*. (2026) 17:1804416. doi: 10.3389/fimmu.2026.1804416

20. Langan D, Rose NR, Moudgil KD. Common innate pathways to autoimmune disease. *Clin Immunol*. (2020) 212:108361. doi: 10.1016/j.clim.2020.108361

21. Pescovitz MD. Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. *Am J Transplant*. (2006) 6:859–66. doi: 10.1111/j.1600-6143.2006.01288.x

22. Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. *Immunol Today*. (1994) 15:450–4. doi: 10.1016/0167-5699(94)90276-3

23. Slifka MK, Ahmed R. Long-lived plasma cells: a mechanism for maintaining persistent antibody production. *Curr Opin Immunol*. (1998) 10:252–8. doi: 10.1016/s0952-7915(98)80162-3

24. Wu Y, Jiang H, Hu Y, Dai H, Zhao Q, Zheng Y, et al. B cell dysregulation and depletion therapy in primary membranous nephropathy: prospects and potential challenges. *Int Immunopharmacol*. (2024) 140:112769. doi: 10.1016/j.intimp.2024.112769

25. Mackay F, Schneider P, Rennert P, Browning J. BAFF AND APRIL: a tutorial on B cell survival. *Annu Rev Immunol*. (2003) 21:231–64. doi: 10.1146/annurev.immunol.21.120601.141152

26. Couser WG. Pathogenesis of glomerular damage in glomerulonephritis. *Nephrol Dial Transplant*. (1998) 13 Suppl 1:10–5. doi: 10.1093/ndt/13.suppl_1.10

27. Takano T, Elimam H, Cybulsky AV. Complement-mediated cellular injury. *Semin Nephrol*. (2013) 33:586–601. doi: 10.1016/j.semnephrol.2013.08.009

28. Pickering M, Cook HT. Complement and glomerular disease: new insights. *Curr Opin Nephrol Hypertens*. (2011) 20:271–7. doi: 10.1097/MNH.0b013e328345848b

29. Scolari F, Delbarba E, Santoro D, Gesualdo L, Pani A, Dallera N, et al. Rituximab or cyclophosphamide in the treatment of membranous nephropathy: the RI-CYCLO randomized trial. *J Am Soc Nephrol*. (2021) 32:972–82. doi: 10.1681/asn.2020071091

30. Zhong H, Li HY, Zhou T, Zhong Z. Clinical efficacy and safety of rituximab with membranous nephropathy: a meta-analysis. *Arch Med Sci*. (2023) 19:411–9. doi: 10.5114/aoms.2020.99899

31. Radhakrishnan Y, Zand L, Sethi S, Fervenza FC. Membranous nephropathy treatment standard. *Nephrol Dial Transplant*. (2024) 39:403–13. doi: 10.1093/ndt/gfad225

32. Fervenza FC, Hou FF, Hao CM, Kirsztajn GM, Gesualdo L, Hryszko T, et al. Obinutuzumab or tacrolimus in primary membranous nephropathy. *N Engl J Med*. (2026). doi: 10.1056/NEJMoa2602678

33. Chen Z, Xu D, Wu S, Liu W, Wu J, Yu S, et al. The role of obinutuzumab in rituximab-refractory membranous nephropathy and minimal change disease. *Clin Kidney J*. (2025) 18:sfaf039. doi: 10.1093/ckj/sfaf039

34. Allinovi M, Teisseyre M, Accinno M, Finocchi C, Esnault VLM, Cremoni M, et al. Anti-rituximab antibodies occurrence and clinical outcomes in patients with primary membranous nephropathy. *Kidney Int Rep*. (2025) 10:2621–9. doi: 10.1016/j.ekir.2025.04.059

35. Ayub F, Arthur J, Hasan MR, Juncos LA, Holthoff JH. Plasma cell-directed rescue with bortezomib in refractory antiphospholipase A2 receptor-positive membranous nephropathy. *Kidney Int Rep*. (2025) 10:4109–12. doi: 10.1016/j.ekir.2025.08.036

36. Frade-Sosa B, Sarmiento-Monroy JC, Bruce IN, Arnaud L, Gómez-Puerta JA. Dual B-cell targeting in systemic lupus erythematosus: the role of combined and sequential therapy with rituximab and belimumab. *Autoimmun Rev*. (2025) 24:103837. doi: 10.1016/j.autrev.2025.103837

37. Chen S, Huang Y, Qu Z. Telitacicept monotherapy for refractory idiopathic membranous nephropathy: a case report and literature review. *Front Med (Lausanne)*. (2025) 12:1571616. doi: 10.3389/fmed.2025.1571616

38. Madan A, Yalavarthy R, Kim DK, Moon JY, Park I, Mandayam S, et al. Povetacicept for IgA nephropathy and primary membranous nephropathy. *Kidney Int Rep*. (2026) 11:106–16. doi: 10.1016/j.ekir.2025.10.029

39. Zhang J, Yin Z, Liang Z, Bai Y, Zhang T, Yang J, et al. Impacts of cryopreservation on phenotype and functionality of mononuclear cells in peripheral blood and ascites. *J Transl Int Med*. (2024) 12:51–63. doi: 10.2478/jtim-2023-0136

40. van de Donk NW, Janmaat ML, Mutis T, Lammerts Van Bueren JJ, Ahmadi T, Sasser AK, et al. Monoclonal antibodies targeting CD38 in hematological Malignancies and beyond. *Immunol Rev*. (2016) 270:95–112. doi: 10.1111/imr.12389

41. Bilen Y, Fischman C, Geara AS. Daratumumab in refractory membranous nephropathy: a report of four cases: TH-PO0773. *J Am Soc Nephrol*. (2025) 36:10.1681/ASN.2025n1643pe1639p. doi: 10.1681/ASN.2025n43pe39p

42. Trillini M, Casiraghi F, Gennarini A, Portalupi V, Marasà M, Podestà MA, et al. Prospective cohort study of felzartamab in rituximab-resistant primary membranous nephropathy. *Kidney Int Rep*. (2026) 11:106468. doi: 10.1016/j.ekir.2026.106468

43. Cravedi P. Complement in membranous nephropathy: what we thought we knew and what we really know. *Kidney Int*. (2021) 100:499–501. doi: 10.1016/j.kint.2021.03.010

44. Yu S, Sun J. A review of progress on complement and primary membranous nephropathy. *Med (Baltimore)*. (2024) 103:e38990. doi: 10.1097/md.0000000000038990

45. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol*. (2017) 28:2756–67. doi: 10.1681/asn.2016111179

46. Rubin EJ. Retraction: Jayne DRW et al. Avacopan for the treatment of ANCA-associated vasculitis, N Engl J Med 2021;384:599-609. *N Engl J Med*. (2026). doi: 10.1056/NEJMe2608684

47. Lafayette RA, Rovin BH, Reich HN, Tumlin JA, Floege J, Barratt J, et al. Safety, tolerability and efficacy of narsoplimab, a novel MASP-2 inhibitor for the treatment of IgA nephropathy. *Kidney Int Rep*. (2020) 5:2032–41. doi: 10.1016/j.ekir.2020.08.003

48. Macciò L, Russo E, Costigliolo F, Battaglia Y, Viazzi F, Esposito P, et al. New anticomplement drugs in nephrology: mechanism and indication. *Kidney Blood Press Res*. (2026) 51:365–77. doi: 10.1159/000551965

49. Jesiołowski P, Krzywda M, Furmańczyk-Zawiska A, Durlik M. Complement dysregulation in kidney diseases: mechanisms, biomarkers, and emerging targeted therapies. *Int J Mol Sci*. (2026) 27(8):3466. doi: 10.3390/ijms27083466

50. Altun B, Zhao G, Wang B, Mao X, Manfredo-Vieira S, Willis E, et al. Preclinical evaluation of antigen-specific B-cell depletion for phospholipase A2 receptor membranous nephropathy with chimeric autoantibody receptor T cells. *Kidney Int*. (2026) 109:89–100. doi: 10.1016/j.kint.2025.09.028

51. Hyodo T, Hara S, Goto S, Fujii H, Nishi S, Yoshimoto A, et al. Clinicopathological characteristics of neural epidermal growth factor-like 1 protein-associated membranous glomerulonephritis. *Virchows Arch*. (2025) 486:991–1000. doi: 10.1007/s00428-024-03921-6

52. Weinkove R, George P, Dasyam N, McLellan AD. Selecting costimulatory domains for chimeric antigen receptors: functional and clinical considerations. *Clin Transl Immunol*. (2019) 8:e1049. doi: 10.1002/cti2.1049

53. Ellebrecht CT, Bhoj VG, Nace A, Choi EJ, Mao X, Cho MJ, et al. Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. *Science*. (2016) 353:179–84. doi: 10.1126/science.aaf6756

54. Cheever A, Lindsay HG, Kang CC, Hansen M, Demars K, O'Neill KL, et al. Chimeric autoantibody receptor T cells specifically eliminate Graves' Disease autoreactive B cells. *Front Immunol*. (2025) 16:1562662. doi: 10.3389/fimmu.2025.1562662

55. Korhonen R, Moilanen E. Abatacept, a novel CD80/86-CD28 T cell co-stimulation modulator, in the treatment of rheumatoid arthritis. *Basic Clin Pharmacol Toxicol*. (2009) 104:276–84. doi: 10.1111/j.1742-7843.2009.00375.x

56. Chung EYM, Wang YM, Shaw K, Ronning E, Wang Y, Zhang GY, et al. T cell costimulatory blockade ameliorates induction of experimental membranous nephropathy potentially through T-helper 17 cell suppression in the kidney. *Nephrol Dial Transplant*. (2025) 40:2058–73. doi: 10.1093/ndt/gfaf030

57. Trachtman H, Gipson DS, Somers M, Spino C, Adler S, Holzman L, et al. Randomized clinical trial design to assess abatacept in resistant nephrotic syndrome. *Kidney Int Rep*. (2018) 3:115–21. doi: 10.1016/j.ekir.2017.08.013

58. Yu CC, Fornoni A, Weins A, Hakroush S, Maiguel D, Sageshima J, et al. Abatacept in B7-1-positive proteinuric kidney disease. *N Engl J Med*. (2013) 369:2416–23. doi: 10.1056/NEJMoa1304572

59. Motavalli R, Etemadi J, Soltani-Zangbar MS, Ardalan MR, Kahroba H, Roshangar L, et al. Altered Th17/Treg ratio as a possible mechanism in pathogenesis of idiopathic membranous nephropathy. *Cytokine*. (2021) 141:155452. doi: 10.1016/j.cyto.2021.155452

60. Saiki R, Katayama K, Hirabayashi Y, Oda K, Fujimoto M, Murata T, et al. Membranous nephropathy associated with multicentric Castleman's disease that was successfully treated with tocilizumab: a case report and review of the literature. *BMC Nephrol*. (2021) 22:216. doi: 10.1186/s12882-021-02423-w

61. Cremoni M, Brglez V, Perez S, Decoupigny F, Zorzi K, Andreani M, et al. Th17-immune response in patients with membranous nephropathy is associated with thrombosis and relapses. *Front Immunol*. (2020) 11:574997. doi: 10.3389/fimmu.2020.574997

62. Scolari F, Alberici F, Mescia F, Delbarba E, Trujillo H, Praga M, et al. Therapies for membranous nephropathy: A tale from the old and new millennia. *Front Immunol*. (2022) 13:789713. doi: 10.3389/fimmu.2022.789713

63. Guo Z, Liu Y, Chen D, Sun Y, Li D, Meng Y, et al. Targeting regulated cell death: Apoptosis, necroptosis, pyroptosis, ferroptosis, and cuproptosis in anticancer immunity. *J Transl Int Med*. (2025) 13:10–32. doi: 10.1515/jtim-2025-0004

64. Li Y, Liu H, Yan H, Xiong J. Research advances on targeted-Treg therapies on immune-mediated kidney diseases. *Autoimmun Rev*. (2023) 22:103257. doi: 10.1016/j.autrev.2022.103257

65. Bulliard Y, Freeborn R, Uyeda MJ, Humes D, Bjordahl R, De Vries D, et al. From promise to practice: CAR T and Treg cell therapies in autoimmunity and other immune-mediated diseases. *Front Immunol*. (2024) 15:1509956. doi: 10.3389/fimmu.2024.1509956

66. Honaker Y, Dahl NP, Singh S, Singh AK, Lopez C, Gruber D. Preclinical efficacy and safety assessment of engineered regulatory T cells for treatment of IPEX and other autoimmune disorders. *Mol Ther*. (2026) 34:4035–53. doi: 10.1016/j.ymthe.2026.03.017

67. Barde F, Lorenzon R, Vicaut E, Rivière S, Cacoub P, Cacciatore C, et al. Induction of regulatory T cells and efficacy of low-dose interleukin-2 in systemic sclerosis: interventional open-label phase 1-phase 2a study. *RMD Open*. (2024) 10(2):e003500. doi: 10.1136/rmdopen-2023-003500

68. Zhang X, Feng R, Wang Y, Fan W, Gao X, Ma M, et al. Low dose IL-2 therapy restores regulatory T cells in patients with systemic lupus erythematosus in a dose-dependent manner: a phase IIb trial. *Nat Commun*. (2026) 17(1):5493. doi: 10.1038/s41467-026-72245-7

69. Saadoun D, Rosenzwajg M, Joly F, Six A, Carrat F, Thibault V, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. *N Engl J Med*. (2011) 365:2067–77. doi: 10.1056/NEJMoa1105143

70. Buckner JH. Antigen-specific immunotherapies for autoimmune disease. *Nat Rev Rheumatol*. (2025) 21:88–97. doi: 10.1038/s41584-024-01201-w

71. Kim A, Xie F, Abed OA, Moon JJ. Vaccines for immune tolerance against autoimmune disease. *Adv Drug Delivery Rev*. (2023) 203:115140. doi: 10.1016/j.addr.2023.115140

72. Cybulsky AV, Quigg RJ, Salant DJ. Experimental membranous nephropathy redux. *Am J Physiol Renal Physiol*. (2005) 289:F660–671. doi: 10.1152/ajprenal.00437.2004

73. Wang Y, Wang YM, Wang Y, Zheng G, Zhang GY, Zhou JJ, et al. DNA vaccine encoding CD40 targeted to dendritic cells in situ prevents the development of Heymann nephritis in rats. *Kidney Int*. (2013) 83:223–32. doi: 10.1038/ki.2012.374

74. Fresquet M, Lockhart-Cairns MP, Rhoden SJ, Jowitt TA, Briggs DC, Baldock C, et al. Structure of PLA2R reveals presentation of the dominant membranous nephropathy epitope and an immunogenic patch. *Proc Natl Acad Sci USA*. (2022) 119:e2202209119. doi: 10.1073/pnas.2202209119

75. Cheng X, Zhou M, Chen C, Xue J, Liu B, Zhang Z, et al. Clinical study of PLA2R epitope spreading for predicting proteinuria remission in primary membranous nephropathy. *Front Immunol*. (2025) 16:1685738. doi: 10.3389/fimmu.2025.1685738

76. Olivieri B, Betterle C, Zanoni G. Vaccinations and autoimmune diseases. *Vaccines (Basel)*. (2021) 9(8):815. doi: 10.3390/vaccines9080815

77. Peng M, Wang Z. Vaccine-associated autoimmunity: from clinical signals to immune pathways. *Vaccines (Basel)*. (2025) 13(11):1112. doi: 10.3390/vaccines13111112

78. Krienke C, Kolb L, Diken E, Streuber M, Kirchhoff S, Bukur T, et al. A noninflammatory mRNA vaccine for treatment of experimental autoimmune encephalomyelitis. *Science*. (2021) 371:145–53. doi: 10.1126/science.aay3638

79. Lohse AW, Cohen IR. Immunoregulation: studies of physiological and therapeutic autoreactivity by T cell vaccination. *Springer Semin Immunopathol*. (1992) 14:179–86. doi: 10.1007/bf00195293

80. Chung EYM, Wang YM, Shaw K, Ronning E, Wang Y, Zhang GY, et al. CD8(+) regulatory T cells induced by peptide vaccination ameliorates experimental model of membranous nephropathy. *Nephrol (Carlton)*. (2025) 30:e70005. doi: 10.1111/nep.70005

81. Wang YM, Zhang GY, Hu M, Polhill T, Sawyer A, Zhou JJ, et al. CD8+ regulatory T cells induced by T cell vaccination protect against autoimmune nephritis. *J Am Soc Nephrol*. (2012) 23:1058–67. doi: 10.1681/asn.2011090914

82. Specht Grijp-Glandorf RJ, De Heer E, Dekker-Nooren CC, Daha MR, Van Es LA. Specificity and cross-reactive idiotypes of anti-gp330 autoantibodies in active Heymann nephritis. *Immunology*. (1990) 70:290–5.

83. Wu H, Walters G, Knight JF, Alexander SI. DNA vaccination against specific pathogenic TCRs reduces proteinuria in active Heymann nephritis by inducing specific autoantibodies. *J Immunol*. (2003) 171:4824–9. doi: 10.4049/jimmunol.171.9.4824

84. Zaslavsky ME, Craig E, Michuda JK, Sehgal N, Ram-Mohan N, Lee JY, et al. Disease diagnostics using machine learning of B cell and T cell receptor sequences. *Science*. (2025) 387:eadp2407. doi: 10.1126/science.adp2407

85. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov*. (2018) 17:261–79. doi: 10.1038/nrd.2017.243

86. Wardell CM, Levings MK. mRNA vaccines take on immune tolerance. *Nat Biotechnol*. (2021) 39:419–21. doi: 10.1038/s41587-021-00880-0

87. Maldonado RA, Lamothe RA, Ferrari JD, Zhang AH, Rossi RJ, Kolte PN, et al. Polymeric synthetic nanoparticles for the induction of antigen-specific immunological tolerance. *Proc Natl Acad Sci USA*. (2015) 112:E156–165. doi: 10.1073/pnas.1408686111

88. Carambia A, Freund B, Schwinge D, Bruns OT, Salmen SC, Ittrich H, et al. Nanoparticle-based autoantigen delivery to Treg-inducing liver sinusoidal endothelial cells enables control of autoimmunity in mice. *J Hepatol*. (2015) 62:1349–56. doi: 10.1016/j.jhep.2015.01.006

89. Seitz-Polski B, Dolla G, Payré C, Girard CA, Polidori J, Zorzi K, et al. Epitope spreading of autoantibody response to PLA2R associates with poor prognosis in membranous nephropathy. *J Am Soc Nephrol*. (2016) 27:1517–33. doi: 10.1681/asn.2014111061

90. Vuttaradhi VK, Vermelle CM, Choi JY, Niu L, Tang X, Azzi JR, et al. CD8+ Regulatory T cells. *Annu Rev Immunol*. (2026) 44:21–40. doi: 10.1146/annurev-immunol-083024-030412

91. Fink K. Can we improve vaccine efficacy by targeting T and B cell repertoire convergence? *Front Immunol*. (2019) 10:110. doi: 10.3389/fimmu.2019.00110

92. Nachod BE, Thatte AS, Palanki R, Mitchell MJ. Nanoparticle-based tolerogenic vaccines: next-generation strategies for autoimmune and allergic disease therapies. *Angew Chem Int Ed Engl*. (2026) 65:e24097. doi: 10.1002/anie.202524097

93. Payne AS, Wang B, Manfredo-Vieira S, Mao X, Gill S, Hogan J, et al. Chimeric autoantibody receptor (CAAR) T cells as a precision therapy for antigen-specific B cell depletion in PLA2R membranous nephropathy: FR-OR32. *J Am Soc Nephrol*. (2021) 32:30. doi: 10.1681/ASN.20213210S130c

94. Tesar V, Hruskova Z. Autoantibodies in the diagnosis, monitoring, and treatment of membranous nephropathy. *Front Immunol*. (2021) 12:593288. doi: 10.3389/fimmu.2021.593288

95. KDIGO Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. (2021) 100:S1–S276. doi: 10.1016/j.kint.2021.05.021