Targeting B cells in immune-mediated kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Jürgen Floege[1], Isabelle Ayoub[2], Silke R. Brix[3,4,5], Kirk N. Campbell[6], Richard Furie[7], Patrick H. Nachman[8], Sydney C.W. Tang[9], Nicola M. Tomas[10,11], Marina Vivarelli[12], Michael Cheung[13], Jennifer M. King[13], Morgan E. Grams[14], Michel Jadoul[15] and Brad H. Rovin[16]; for Conference Participants[17]

[1]*Department of Nephrology & Rheumatology, University Hospital, Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Aachen, Germany;* [2]*Division of Nephrology, The Ohio State University, Columbus, Ohio, USA;* [3]*Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust, Manchester, UK;* [4]*Renal, Transplantation and Urology Unit, Manchester University NHS Foundation Trust, Manchester, UK;* [5]*Division of Cell Matrix Biology and Regenerative Medicine, University of Manchester, Manchester, UK;* [6]*Division of Renal-Electrolyte and Hypertension, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA;* [7]*Division of Rheumatology, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra-Northwell, Great Neck, New York, USA;* [8]*Division of Nephrology and Hypertension, University of Minnesota, Minneapolis, Minnesota, USA;* [9]*Division of Nephrology, Department of Medicine, School of Clinical Medicine, University of Hong Kong, Hong Kong, China;* [10]*III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [11]*Hamburg Center for Kidney Health (HCKH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [12]*Nephrology Research Unit and Clinical Trial Center, Bambino Gesù Children's Hospital IRCCS, Rome, Italy;* [13]*KDIGO, Brussels, Belgium;* [14]*Department of Medicine, New York University Langone School of Medicine, New York, New York, USA;* [15]*Division of Nephrology, Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium; and* [16]*Division of Nephrology, Department of Internal Medicine, The Ohio State Wexner Medical Center, Columbus, Ohio, USA*

Treatments that deplete or modulate B cells are in use or being investigated for several immune-mediated glomerular diseases. Kidney Disease: Improving Global Outcomes (KDIGO) convened a Controversies Conference in Panama City, Panama, in June 2025 to review current evidence and identify key gaps in knowledge and research needs to effectively apply such therapies. Availability, effectiveness, and safety of B cell–targeted therapies vary substantially across glomerular diseases. In IgA nephropathy, anti-CD20 therapy (rituximab) has shown limited efficacy, although inhibitors of survival factors BAFF (B cell activating factor) and APRIL (a proliferation-inducing ligand) and anti-CD38 antibodies can lead to reduction in proteinuria and reduction in decline in estimated glomerular filtration rate. In contrast, for membranous nephropathy, anti-CD20 antibodies have become first-line therapy, achieving at least partial remission in most patients by 18 months. In steroid-dependent nephrotic syndrome, rituximab effectively prevents relapses, particularly in children, though benefits are transient. For lupus nephritis, newer approaches including obinutuzumab and chimeric antigen receptor (CAR) T cell therapy have shown promising results, with CAR T cells introducing the possibility of being free of disease activity and treatment for a prolonged time. In antineutrophil cytoplasmic antibody–associated glomerulonephritis, rituximab has proven effective for both induction and maintenance therapy, with ongoing trials investigating CAR T cell approaches. Safety considerations of B cell–targeting therapies vary by intensity of therapy, with conventional anti-CD20 therapy showing favorable safety profiles and CAR T cell therapy requiring careful patient selection because of the potential for cytokine release syndrome and other serious adverse events. Validating biomarkers for patient selection and monitoring is a critical research need, along with optimizing treatment protocols and determining optimal therapy duration.

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Correspondence: *Jürgen Floege, Department of Nephrology & Rheumatology, University Hospital, Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Pauwelsstr. 30, 52074 Aachen, Germany. E-mail: jfloege@ukaachen.de; or Brad H. Rovin, Ohio State University Nephrology, 1654 Neil Avenue, Fourth Floor, Columbus, Ohio, USA. E-mail: brad.rovin@osumc.edu*

[17]Additional Conference Participants are listed in the Appendix.

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Recent clinical trials using biologics or cell therapies that deplete or modulate B cells have enhanced clinical responses across immune-mediated glomerular diseases. Despite the early failure of rituximab in lupus nephritis (LN),[1] using anti-CD20 monoclonal antibodies for

depleting B cells has become commonplace for managing podocytopathies,[2,3] membranous nephropathy (MN), vasculitis, and LN.[4,5] Monoclonal antibodies against the B cell growth and survival factors BAFF (B cell activating factor) and APRIL (a proliferation-inducing ligand) and anti-CD38 plasma cell antibodies have shown robust effects on proteinuria and glomerular filtration rate (GFR) stability in phase II to III IgA nephropathy (IgAN) trials. Chimeric antigen receptor (CAR) T cells constructed to bind and kill B lineage cells that express CD19 and/or B cell maturation antigen (BCMA) may change treatment paradigms for autoimmune diseases such as LN and have introduced the concepts of *deep B cell depletion*, *immunologic reset*, and even *cure*. A key question is whether deep B cell depletion is due to the greater breadth of B-lineage cells being depleted by CD19 and/or BCMA CAR T, or because CAR T cells achieve more complete peripheral and lymphoid tissue B cell depletion, or both. Trailing closely behind cell therapy in development are the T cell engagers, uniquely constructed antibodies that redirect the host's T cells to kill B cells or other specific cells of the host immune system (Figure 1).[6,7] Although these biologics and cell therapies offer the opportunity to titrate the level of B cell depletion, several issues need further clarification. These include the risk-benefit ratio and the required depth and method of B cell modulation and depletion for specific glomerular diseases and an individual's disease manifestations. To address these issues, adult and pediatric nephrologists, rheumatologists, pathologists, hematologists/cell therapists, B cell scientists, and patients with glomerular disease were assembled in Panama City, Panama, in June 2025 for the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on Therapies Targeting B Cells in Immune-Mediated Kidney Diseases.

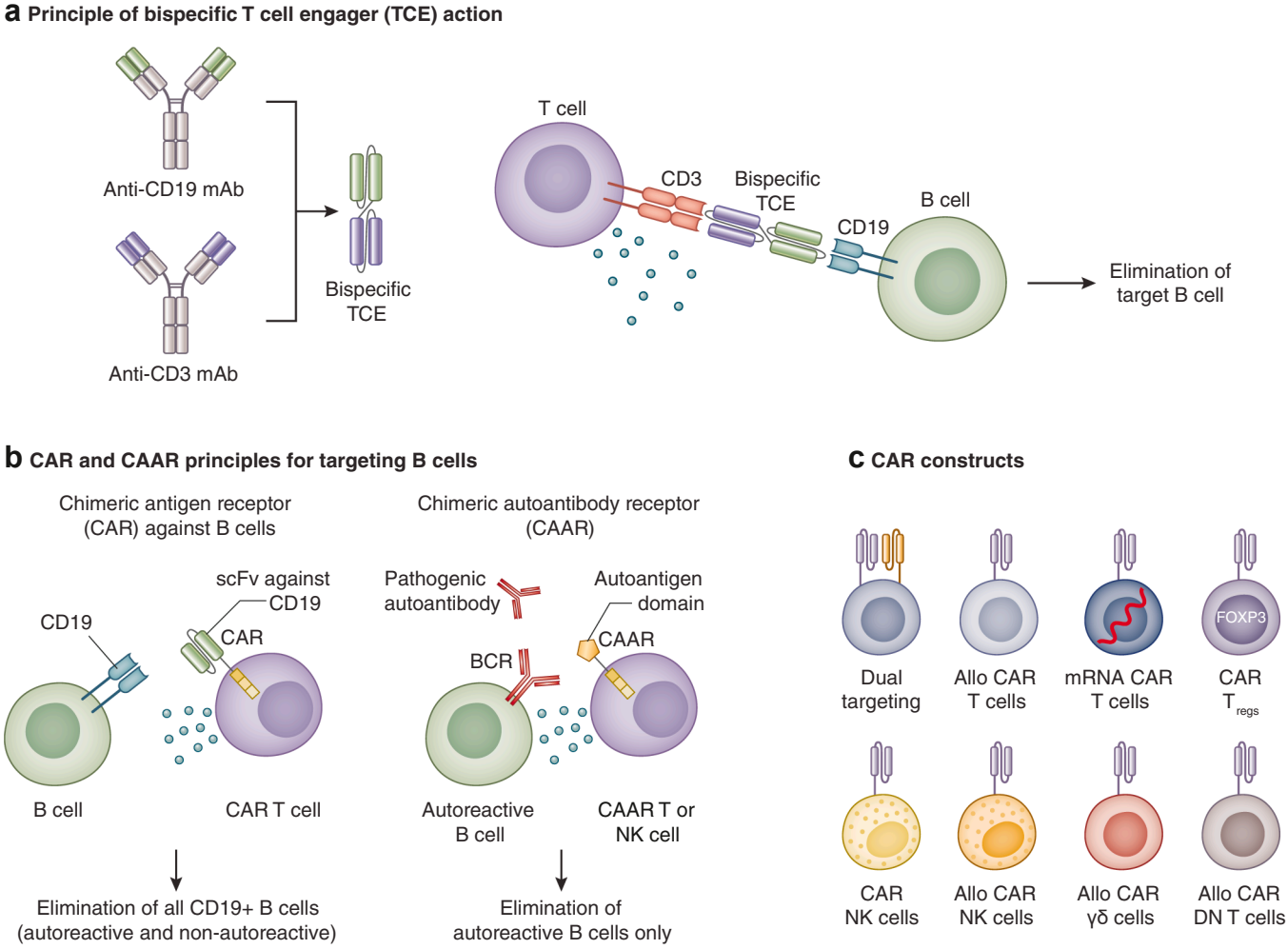

Figure 1 | Strategies for deep B cell depletion. (**a**) Principle of bispecific T cell engager (TCE) action using a nonantibody base. (**b**) Chimeric antigen receptor (CAR)–based approaches include the simultaneous targeting of multiple antigens, the use of autologous or allogeneic T cells to generate CAR T cells, mRNA-based genetic modification leading to transient expression of CARs, and the use of alternative cellular backbones such as regulatory T cells (T_{regs}), natural killer (NK) cells, γδ T cells, and CD3+ CD4/CD8 double-negative (DN) T cells (as shown in [**c**]). Chimeric autoantibody receptor (CAAR) T cells are engineered with a receptor that mimics the structure of an autoantigen and specifically binds to B cells and CD19+ plasma cells that express surface autoantibodies responsible for the production of pathogenic autoantibodies. BCR, B cell receptor; mAb, monoclonal antibody; scFv, single-chain variable fragment. (**c**) Reproduced with permission from Mougiakakos D, Meyer EH, Schett G. CAR T cells in autoimmunity: game changer or stepping stone? *Blood* 2025; 145:1841–1849.[8]

Rationale for targeting B cells in glomerular diseases

Many—maybe most—glomerular diseases are driven, at least in part, through (auto)antibodies. These secreted antibodies found in serum may arise in the setting of autoimmunity or may be normally present but altered or overproduced, may be directly pathogenic, or may activate other arms of the immune system to induce kidney injury.

A recent review of B cell and plasma cell biology has revealed the importance of long-lived, nonreplicating CD19+ plasma cells as possible key players in autoimmune disease. Contrary to popular belief, the vast majority of plasma cells in the human body are CD19+, including two-thirds of plasma cells in the bone marrow.[9,10] These CD19+ plasma cells are not short-lived plasmablasts; in the bone marrow <5% of both CD19+ and CD19− plasma cell subsets express the proliferation marker Ki-67,[9] and both subsets may live for years to decades (reviewed in Suan *et al.*[11]). Like short-lived plasmablasts and CD19− plasma cells, CD19+ plasma cells do not express CD20. Because CD19 is the cell surface reporter for paired box protein 5 (PAX5), the master transcription factor for the B cell program, these CD19+ plasma cells are also B cells, highlighted by their coexpression of surface Ig and major histocompatibility complex II. While functioning normally as plasma cells to secrete soluble antibody, CD19+ plasma cells may simultaneously perform the operations of a B cell: capturing antigen, presenting peptide–major histocompatibility complex II to CD4+ T cells, and clonally proliferating. Of note, secreted autoantibody in circulation may or may not be pathogenic, but the surface autoantibody on B cells and CD19+ plasma cells may be pathogenic by turning these cells into key autoantigen-presenting cells that activate CD4+ T cells. The recognition of this numerically dominant population of long-lived CD19+ CD20− plasma cells, which also function as B cells, provides one explanation for the differences observed between targeting CD20 and CD19 for depletion in autoimmune disease.[11]

Eliminating or suppressing B cells and/or plasma cells has emerged as a very appealing treatment strategy for glomerular diseases. This Controversies Conference was focused on IgAN, MN, podocytopathies, LN, and antineutrophil cytoplasmic antibody–associated glomerulonephritis (ANCA GN), as the pathogenesis of these glomerular diseases represents the breadth of antibody-mediated kidney injury.

IgA nephropathy. IgAN is an immune-mediated disease believed to be driven by altered gut and respiratory tract mucosal responsiveness, increased circulation of galactose-deficient IgA1 (Gd-IgA1) and likely other pathogenic IgA species, and cross-reactive anti-pathogen antibodies plus pathogenic autoantibodies (anti-Gd-IgA1 IgG and IgA autoantibodies) through oligoclonal expansion of autoantibody-producing cells. Increased BAFF and APRIL levels are associated with increased circulating levels of Gd-IgA1 and anti-Gd-IgA1 antibodies in IgAN,[12] and genetic loci encoding APRIL and its cognate B cell receptor transmembrane activator and calcium modulator and cyclophilin ligand interactor are risk loci for IgAN.[13] These B cell–associated factors contribute to the formation, circulation, and deposition of IgA-containing immune complexes in glomeruli, leading to progressive injury.[14]

Membranous nephropathy. MN is a classical autoimmune disease characterized by glomerular subepithelial Ig and complement deposition.[15,16] The identification of multiple autoantigens has led to a new antigen-based classification of MN.[17–19] Experimental studies verified that antibodies against M-type phospholipase A2 receptor (PLA2R) or thrombospondin type-1 domain-containing 7A (THSD7A) induce typical manifestations of MN.[20–25] In addition, emergence of anti-PLA2R autoantibodies may predict disease development[26] or relapse, and disappearance of anti-PLA2R autoantibodies precedes disease remission.[27] Higher antibody levels correlate with an increased risk of loss of kidney function, disease relapse, and disease recurrence after kidney transplantation as well as a lower likelihood for remission.[27–33]

Podocytopathies. Podocytopathies are characterized by pronounced, often nephrotic proteinuria and podocyte damage on biopsy. The classic examples are minimal change disease and focal segmental glomerulosclerosis (FSGS).[34] Until recently, minimal change disease had been considered a T cell–mediated disease, and FSGS was thought to be due to a circulating "permeability" factor, possibly derived from lymphocytes. Importantly, an FSGS pattern of injury can also be seen in diseases caused by genetic variations in podocyte proteins, and FSGS is a final common pathway of other glomerular injuries resulting in nephron loss. The idea that at least some podocytopathies could be mediated by B cells grew from observations that children and adults—mostly with minimal change disease but some with FSGS—responded to treatment with the B cell–depleting agent rituximab. The recent identification of anti-nephrin antibodies in adults and, more frequently, children with immunosuppression-responsive podocytopathies has now provided a possible explanation for these observations (Table 1).[35–41] In addition, proteinuria and podocyte injury developed in a rabbit after transfer of anti-nephrin IgG from a patient with minimal change disease, suggesting a pathogenic role of anti-nephrin autoantibodies.[42] Antibodies directed against other podocyte proteins, that is, podocin and Kirrel1 (kirre-like nephrin family adhesion molecule 1),[43] have since been described. Finally, levels of memory B cells have been shown to predict disease relapse in children.[44–47] Taken together, these findings suggest that at least some podocytopathies may be effectively treated with anti–B cell agents.

Systemic autoimmune diseases that affect the kidneys: LN and ANCA-associated vasculitis. The pathogenesis of systemic lupus erythematosus (SLE) involves most of the components of the immune system but seems to begin with loss of tolerance to self-antigens, possibly related to ineffective disposal of cellular debris.[48] Circulating autoantibodies to endogenous self-antigens are present in patients destined to develop SLE years before clinical disease is apparent.[49] As

Table 1 | Anti-nephrin antibodies in different forms of podocytopathy

Study	Detection method	Population	Positivity rate	Additional findings
Watts *et al.*[35]	Immunoprecipitation + signal-enhanced ELISA (laboratory nephrin-ECD-His)	MCD 41 children /21 adults (NEPTUNE)	18/62 (29%)	Shorter relapse-free in anti-nephrin (+)
Hengel *et al.*[37]	Immunoprecipitation or hybrid immunoprecipitation/ELISA (laboratory nephrin-ECD-His)	INS 182 children MCD 105 adults Primary FSGS 74 adults Secondary FSGS 40 adults	INS 94/182 (52%) MCD 46/105 (44%) Primary FSGS 7/74 (9%) Secondary FSGS 1/40 (3%)	Correlation of proteinuria with anti-nephrin titers Increased prevalence in IST naive
Raglianti *et al.*[41]	Standard ELISA (commercial RDnephrin-ECD-His)	MCD/FSGS 12 children SSNS 13 children MCD/FSGS 19 adults	MCD/FSGS 4/12 (33%) SSNS 5/13 (38%) MCD/FSGS 2/19 (11%)	Super-resolution microscopy showed colocalization with nephrin
Hengel *et al.*[38]	Immunoprecipitation (laboratory nephrin-ECD-His)	INS 333 children SSNS 101 SDNS 67 Nongenetic SDNS 103 Genetic SDNS 62	SSNS 69/101 (68%) SDNS 19/67 (28%) Nongenetic SDNS 14/103 (14%) Genetic SDNS 1/62 (2%)	Higher prevalence in active disease Positive nongenetic SDNS 18% response versus 0% negative
Shirai *et al.*[36]	Signal-enhanced ELISA (commercial RDnephrin-ECD-His)	FSGS 8 Nongenetic FSGS transplant 14 (11 recurrence)	Recurrent 11/11 (100%) Nonrecurrent 1/3 (33%)	
Batal *et al.*[39]	Signal-enhanced ELISA (laboratory nephrin-ECD-his)	MCD/FSGS transplant 38 (21 recurrence) *Before transplant*	Recurrent 8/21 (38%) Nonrecurrent 0/17 (0%)	(+) Anti-nephrin HR 4.29 (IQR, 1.25–18.8) for recurrence
Shu *et al.*[40]	Standard ELISA IgG/IgM-validated WB and microscopy (commercial SB nephrin-ECD-His)	MCD 436 Primary FSGS 160	MCD 196/436 (45%) (30% IgG/27% IgM/12% both) Primary FSGS 60/160 (37.5%) (29% IgG/24% IgM/16% both)	Higher prevalence active disease Positive > nephrotic syndrome Positive > relapse/frequent relapse Decreased at remission

ELISA, enzyme-linked immunosorbent assay; FSGS, focal segmental glomerulosclerosis; HR, hazard ratio; INS, idiopathic nephrotic syndrome; IQR, interquartile range; IST, immunosuppressive therapy; MCD, minimal change disease; nephrin-ECD-His, extracellular domain of nephrin fused to a polyhistidine tag; NEPTUNE, Nephrotic Syndrome Study Network; RD, R&D Systems; SB, Sino Biological; SDNS, steroid-dependent nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; WB, Western blot.

autoantibodies accumulate in patients with SLE and their repertoire of target antigens expands, clinical disease ensues. LN develops in ∼50% of patients with SLE owing to glomerular immune complex accumulation, activation of the complement system, and recruitment of leukocyte populations. The glomerular location of the immune complexes determines the subsequent histology of the LN (e.g., mesangial, membranous, and proliferative).

In contrast, ANCA GN is characterized by a pauci-immune glomerulonephritis, usually in the presence of circulating antibodies directed against myeloperoxidase (MPO) or proteinase 3 (PR3) present in the granules of neutrophils and lysosomes of monocytes. These antibodies activate neutrophils that have been primed to express MPO or PR3 on their surface, resulting in a respiratory burst that generates toxic oxygen free radicals and degranulation, initiating vasculitis. Glomerular and alveolar capillaries are particularly vulnerable to this injury, leading to glomerulonephritis and pulmonary hemorrhage, respectively.

Lessons from the application of B cell–directed therapies to glomerular diseases

B cell therapeutics tool box. An overview of established and emerging approaches discussed during the conference can be found in Table 2[11,50–53] and Figure 1.[8]

IgAN. In an open-label multicenter trial, rituximab did not significantly decrease proteinuria or affect kidney function over 12 months, nor did it reduce levels of Gd-IgA1 or

Table 2| Established and emerging approaches of therapies targeting B cells

Agent	Description and comments
Glucocorticoids, antimetabolites, and cytotoxic drugs	• Can deplete or affect the function of B cells,[52] but are not targeted B cell therapies and broadly affect other immune cell types, leading to a wide range of adverse events.
B cell–modulating agents	• Neutralize BAFF, APRIL, or BAFF plus APRIL. • BAFF binds to BCMA, TACI, and BAFF receptors on B cells and plasma cells; APRIL binds to BCMA and TACI receptors.[51] • BAFF inhibition impairs B cell maturation; APRIL does not. Both decrease Ig production, but APRIL is more selective for IgA than IgG. • APRIL inhibition may affect plasmablast and plasma cell differentiation, trafficking, and survival. • The BAFF inhibitor belimumab has been approved for treatment of LN.[50] • Anti-APRIL monoclonal antibodies (sibeprenlimab and zigakibart) or TACI receptor–IgG fusion proteins that block the effects of BAFF and APRIL (atacicept, telitacicept, and povetacicept) are being investigated mainly in IgAN. • The anti-APRIL monoclonal antibody sibeprenlimab has been approved for the treatment of IgAN.
Type I CD20 antibodies	• Anti-CD20 antibodies kill naive, germinal center, and memory B cells. • Rituximab kills B cells through complement and ADCC. • Used on-label to treat ANCA GN and off-label in IgA vasculitis, MCD, FSGS, MN, and LN. • Neutralized after cellular internalization through lipid rafts.
Type II CD20 antibodies	• Kill B cells through ADCC and programmed cell death, which do not require complement and are not internalized, so tend to be more potent than type I antibodies. • Obinutuzumab has been approved for the treatment of LN.
CD19 antibodies	• Extend the range of B cell and plasma cell subsets that are depleted to CD20− B lineage cells (e.g., short-lived plasmablasts and long-lived CD19+ plasma cells, but not very long-lived CD19 − plasma cells that mostly reside in the bone marrow).[9,11] • Inebilizumab is being investigated in LN in a phase II study (ClinicalTrials.gov Identifier: NCT06570798).
CD38 antibodies and other agents	• Monoclonal antibodies directed toward CD38 (daratumumab, felzartamab, and mezagitamab) and small molecules (bortezomib) kill both short-lived plasmablasts and long-lived plasma cells.
CAR T cells directed against B cells and CD19+ plasma cells (CD19-CAR T cells) or B cells plus all plasma cells (CD19-BCMA CAR T cells)	• Currently being applied mainly to autoimmune diseases including LN. • Most programs use autologous cells; allogeneic and *in vivo* CAR T cell choices are emerging.[53] • Trial results raise new concepts such as depth of B cell depletion, immune reset, and the possibility of cure. • Need to determine the appropriate level of B cell depletion for an individual patient, given the choice of B cell therapies that result in different levels of depletion.
Bispecific antibodies and T cell engagers	• Engineered bispecific antibodies can be made, for example, to bind CD3 on T cells and CD19, CD20, or BCMA on B and plasma cells. • Binding B and T cells simultaneously allows the activated T cell to kill the B cell or plasma cell. • Conceptually like cell therapy without the need for cell infusions. • Range of adverse events due to activation of T cells and B cell killing is similar to those due to cell therapies. • Blinatumomab is being investigated in LN in a phase II study (ClinicalTrials.gov Identifier: NCT06570798).

ADCC, antibody-dependent cytotoxicity; ANCA GN, antineutrophil cytoplasmic antibody–associated glomerulonephritis; APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor; BCMA, B cell maturation antigen; CAR T cell, chimeric antigen receptor T cell; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; LN, lupus nephritis; MCD, minimal change disease; MN, membranous nephropathy; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor.

its corresponding autoantibodies.[54] Because plasma cells, which are not depleted by anti-CD20 treatment, likely produce Gd-IgA1 and anti-Gd-IgA1 antibodies, plasma cell depletion with proteasome inhibition or anti-CD38 monoclonal antibodies was tried in IgAN. Plasma cell depletion decreased proteinuria and slowed the rate of GFR decline.[55–57] Similarly, recent studies investigating anti-APRIL antibodies (such as sibeprenlimab[58,59] and zigakibart[60]) and dual BAFF/APRIL inhibitors (including atacicept,[61–63] telitacicept,[64] and povetacicept[65]) showed that compared with placebo, these B cell modulators decreased Gd-IgA1 and anti-Gd-IgA antibodies, reduced proteinuria, and slowed the rate of estimated glomerular filtration rate (eGFR) loss to levels comparable with physiologic decline during the treatment period. Despite overall reductions in serum IgA, IgG, and IgM, there was no increase in adverse events, including infections. However, upon treatment discontinuation, Gd-IgA1 levels rebounded toward baseline levels, suggesting that long-term suppression with these agents may be needed.[58,66]

In summary, peripheral depletion of CD20-expressing B cells is not sufficient to control IgAN. These results do not exclude the possibility that an anti-CD20 agent with better tissue B cell depletion or an anti-CD19 agent that broadens the scope of B cells depleted to include plasmablasts and CD19+ plasma cells could be effective. Very deep B cell depletion by CAR T cells, natural killer cells, or T cell engagers has not yet been tested in IgAN but may be of interest in treatment-refractory cases, where medication nonadherence or other injurious conditions have been excluded. A clinical trial from mainland China using CD19-CAR T cell therapy (ClinicalTrials.gov Identifier: NCT06690359) is underway in adults with biopsy-proven IgAN. If the phase II GFR slope data for APRIL and BAFF/APRIL inhibition are replicated in phase III trials, there may be no rationale for additional or combination therapy for IgAN, as achieving a physiologic rate of eGFR decline represents an optimal outcome and goal. Patients treated with a B cell modifier who continue to experience a decline in eGFR of >1 ml/min/yr may need additional therapy, possibly guided by kidney biopsy. It is even conceivable that foundational antiproteinuric chronic kidney disease agents, such as renin-angiotensin system blockers, may no longer be necessary in this context, even though this seems unlikely in the presence of advanced chronic kidney disease.

Membranous nephropathy. Anti-CD20 antibodies have become the first-line therapy for most patients with MN, and single agent treatment appears to be sufficient for the majority of patients requiring immunosuppressive therapy to attain at least partial remission by 18 months.[4,67–75] Obinutuzumab, a more potent anti-CD20 antibody than rituximab, has been successfully used, mainly in refractory MN.[76–78] It remains to be seen whether obinutuzumab has advantages over rituximab, particularly in rapidity, completeness, and duration of response. A phase III randomized controlled trial (RCT) (ClinicalTrials.gov Identifier: NCT04629248) testing obinutuzumab versus tacrolimus for MN is underway. A preliminary study of ofatumumab, a fully human anti-CD20 monoclonal antibody with strong complement-dependent cytotoxicity, revealed promising results, mainly in patients with refractory or complicated MN.[79]

Depending on the origin of autoantibodies in MN (CD19+ or CD19− plasma cells), an anti-CD19 monoclonal antibody may offer an advantage over anti-CD20 antibodies and/or may be similar to treatment with a combination of anti-CD20 and plasma cell inhibition.

Plasma cell–directed therapy with the anti-CD38 monoclonal antibody felzartamab was tested in an exploratory phase II trial in patients with PLA2R-associated MN with relapsing and refractory disease[80] and led to a rapid decline in anti-PLA2R levels in most patients and a decline in proteinuria of ≥50% in 35% of patients. Therapy was generally well-tolerated.

Combination B cell therapies are only beginning to be studied in MN. Because B cell depletion with anti-CD20 antibodies causes a rise in BAFF levels, which may promote the maturation of undepleted autoreactive B cells, an RCT exploring the combined use of "sandwich" belimumab-rituximab-belimumab in comparison to rituximab alone is underway (ClinicalTrials.gov Identifier: NCT03949855).[81] Other potential therapies being explored for MN include inhibitors of either APRIL or BAFF plus APRIL, and phase I/II study data of a BAFF/APRIL inhibitor were promising.[82] All the RCTs of rituximab in MN show that anti-PLA2R antibody levels decline within several weeks.[4,83] A proof-of-concept observational study evaluated the combination of plasmapheresis followed by an anti-CD20 agent with a goal to accelerate the reduction of anti-PLA2R antibodies.[84] This begs the question of whether a more rapid response for patients with MN may be achieved by using anti-CD38 therapy to rapidly reduce anti-PLA2R, followed by anti-CD20 therapy.

Although there is great enthusiasm over the potential of CAR T cell therapies for autoimmune diseases,[85–87] MN is typically not a rapidly progressive disease, does not usually require chronic immunosuppressive therapy, affects an older patient population that may be less able to tolerate CAR T cell therapy, and is rarely truly treatment-resistant. Thus, CAR T cell therapies are not felt to address an "urgent" unmet need in the treatment of MN and would be considered only for patients with severe nephrotic syndrome who fail to respond to anti–B cell therapy as well as to second-line treatment with cyclophosphamide and glucocorticoids. At the same time, the field is evolving rapidly. To further enhance treatment specificity and reduce adverse effects, application of more tolerable approaches may become an option for MN, and these may include "off-the-shelf" allogeneic CAR T cells, *in vivo* CAR T cells,[53] or CAR natural killer cells[88] or the use of antigen-specific strategies (e.g., exclusively targeting anti-PLA2R autoantibody–producing cells) (Figure 1).[89,90] A CD19XCD3 bispecific antibody is

currently being trialed in MN (ClinicalTrials.gov Identifiers: NCT07234474 and NCT06982729), but results are not yet available.

Podocytopathies. In children, B cell depletion with anti-CD20 antibodies is effective for preventing relapses of steroid-dependent nephrotic syndrome (SDNS)[91,92]; however, the evidence for rituximab to induce remission at initial disease presentation is lacking.[92,93] A meta-analysis of RCTs in children with SDNS/frequently relapsing nephrotic syndrome comparing rituximab with conventional immunosuppressive therapy showed that rituximab significantly increased short-term complete remission rates and long-term complete remission rates with some reduction in cumulative glucocorticoid dose and improvement in linear growth, albeit no significant differences in severe adverse events.[94] However, the benefit of rituximab is transient and retreatment protocols remain to be established.[95] In severe forms of SDNS, the sequential use of mycophenolate mofetil after rituximab has been shown to prolong the time to relapse.[96] Importantly, rituximab is less effective in severe childhood nephrotic syndrome[97] and in children younger than 10 years.[46] This may be because during the first 10 years of life, memory B cells are still developing and reconstitute more rapidly after B cell depletion.[98] The fully humanized anti-CD20 antibody ofatumumab has similar efficacy as rituximab.[99] Obinutuzumab was associated with remission in pediatric case reports[100] and is currently being compared in RCTs with mycophenolate mofetil (ClinicalTrials.gov Identifier: NCT05627557, phase II) and rituximab (ClinicalTrials.gov Identifier: NCT05786768, phase II–III).

In adults with SDNS/frequently relapsing nephrotic syndrome, case series and observational studies demonstrate a role for B cell depletion with rituximab in inducing complete remission (albeit with variable efficacy), decreasing the number of relapses, and prolonging the duration of remission.[101–105] There are some published data evaluating initial anti-CD20 use in adults, mostly in small case series with variable efficacy for achieving complete remission.[106,107]

Belimumab, an anti-BAFF monoclonal antibody, was not effective in a small study of children with frequently relapsing nephrotic syndrome.[108] Combination therapies of B cell depletion with anti-CD20 antibodies (rituximab, obinutuzumab) and plasma cell depletion with anti-CD38 antibodies (daratumumab) have been successfully used in some adults and children with treatment-resistant nephrotic syndrome or relapsing FSGS post-transplant.[109–112]

Although the identification of anti-nephrin and other anti-podocyte antibodies raises the intriguing possibility of very deep (tissue) B cell depletion including plasma cells as a possible therapeutic approach, anti-nephrin positivity has been associated with the most benign, treatment-responsive, steroid-sensitive conditions[38] that are least in need of more aggressive treatment options. Nonetheless, very deep B cell depletion could have a role in very severe cases, for example, recurrent FSGS post-transplant or severe multi–drug-dependent patients, especially in cases with comorbidities related to prolonged and intense immunosuppression.

Lupus nephritis. In LN clinical trials, therapies targeting B cells have been added to standard-of-care (SOC) immunosuppressive regimens, usually either cyclophosphamide or mycophenolate mofetil plus glucocorticoids.[1,3,50,113,114] Belimumab provided a significant benefit to patients with LN over SOC alone and was approved for LN in 2020.[50] Rituximab was similarly tested against SOC and failed in a phase III RCT.[1] However, patients who demonstrated peripheral B cell depletion with rituximab experienced a kidney remission advantage compared to SOC.[115]

Exploring the possibility that intensified B cell depletion would improve outcomes of anti-CD20 treatment, obinutuzumab was studied in LN. The phase II NOBILITY trial (ClinicalTrials.gov Identifier: NCT02550652) showed that nearly all patients treated with obinutuzumab achieved peripheral B cell depletion and had more complete kidney responses than did those treated with placebo.[114] B cell depletion by obinutuzumab is not limited to circulating cells. In a study of sensitized patients with kidney failure who were treated with obinutuzumab in preparation for kidney transplantation, lymph node biopsies were performed and showed B cell depletion.[116] A phase III trial of obinutuzumab in proliferative LN (REGENCY, ClinicalTrials.gov Identifier: NCT04221477) recently read out. The complete kidney response rate of patients treated with obinutuzumab in REGENCY was 13.1% higher than that of patients treated with placebo, leading to the drug's approval by the US Food and Drug Administration and European Medicines Agency for the treatment of proliferative LN in 2025.[3] In addition to complete peripheral B cell depletion in almost every obinutuzumab-treated patient, a subset of patients from REGENCY had a kidney biopsy after 18 months of treatment; B cells were absent from the kidneys of patients who received obinutuzumab but were present and unchanged from baseline kidney biopsies in patients who received placebo.[117] The successes of obinutuzumab compared with rituximab are likely explained by its intensified peripheral and tissue-level B cell depletion.[118]

Belimumab added to SOC has been endorsed as a first-line LN treatment by the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis[119] and the 2024 American College of Rheumatology Guideline for the Screening, Treatment, and Management of Lupus Nephritis.[120] The 2025 LN guideline from the European Alliance of Associations for Rheumatology endorsed belimumab or obinutuzumab plus SOC as a first-line LN therapy.[121]

Therapies targeting plasma cells have been used in small uncontrolled studies of patients with refractory LN. Bortezomib treatment was given to 12 patients with LN who did not respond to several standard immunosuppressive regimens and resulted in 1 complete kidney response and 10 partial responses.[122] Because of toxicity concerns with

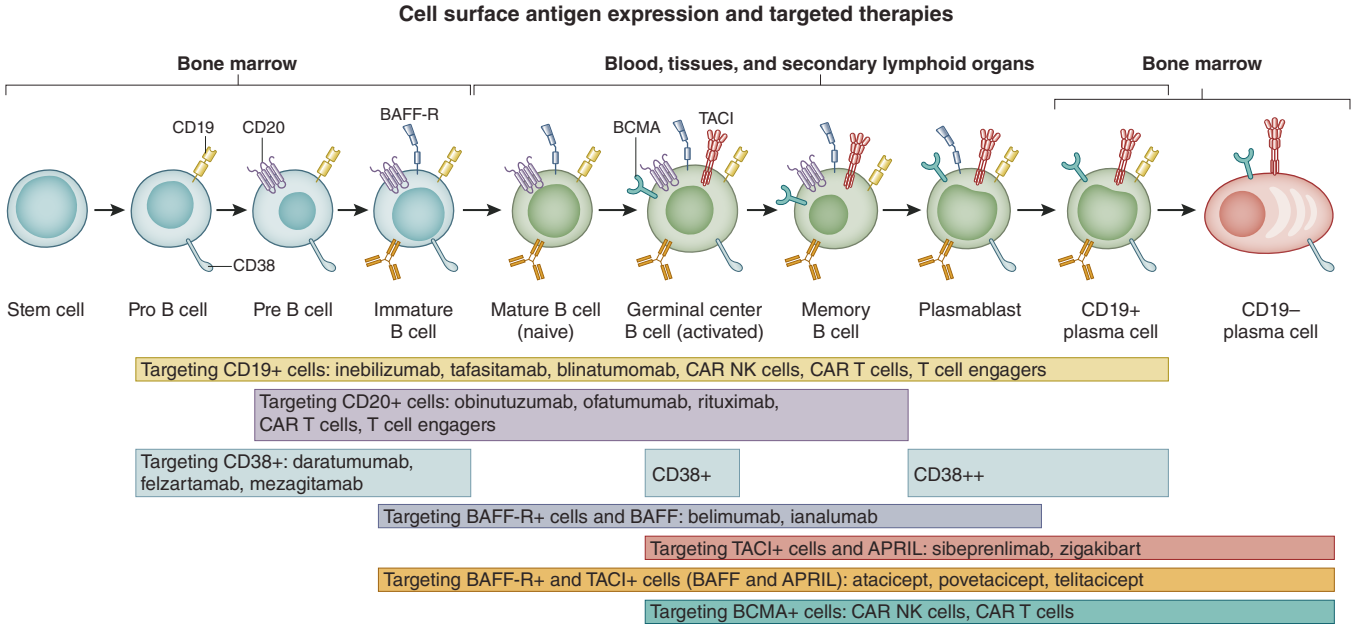

Figure 2 | B cell maturation, treatment targets, and therapies. APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor; BAFF-R, B cell activating factor receptor; BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; CAR NK, chimeric antigen receptor natural killer; Pro, progenitor; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor.

bortezomib, plasma cell depletion was studied using anti-CD38 antibodies, which did induce responses in several patients with refractory LN.[123,124] The use and positioning of plasma cell therapies in LN remains to be defined.

CAR T cell therapies directed against CD19 or CD19 and BCMA (Figure 2) demonstrated impressive short- and long-term resolution of LN in a small phase I study[125] and a case series.[85] The CAR T cell therapies were administered after all other immunosuppressive medications, including glucocorticoids and anti-malarial agents, had been stopped. However, to create an environment favorable to the expansion of infused CAR T cells, a lymphodepleting regimen, usually consisting of cyclophosphamide and fludarabine, is routinely administered; its contribution, if any, to the clinical outcomes is not known. In addition to yielding kidney response outcomes far better than those seen with conventional B cell–directed therapies, many patients have remained in immunosuppressive-free remission for up to 4 years after a single infusion of CD19-CAR T cells (~~https://www.youtube.com/watch?v=OG8Mdkx29b0&t=880s~~).[85]

In summary, intensified B cell depletion may provide better LN response results, and it is possible CD19 offers improved benefits over CD20 as a target because targeting CD19 depletes a larger number of B cell phenotypes that may retain autoimmune memory. Deep B cell depletion includes an absence of circulating B cells as well as depletion of B cells in lymphoid tissues and, possibly, the kidney (Figures 3 and 4). This is accomplished to some extent by obinutuzumab but to a greater extent by cell therapies. In addition, an early return of a naive B cell phenotype (CD20+, CD27−, IgD+, and IgM+) has been observed with CAR T cell therapy, raising the possibility that cell therapies may reset the immune system in autoimmunity.[87]

ANCA-associated vasculitis. B cell depletion with rituximab has become central in ANCA-associated vasculitis (AAV) induction and maintenance therapy, reducing cyclophosphamide use and replacing azathioprine for long-term maintenance immunosuppression. Different intensities and frequencies of rituximab administration achieve differing results, reinforcing the concept that the extent of B cell depletion may determine treatment efficacy.[128] Currently, there are no trial data on obinutuzumab, although it is used as rescue treatment in patients with therapy-resistant disease.[129] Unlike for LN, the B cell modifier belimumab failed to prevent flares of AAV in the Belimumab in Remission of VASculitis (BREVAS) study.[130]

Case reports demonstrate induction of complete remission in patients with treatment-refractory MPO and PR3 AAV treated with CD19-CAR T cells.[131,132] Phase I and II trials are underway to investigate CAR T cell therapy directed against CD20+ cells in AAV, and research aims to selectively target autoreactive MPO and PR3 ANCA-producing cells.

Expectations of treatment

Cure. Although there have always been patients with autoimmune disease who respond well to treatment with conventional therapies and became disease-free off medications, most patients achieve alternative outcomes (discussed later). "Cure" entered the vernacular after the introduction of CAR T cell therapy, specifically in LN. The LN and AAV discussion group at this conference defined *cure* as the

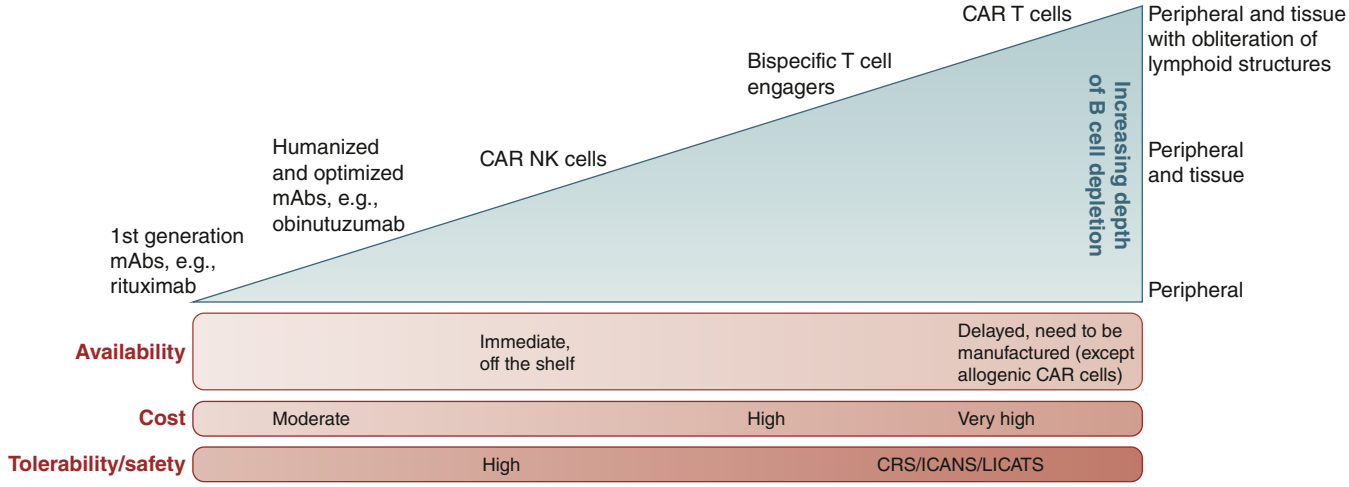

Figure 3 | Depth and breadth of B cell depletion via various therapies in kidney disease. The various agents targeting B cells and their depth of B cell depletion peripherally and in tissue along with factors related to treatment availability, cost, and toxicity. CAR NK cell, chimeric antigen receptor natural killer cell; CAR T cell, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; LICATS, local immune effector cell–associated toxicity syndrome; mAb, monoclonal antibody.

absence of clinical, immunologic, and histologic signs of disease activity while the patient is off all immunosuppressive therapies. Simply put, cure is a reversion of the immune system to the premorbid state when medications were unnecessary. There was no consensus about the minimum duration of medication-free disease activity to declare cure, but a patient's lifetime was considered ideal.

Although safety is not an element of the definition of cure, it must be considered when assessing the benefit of a therapeutic intervention. A curative treatment that poses a significant safety risk may be less appealing to patients and clinicians than a safer therapy that may not be curative.

Alternative outcomes to cure. Cure as defined above will likely be an infrequent event for the foreseeable future and is therefore aspirational. Short of lifelong cure, being free of disease activity, or being off treatment for at least a few years was considered a clinically meaningful treatment outcome and attainable. For example, several patients with refractory lupus responded to CAR T cell therapy and have remained disease free off all immunosuppressive therapies for up to 4 years (https://www.youtube.com/watch?v=OG8Mdkx29b0&t=880s).[85] *Activity-free disease* implies immunologic, histologic, and clinical resolution. Determination of clinical resolution may be straightforward, but histologic and immunologic resolution are more nuanced. To avoid the need for repeat kidney biopsies, the availability of noninvasive biomarkers that reflect kidney pathology will be critical (discussed later). Immunologic resolution may not equate with disappearance of autoantibodies, given the observation that some patients with autoimmune diseases achieve complete response after CAR T cell therapy despite persistence of autoantibodies.[85,133]

The concept of being free of disease activity and free of treatment can be applied generally to other glomerular or autoimmune diseases. In a few children with podocytopathies, the use of anti-CD20 therapy after glucocorticoid-induced remission has been disease-modifying, inducing prolonged remission off therapy. Patients with MN who have complete remission of proteinuria can often be treatment-free for years. In AAV, immunosuppression can often be held after maintenance therapy with rituximab. In contrast, it is not clear whether IgAN treatment can achieve this composite outcome goal. For example, B cell–modulating therapies seem to stabilize GFR, but presumed signs of disease activity, such as presence of Gd-IgA1 and anti-Gd-IgA1, return quickly after the BAFF/APRIL or APRIL inhibitors are stopped.[58,66] Thus, for some glomerular diseases, an outcome of absence of disease activity while on treatment may be a reasonable treatment outcome, especially if ongoing therapy is well-tolerated.

Biomarkers to guide the implementation and monitoring of B cell therapies in glomerular diseases

IgA nephropathy. It is unlikely that every patient with IgAN needs B cell therapy to achieve disease remission (i.e., stable eGFR and minimal to no proteinuria). Guiding patient selection for B cell–targeting therapies using only proteinuria and eGFR is too crude, and there are no validated histologic biomarkers. Furthermore, even if tissue B cells could serve as a biomarker for choosing a B cell therapy in IgAN, the relevant tissue of interest for analyzing B cells is unclear and could include the kidney, gut mucosa, regional (gut and kidney) lymph nodes, or even tonsils.

Gd-IgA1 and anti-Gd-IgA1 antibodies are often discussed as biomarkers for identifying patients who may respond to B cell treatment, but validated and standardized clinical assays are lacking, as are prospective studies showing that they, or total IgA, can guide selection for B cell treatment. Finally, Gd-IgA1 levels in patients with IgAN are modestly elevated above normal, and substantial overlaps exist between patients and healthy controls.[134] Mass spectrometry confirmed that sialylation of IgA1 O-glycans was associated with

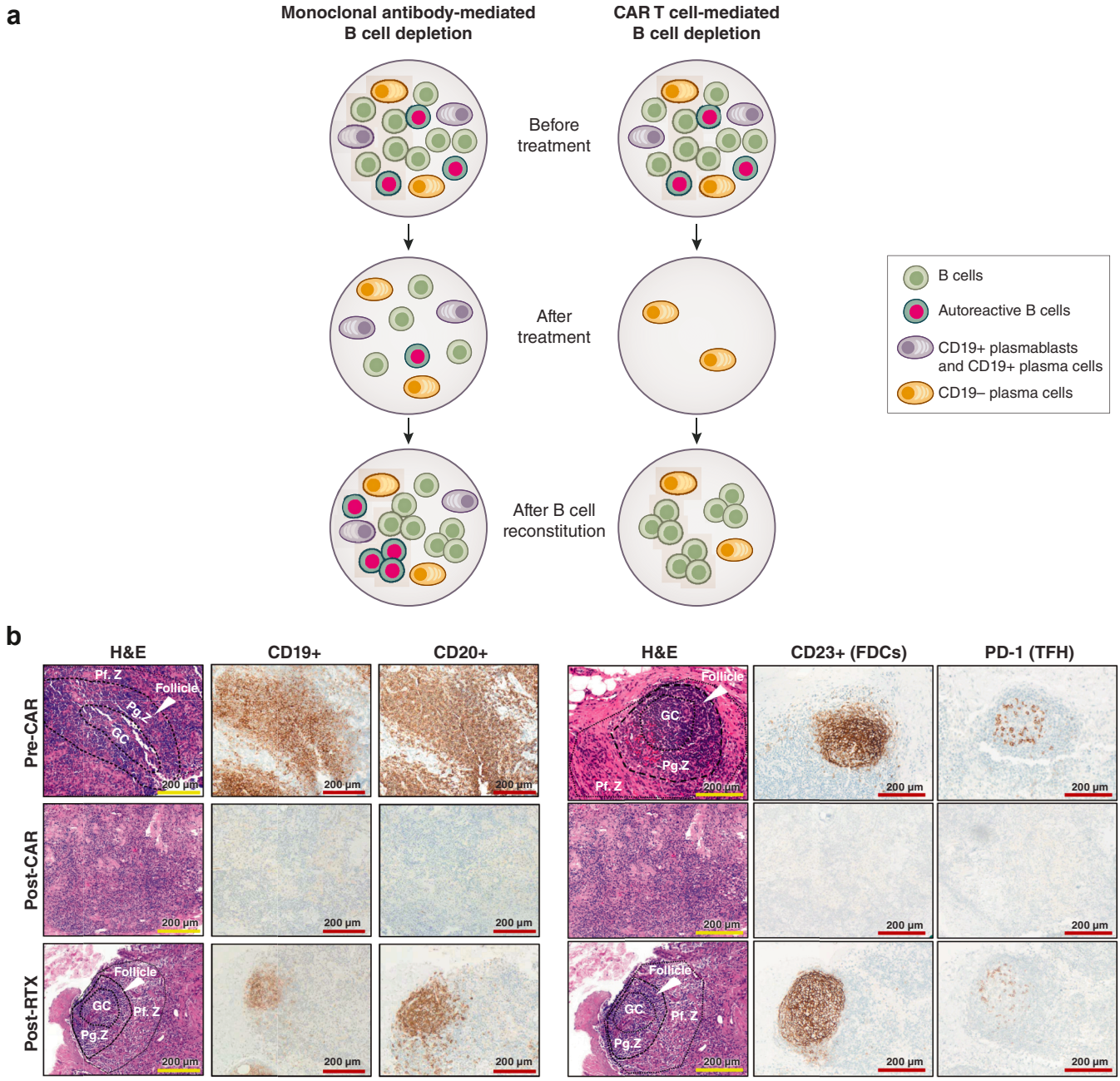

Figure 4 | Comparison of B cell depletion by monoclonal antibodies and cell therapies. (**a**) Effects of antibody-based and cell-based B cell targeting in autoimmune disease. Pretreatment, autoreactive B cells and plasmablasts are interspersed in a larger number of alloreactive B cells and plasmablasts. Posttreatment, *in situ* autoreactive and alloreactive B cells are reduced but not eradicated with antibody-mediated B cell depletion; plasmablasts and plasma cells are not depleted by anti-CD20 monoclonal antibodies; CD19-CAR (chimeric antigen receptor) T cells lead to a deep depletion of autoreactive and alloreactive B cells, plasmablasts, and CD19+ plasma cells without reducing CD19− plasma cells. During B cell reconstitution after anti-CD20 monoclonal antibody–mediated B cell depletion, autoreactive and alloreactive B cells are replenished. CD19-CAR T cell therapy autoimmune B cell clones and plasmablasts remain absent. (**b**) Peripheral blood and lymph node changes on CD19-CAR T cell therapy. Left: Representative hematoxylin and eosin (H&E)–stained images of lymph node biopsies obtained from 1 patient treated before (pre-CAR) and after (post-CAR) CD19-CAR T cell therapy and from 1 patient after RTX therapy (post-RTX), together with representative immunohistochemistry images of CD19+ B cells and CD20+ B cells. White arrows indicate follicular B cell areas in the lymph node tissue. Right: Changes in the B cell maturation compartment in the lymph nodes. Representative H&E–stained images of lymphoid follicles/germinal centers pre-CAR and post-CAR as well as post-RTX, together with representative immunohistochemistry images of CD23+ follicular dendritic cells (FDCs) and programmed cell death protein 1+ (PD-1+) T follicular helper cells (TFHs). GC, germinal center; Pf. Z, peri-follicular zone; Pg.Z, peri-germinal zone. (**a**) Reproduced with permission from Schett G, Nagy G, Krönke G, et al. B-cell depletion in autoimmune diseases. *Ann Rheum Dis* 2024;83:1409–1420.[126] (**b**) Reproduced with permission from Tur C, Eckstein M, Velden J, et al. CD19-CAR T-cell therapy induces deep tissue depletion of B cells. *Ann Rheum Dis*. 2025;84:106–114.[127]

IgAN[135]; however, there is substantial overlap in glycosylation patterns between IgAN and controls. The levels of autoantibodies or cross-reactive antibodies (IgG or IgA) targeting Gd-IgA1 also overlap with healthy controls.[134] All recent trials of B cell modulators reduced Gd-IgA1, total IgA, and IgG levels, indicating a nonspecific rather than targeted reduction in Ig production.

Several other potential targets of B cell therapies are exploratory, untested, or unvalidated as biomarkers in the setting of IgAN, such as tertiary lymphoid structures[136] or IgA class-switched CD27−CD21+ B cells/IgA+ plasmablasts.[137]

Membranous nephropathy. In anti-PLA2R–positive MN, it is assumed most patients who need treatment will be offered a B cell therapy. Although patients with the highest tertile anti-PLA2R antibody levels often require immunosuppressive treatment, spontaneous proteinuria remission is common in patients with the lowest tertile of anti-PLA2R antibody levels.[33] The clinical utility of the non–anti-PLA2R autoantibodies in guiding treatment of MN is currently unknown, but it seems likely that at least anti-THSD7A antibodies behave similarly to anti-PLA2R antibodies.[18,138]

Measuring circulating CD19− or CD20+ B cells after the use of an anti–B cell agent is recommended, but whether there is a role for monitoring B cell repopulation in deciding when or whether to repeat dosing of these agents is currently unknown. The measurement of B cell subsets (naive, double negative, CD38+, transitional, or memory) for prognostic or disease monitoring purposes[139] is not available outside of research settings. Measuring antigen-specific B cells, which could be the best indicators of ongoing immunological disease activity, should be explored in future research.

Podocytopathies. For immunological biomarkers, changes in certain lymphocyte subpopulations, that is, increased circulating memory B cells and plasmablasts and decreased regulatory T cells, in children[140–143] and adults[144,145] have been linked to immune-responsive (especially steroid-dependent) forms of nephrotic syndrome. According to a retrospective analysis of a large cohort of patients with SDNS/frequently relapsing nephrotic syndrome, baseline total memory and switched memory B cells before anti-CD20 therapy were independently associated with a small but statistically significant increased risk of subsequent relapse.[46] In the pediatric setting, post-rituximab reconstitution of switched memory B cells was likewise associated with a significantly increased risk of relapse, independent of ethnicity.[44,45,47] Promising approaches for finding better biomarkers include more sophisticated deep lymphocyte phenotyping, such as single-cell RNA sequencing[146] and elucidating the role of B cells directly in disease-relevant tissues (kidney, lymph nodes, spleen, tonsils, etc.) (Figure 4). Consistent with previous findings, single-cell RNA sequencing analyses have also identified the recovery of memory B cells as a predictor of post-rituximab response.[146] However, because this association has only been found in observational studies, it requires validation in prospective clinical trials before clinical implementation.

The pathogenic role of anti-podocyte protein antibodies is supported in murine models by passive transfer of autoantibodies[42] and by direct immunization with recombinant nephrin.[37] In humans, circulating anti-nephrin titers are low, and detection techniques have proved technically challenging and difficult to reproduce.[147–149] Some very preliminary data have shown anti-podocyte antibody negativity in remission and after rituximab treatment both in native kidney disease[36,37] and after kidney transplantation.[150]

Systemic autoimmune diseases. In LN, there are neither predictive biomarkers to guide clinicians in the selection of initial therapy nor monitoring biomarkers to indicate response to treatment. Studies in individuals with LN have yet to correlate changes in anti–double-stranded DNA titers with clinical response. In contrast, complement factors have predictive power; for patients treated with mycophenolate mofetil or cyclophosphamide, normalization of C3 and C4 by week 8 is predictive of kidney response at week 24.[151] Entry into clinical trials evaluating deep B cell–depleting regimens (CAR T cells or bispecific antibodies) has been entirely based on the disease being refractory to prior therapies.

In ANCA GN, it is assumed that most patients will be treated with a B cell–depleting agent (anti-CD20) alone or in combination with cyclophosphamide as initial therapy. The ANCA antibody subtype associates with relapse risk, and PR3 ANCA is generally regarded as carrying a higher relapse risk.[5,152,153] After treatment, ANCA levels are expected to fall or disappear; ANCA persistence and reoccurrence after B cell depletion seems to confer a higher relapse risk in patients with PR3 and MPO.[153,154] Seroconversion of ANCA from negative to positive therefore warrants close monitoring for relapse, but there is insufficient evidence that autoantibody reappearance mandates retreatment.[152,155]

Given the growing number of B cell–directed agents and their likely future use in ANCA GN and LN, it will be crucial to monitor B cell depletion, repletion, and modulation. Peripheral blood B cell numbers and subsets after therapy and during recovery can be measured, but the CAR T cell trial experience suggests that outcomes depend on the depth of B cell depletion in the tissue, not in the periphery (Figure 3).[126,127] It would be ideal to measure B cells in tissue, but the acquisition of lymphoid tissue, such as lymph nodes or tonsils, poses a challenge, and serial kidney biopsies to assess B cell tissue kinetics are not feasible. A promising and relatively noninvasive technique to assess B cell depletion, including germinal center B cells in tissues, uses nasal-associated lymphoid tissue acquired from the nasal cavity by swabbing.[156] Somatic mutational analysis of Ig and non-Ig genes comparing memory B cells before treatment with repopulated cells may also provide an indication of the depth of B cell depletion.

What is immune reset, and is this possible and desirable? The term *immune reset*, coined after CAR T cells began to be trialed in autoimmune diseases, has become the goal of treatment for cell therapies and other agents designed

to achieve deep B cell depletion.[85] After such therapies the immune system appears to revert to a naive immune phenotype characterized by the disappearance of autoantibodies, the elimination of IgG and IgA memory B cells, and repopulation by B cells that display a naive phenotype (CD19+, CD27−) as opposed to a memory phenotype (CD19+, CD27+). Although not an official definition, the conference participants agreed that immune reset is the complete depletion of clonal autoreactive B cells and therefore deletion of B cell memory; it is a prerequisite for achieving a cure in chronic immune-mediated inflammatory conditions, such as SLE or AAV. It may also be beneficial in severe recurring forms of MN, although there is currently insufficient evidence for most forms of immune-mediated podocytopathies (excluding some recurring forms of FSGS) and in IgAN.

Although the concept of immune reset was popularized in CAR T cell studies for LN,[87] treatment with obinutuzumab in patients with LN resulted in a similar B cell repletion consisting primarily of a naive phenotype, and memory B cells were slow to return.[114] Treatment with $CD19^+$ CAR T cells does not completely eliminate autoantibodies. Antibodies directed against RNA-binding proteins (e.g., Smith [Sm] and Sjögren's-syndrome-related antigen A [SSA]) are not eliminated, indicating that long-lived autoreactive plasma cells, likely the CD19− subset, are not "reset."[87] In contrast to treatment with $CD19^+$ CAR T cells, administration of bispecific anti-CD19/BCMA+ CAR T cells resulted in reductions of antibodies to both DNA- and RNA-binding proteins, suggesting plasma cells as the source of antibodies to Sm, ribonucleoprotein (RNP), SSA, and Sjögren's-syndrome-related antigen B (SSB).[125,157–159] Conference participants discussed the controversies around the term immune reset and the necessary extent of the immune cell depletion to be considered *reset* and suggested labeling the immune phenomenon observed after CAR T cell therapy as either *immune system remodeling* or *immune system reprogramming*.

Safety considerations

B cell depletion is accompanied by an increased risk of infection, transient neutropenia, thrombocytopenia, hypogammaglobulinemia, and vaccine failure.[3,114,160,161] A very rare complication is progressive multifocal leukoencephalopathy in patients after a John Cunningham (JC) virus (human polyomavirus 2) infection. A proportion of patients develop persistent and progressive hypogammaglobulinemia; the risk is increased in elderly patients and young children and is influenced by coadministered glucocorticoids and previous immunosuppressive burden.[19,162] After B cell depletion, antibody titers from vaccinations may be reduced.[19,163,164] Vaccine boosters should therefore be given when B cells reappear in the circulation. If urgent treatment with a B cell–directed therapy is needed, for example, in organ-threatening ANCA GN, delaying treatment to receive vaccination is not recommended. Attention to Ig levels, neutrophil counts, and platelet counts is imperative. Therapies targeting plasma cells invoke yet additional precautions in that patients may require replacement i.v. Ig or a full vaccination panel if immune memory is destroyed.[125] Compared with adults, toxicity of B cell depletion, including hypogammaglobulinemia, appears to be more prevalent and profound in children, particularly those younger than 10 years.[19,165]

Deep B cell depletion with CAR T cell therapy or bispecific antibodies in autoimmune diseases can lead to toxicities previously exclusive to patients treated for malignant neoplasms. The limited experience to date has not demonstrated a significant increase in infectious complications. However, potentially severe acute treatment-related toxicities have emerged, including cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome.[166] Long-term follow-up of patients treated for hematologic neoplasms has revealed that toxicities such as Parkinson disease, enteritis, and T cell lymphoproliferative disorders may occur years after CAR T cell administration.[167–169] In cell therapies and bispecific antibody protocols, the risk of developing some of these syndromes may be reduced by careful patient selection. Patients with preexisting cardiopulmonary disease are at an increased risk of adverse outcomes from cytokine release syndrome. Recognition of immune effector cell–associated neurotoxicity syndrome may be challenging in patients with central nervous system lupus. It is, however, important to aim for inclusive trial platforms and not to exclude certain comorbidities such as central nervous system lupus *per se* to allow patients with an acceptable risk profile to access novel therapies. Attention needs to be paid to baseline Ig levels because patients with nephrotic syndrome may experience resolution of their initial hypogammaglobulinemia. Ongoing B cell depletion with rituximab and the accompanied loss of protective antibodies such as hepatitis B surface antibodies (anti-HBsAB) conveys viral infection risk requiring monitoring, revaccination, and antiviral prophylaxis. The relationship between the depth of B cell depletion and the absence of specific antiviral antibodies is not well understood, and determining when B cell targeting renders the patients more susceptible to particular serious infections is a research priority.

Patient and public engagement

B cell–targeted therapies, especially with CAR T cells, are more complex than prior treatments of glomerular disease. Thus, the need for patient education and shared decision making has increased significantly. There is a major concern that health professionals are not currently equipped with appropriate resources and manpower to handle these demands. Enhancing the alliance between the medical community and patient advocacy groups will offer a solution to these newfound challenges.

Cost/pharmacoeconomics. Most of the treatment approaches that target B cells in glomerular disease will undoubtedly remain very expensive and are unlikely to be available in resource-limited parts of the world for a long

Table 3 | Research priorities for therapies targeting B cells in kidney diseases

General
• Generate biorepositories from all sponsored trials—including enrolled and screen-failed subjects within a federated biobank managed by an academic committee to facilitate data sharing, biomarker analysis, and patient profiling in glomerular diseases.

• Optimize disease phenotyping across immune-mediated glomerular diseases to select the right intensity of B cell–directed therapy for the right patient:
  • Establish clinical risk profiles.
  • Determine reliable serologic and histologic biomarkers needed to measure treatment response earlier and predict disease trajectory.
  • Repeat kidney biopsies to assess treatment response.
  • Optimize analysis of peripheral blood lymphocyte subsets to identify correlates of response and safety.
  • Acquire lymphoid tissue at the time of diagnosis and follow-up, for example, lymph nodes, bone marrow, and nasal cavity, to determine treatment algorithm.

• Establish criteria for discontinuation of B cell therapies.
• Incorporate artificial intelligence into optimizing and personalizing treatment choice and dosing.
• Determine the long-term effects of B cell depletion on immune competence and risk of malignancy.
• Define the age-specific safety profiles of B cell–depleting and –modulating agents across the lifespan of glomerular diseases.
• Define cure and immune reset specifically for each glomerular disease.
• Perform platform trials incorporating novel trial designs to overcome enrollment challenges, accelerating drug approvals.
• For complex treatment options, increase resources for patient education and involvement.
IgA nephropathy
• Examine the contribution of the change in Gd-IgA1, other potentially pathogenic IgA species, and anti-Gd-IgA1 antibody levels to eGFR preservation in completed or soon-to-be-completed trials through mediation analysis. Examine their potential role in predicting treatment response and relapses in IgAN and in determining the optimal dosing of B cell agents.
• In patients who achieve a physiologic decline in eGFR with B cell therapy, determine whether general therapies for chronic kidney disease can or should be discontinued.
• In patients who achieve a physiologic decline in eGFR with B cell therapy, determine whether residual proteinuria matters.
• Compare depth and durability of selective APRIL inhibitors versus dual BAFF/APRIL inhibitors.
Membranous nephropathy
• Characterize more completely the relationship between improvement in anti-PLA2R levels and clinical manifestations of disease including complete and partial responses.
• Characterize the natural course of non–PLA2R-associated membranous nephropathy and whether anti-PLA2R-negative patients benefit from anti-CD20 therapy.
• Optimize and personalize anti-CD20 dosing schedules and determine whether additional immunosuppressive agents are required in the context of an insufficient response to anti-CD20 treatment.
• Investigate whether earlier initiation of therapy or combination of therapeutic approaches (agents) can lead to faster remission and the prevention of complications of severe nephrotic syndrome (e.g., arterial or venous thromboembolic events)
Podocytopathies
• Explore whether B cell–depleting or –modulating agents can be used alone in adults and children as first-line therapy for podocytopathies.
• Develop biomarkers to identify who has immune-mediated disease and who will or will not benefit from B cell depletion.
• Determine whether anti-podocyte antibodies are pathogenic and/or biomarkers of disease type. Can they be used to monitor treatment response and predict response and relapse?
Lupus nephritis and ANCA-associated vasculitis
• Develop reliable biomarkers that inform therapeutic approach and are predictive of treatment response; the use of such noninvasive monitoring overcomes the circularity of the uPCR end point.
• Develop objective measures to identify those patients with trajectories warranting early escalation of B cell targeting to prevent organ failure and those patients who have achieved immune reset with therapy.
• Perform a liquid kidney biopsy to assess clinical response in the absence of tissue acquisition.
• Repeat kidney biopsies and apply novel diagnostic techniques to determine the critical point when kidney inflammation loses reversibility and results in fibrosis. Evaluate the impact of B cell depletion on fibrotic pathways.
• Determine the role of genetic predisposition and manifestations driven by other pathways, for example, IFN-1 in SLE skin disease.
• Identify the different treatment responses of vasculitic and granulomatous AAV manifestations to B cell–targeting therapies.

AAV, antineutrophil cytoplasmic antibody–associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient IgA1; IFN-1, interferon 1; IgAN, IgA nephropathy; PLA2R, M-type phospholipase A2 receptor; SLE, systemic lupus erythematosus; uPCR urine protein-to-creatinine ratio.

time. Furthermore, some technologies, such as cell therapy requiring manufacturing of CAR T cells, may not be present in many regions. There are no easy solutions to making new therapies available worldwide. Presently, the responsible approach for the global community interested in applying B cell therapies to glomerular diseases will be to understand who needs what level of B cell depletion and to not necessarily assume everyone needs the most expensive regimen. Learning in detail how B cell approaches work in glomerular diseases may offer insights into designing less costly approaches to treatment over time. To balance cost and safety, risk stratification for each glomerular disease should guide the depth of B cell depletion according to disease activity and severity in individual patients.

Research agenda

Research priorities resulting from this Controversies Conference are provided in Table 3.

Conclusion

The role for therapeutically targeting B cells in glomerular diseases has rapidly expanded over the past decade. In IgAN, B cell modulation via APRIL and/or BAFF inhibition or via plasma cell depletion has the potential to stabilize kidney function and reduce GFR loss to levels consistent with normal aging. In MN, these advances have largely been spurred by the discovery of anti-PLA2R and other presumably pathogenic autoantibodies as well as the improved access to and use of rituximab. Autoantibodies have been and continue to be identified in patients with podocytopathies. Their pathogenicity will need to be determined. Nevertheless, in MN and in some forms of podocytopathies, the rate of complete remission remains relatively low, and the time to attain it is long. Achieving more complete and more durable remission within a shorter time frame remains an unmet need in MN and B cell–driven, treatment-dependent podocytopathies. Newer B cell–targeting agents, the use of combination therapies, and the targeting of plasmablasts and plasma cells have all shown promise in addressing this unmet need and are currently under investigation. For MN, the typical course of disease and efficacy of currently available regimens make cell-based therapies in their current form less attractive. This will likely change with the advent of newer cell-based agents as we gain more experience with CAR T cells in LN and other more rapidly progressive glomerular diseases.

In LN and ANCA GN, disease severity and individual patient factors (e.g., age, fertility, comorbidities, and frailty) are varied and necessitate broadening management beyond a *one-size-fits-all* approach. A better understanding of the tissue response to treatment will enable adapting treatment to individual patient needs. Reliable stratification models and improved monitoring methods are needed for selecting the most appropriate therapeutic interventions. Presently, cell therapies are mostly being tested in patients with refractory disease. If these therapies do provide long-term drug-free response, they may be better applied to early LN before several rounds of failed therapies to prevent chronic kidney damage and to provide medication-free time for individuals often starting their careers and families.

Despite these advances, a significant proportion of patients with glomerular diseases develop irreversible organ damage and fail to attain long-term remission. Intensifying B cell depletion in certain patient populations may allow long-lasting disease remission off immunosuppressive therapy, moving our therapeutic goals closer to a cure of kidney diseases.

APPENDIX

Additional Conference Participants

Valeria Alberton, Argentina; Andrea Angeletti, Italy; Jennifer L. Barnas, USA; Jonathan Barratt, UK; Peter Boor, Germany; Roberto Caricchio, USA; Tak Mao Chan, Hong Kong; Eugene Yu-Hin Chan, Hong Kong; Manuela Colucci, Italy; Anne Davidson, USA; Nathan Denlinger, USA; Raphaël Duivenvoorden, The Netherlands; Marie Eggers, Germany; Alessia Fornoni, USA; Eleni Frangou, Cyprus; George E. Georges, USA; Andre G. Gontijo, USA; Shaun W. Jackson, USA; Brittan Kopittke, USA; Maria J. Leandro, UK; Nelson Leung, USA; Adrian Liew, Singapore; Ana Malvar, Argentina; Juan M. Mejía-Vilet, Mexico; Peter A. Merkel, USA; Irene L. Noronha, Brazil; Michelle M. O'Shaughnessy, Ireland; Ioannis Parodis, Sweden; Amber S. Podoll, USA; Anjay Rastogi, USA; Dario Roccatello, Italy; Jorge E. Rojas-Rivera, USA; Barbara Seitz-Polski, France; Saira Z. Sheikh, USA; Dan Suan, Australia; Rita S. Suri, Canada; Vladimír Tesař, Czech Republic; Naotake Tsuboi, Japan; Augusto Vaglio, Italy; Christoph Wanner, UK and Germany; Muh Geot Wong, Australia; Hui-Kim Yap, Singapore; Hong Zhang, China; Ming-hui Zhao, China.

DISCLOSURE

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