REVIEW

# B cells in transplant tolerance and rejection: friends or foes?

Robin Schmitz, Zachary W. Fitch, Paul M. Schroder, Ashley Y. Choi, Annette M. Jackson, Stuart J. Knechtle & Jean Kwun

Department of Surgery, Duke Transplant Center, Duke University Medical Center, Durham, NC, USA

**Correspondence**
Stuart J. Knechtle MD, 330 Trent Drive, DUMC Box 3512, Durham, NC 27710, USA.
Tel.: 919-613-9687;
fax: 919-684-8716;
e-mail: stuart.knechtle@duke.edu
and
Jean Kwun DVM, PhD, 207 Research Drive, DUMC Box 2645, Durham, NC 27710, USA.
Tel.: 919-668-6792;
fax: 919-684-8716;
e-mail: jean.kwun@duke.edu

## SUMMARY

Our understanding of the role of B cells in organ transplantation remains incomplete and continues to grow. The majority of research has focused on the detrimental role of antibodies that drive the development of pathogenesis of the transplanted organ. However, it has been shown that not all donor-specific antibodies are harmful and in some circumstances can even promote tolerance through the mechanism of accommodation. Furthermore, B cells can have effects on transplanted organs through their interaction with T cells, namely antigen presentation, cytokine production, and costimulation. More recently, the role and importance of Bregs was introduced to the field of transplantation. Due to this functional and ontogenetic heterogeneity, targeting B cells in transplantation may bring undesired immunologic side effects including increased rejection. Therefore, the selective control of B cells that contribute to the humoral response against donor antigens will continue to be an important and challenging area of research and potentially lead to improved long-term transplant outcomes.

*Transplant International* 2020; 33: 30–40

**Key words**
alloantibody, antibody-mediated rejection, B cell, tolerance

Received: 17 September 2019; Revision requested: 21 October 2019; Accepted: 4 November 2019

## Introduction

### Historical perspectives—B cells in transplant rejection

In 1990, a Nobel Prize was awarded to Drs. Murray and Thomas "for their discoveries concerning organ and cell transplantation in the treatment of human disease," celebrating the benefits of clinical transplantation. Over the last 30 years, the number of transplants has increased even further, with more than 19 000 transplants performed in the United States in 2018 [1]. Kidney allograft survival dramatically improved between 1956 and 1990, partially due to advancement of immunosuppressive agents that target T lymphocytes. One-year unadjusted graft survival now exceeds 97% and 93% for primary living and deceased donor kidneys, respectively [2,3]. However, the rate of improvement of long-term graft survival over the past five decades does not follow the remarkable positive trend of short-term graft survival in organ transplantation (Figs 1 and 2).

The gradual loss of graft function has been described by various terms and is most often attributed to chronic rejection. As reviewed by our group and others, the etiology of chronic rejection is multifactorial [4–6] and includes progression of underlying kidney disease, drug toxicity, and immune injury. In his commentary on an earlier review by us, Paul Terasaki stated, "The mantra, 'chronic rejection is multifactorial' is the major reason for the lack of progress in reducing the rate of chronic




doi:10.1111/tri.13549

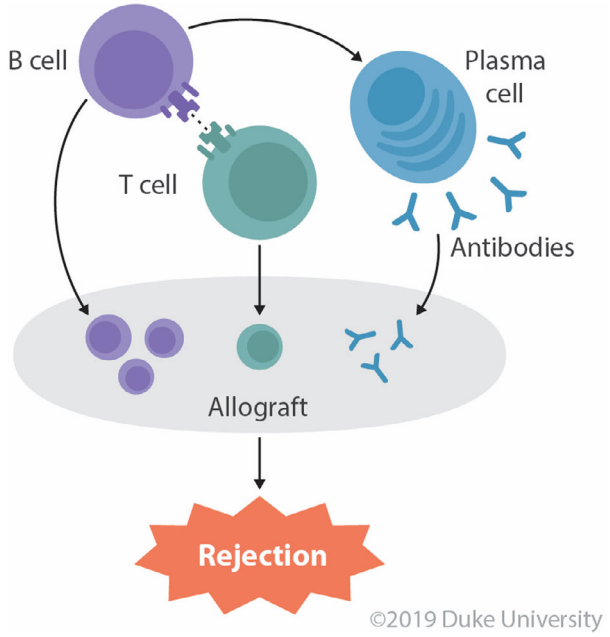


**Figure 1** A schematic and simplified view of the different pathways through which B cells contribute to transplant rejection. B cells contribute to allograft rejection after differentiating into antibody-secreting plasma cells (blue). Additionally, B cells shape the T-cell response through a combination of antigen presentation, cytokine production, and costimulation (green). Lastly, B cells have direct effects on the allograft that can be initiated by an ischemic injury (purple).

rejection these past 30 years." [7]. By this, he was claiming that antibody was the sole important cause of graft failure rather than other etiologies, and perhaps reacting to the emphasis on the T cell as the agent of rejection. Alloantibody-induced pathogenesis had been initially recognized in the 1960s by Patel and Terasaki [8], who showed that donor-specific antibodies (DSAs) were associated with immediate kidney transplantation failure. Later, Terasaki and Cai [9,10] showed that human leukocyte antigen (HLA) antibodies are associated with chronic rejection. As they claimed, the T-cell-centric concept is deeply ingrained in the transplant community, and alloantibody or B cells had not been fully considered as a major barrier to tolerance until recently.

### Current perspectives - B cells in organ transplantation

B cells were initially considered to be associated with graft rejection but were not considered the major component of rejection or tolerance in organ transplantation but rather an adjunct to T-cell-mediated rejection [11,12]. These early conclusions were mainly due to the more obvious role of cellular immunity under suboptimal or no immunosuppression in early graft rejection [11].

In the current immunosuppressive era with low rates of acute cellular rejection, the presence of alloantibody remains associated with poorer outcomes [13]. Post-transplant donor-specific antibody (DSA) and de novo DSA (dnDSA) are major risk factors and barriers to long-term stable graft survival [14,15]. Once DSA develops, almost 40% of affected patients lose their graft in contrast to patients with no dnDSA [16]. Furthermore, patients with preformed DSA, who comprise 40% of transplant waitlists, showed higher risk of rejection, either acute or chronic antibody-mediated rejection (ABMR) regardless of type of organ transplantation [17–19]. Alloantibody is also a major barrier to transplant tolerance. Conceptually, B cells and their downstream effector plasma cells (PCs) play a major role in acute and chronic ABMR [20]. Memory B cells rapidly differentiate to PCs following a secondary anamnestic response [21]. The clinical impact of B cells and antibodies, especially PCs that secrete antibodies against donor antigens, including HLA and non-HLA–specific antibodies, has received increasing attention in the past decade [22–28]. This has included a defined B-cell signature associated with clinical kidney transplant tolerance [29]. Given the association of a B-cell signature with tolerance, the B cell and its associated alloimmune response seems to be a key determinant of stable long-term graft survival or operational tolerance.

B cells are functionally heterogeneous populations. Unique B-cell subsets have been defined based on location, ability to migrate, and contribution to T-dependent or T-independent response [30,31]. However, some B-cell subtypes are well known for their regulatory effect via IL-10, IL-35, or TGF-ß, including transitional B cells, B10 effector cells, and other regulatory B cells [32–35]. In this review, we will focus on potential detrimental and beneficial B-cell functions/mechanisms in transplantation.

## Antibodies in organ transplantation

### Alloantibody as a barrier to transplant

Early in clinical transplantation, it was recognized that pretransplant cytotoxic levels of donor-specific HLA antibody (DSA) were associated with an increased risk for hyperacute rejection and/or allograft dysfunction across all organ types [8,36]. As more sensitive solid-phase immunoassays for DSA detection were developed, the correlation between DSA positivity and ABMR or allograft loss diminished [37–41]. However, surveillance biopsies and more sensitive methods for

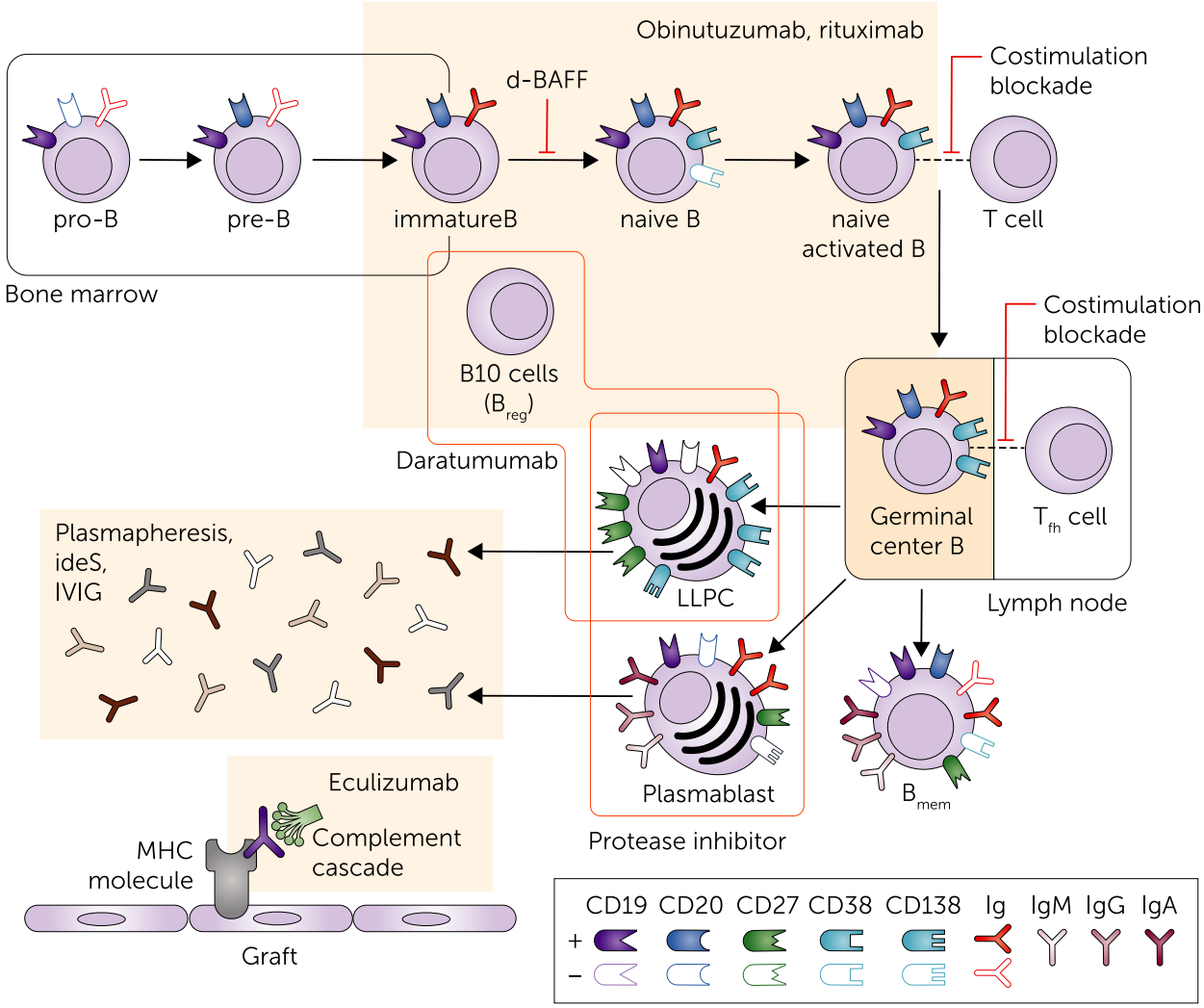


**Figure 2** Overview of commonly used pharmacological agents targeting B cells during different developmental stages.

detecting antibody-mediated injury reestablished a link between ABMR and diminished long-term survival in DSA-positive transplants [42–47]. The decision to transplant across a DSA barrier or wait for a more compatible organ depends on many factors, including the urgency for transplantation, center size, and risk-aversion policy, and center infrastructure that permits rapid initiation of antirejection therapy and close post-transplant monitoring of protocol biopsies and DSA. Single and multicenter studies have developed risk stratifications correlating preformed DSA strength at initiation of desensitization or time of transplantation with risk of ABMR and reduced allograft survival [48–51]. Detailed examinations of DSA characteristics have identified a greater risk for allograft loss and ABMR with complement-fixing DSA and IgG3 subclass DSA [24,52–55]. However, even in the absence of DSA at time of transplantation, the risk for ABMR in sensitized candidates may not be completely eliminated, given the possibility of unrecognized HLA-specific memory with the potential for recall responses immediately post-transplant [56–59]. Risk assessments for humoral alloimmunity require a full assessment of the patient's current and past sensitization events as well as the overall quality of the transplanted organ to include HLA mismatch [60]. Therefore, while avoiding DSA is preferred, it may not be possible in very broadly sensitized transplant candidates even in the era of kidney paired donation and broader deceased donor organ sharing across larger geographical regions [61,62]. Whether preformed DSA represents a barrier to transplantation is multifactorial and must be determined in the context of the patient, the organ type, and the transplant center.

The development of post-transplant de novo DSA can occur in the absence of pretransplant HLA sensitization and has been shown to impact long-term

allograft survival. DSA that arises post-transplant is primarily directed toward donor HLA class II mismatches and occurs in the setting of inadequate immunosuppression and/or increased HLA class II mismatching [63–72]. The incidence of de novo DSA depends upon allograft type ranging from 12% in primary kidney transplants with a median time to development of 4 years [16] and up to 30% in lung recipients within the first year post-transplant [45,73]. De novo DSA is more strongly associated with ABMR and allograft loss and thus appears to be more pathologic than preformed DSA. The reasons for this observation may reflect the generation of antibodies with higher specificity and affinity for mismatched donor HLA, increased immunogenicity of HLA class II molecules, or the upregulation and exposure to donor HLA class II in the context of inflammation and infection [45,73–76]. Greater attention to alloimmune risk assessments at time of transplant may better inform individualized immunosuppression and post-transplant monitoring strategies to detect incomplete suppression of humoral alloimmune response and avoid DSA formation [60,74].

### Accommodation: enigmatic role of alloantibody

In contrast to the above-described harmful effects of alloantibodies to vascularized grafts, under some circumstances humoral immunity causes little or no damage to an organ graft. Recent studies have shown that 30% of nonsensitized patients develop de novo DSA post-transplantation without demonstrating clinical signs of rejection [63,77]. This condition is referred to as accommodation [78,79]. Accommodation describes a biologic state in which grafts function despite noxious stimuli, like alloantibodies, against them, which was first described in the 1980s in the context of clinical ABO incompatible renal transplantation [80,81].

Accommodation can be mediated by the graft or by the host. The proposed mechanism of host accommodation includes a qualitative change in the humoral immune response with altered affinity and/or specificity for the graft [82]. One example in humans is the shift of IgG subclass to IgG2, which inefficiently activates complement and therefore indirectly blocks the effect of more cytotoxic IgG subclasses, as described by Yu *et al.* [83]. However, data also suggest that a healthy balance between complement-fixing and noncomplement-fixing antibodies may be required to induce accommodation [84]. A xenotransplantation model has shown evidence that antibodies against the graft are required to induce accommodation, and accommodation was not evident when anti-donor antibodies were suppressed [85]. In a cardiac xenograft model, investigators hypothesized that control of the complement cascade can support accommodation [86]. In sensitized murine models, investigators observed durable accommodation in heart and kidney allotransplantation models with terminal complement inhibition (anti-C5 mAb) [87,88]. Other observations in sensitized human renal transplant recipients have shown that removal of anti-HLA antibodies by immunoadsorption prior to transplantation is leading to accommodation in selected patients [89]. Subsequently, it was postulated that graft exposure with a low concentration of DSAs induces accommodation instead of causing graft injury. This was demonstrated in an in vitro model by Salama *et al.* [90], who identified Bcl-xl in graft endothelial cells as a possible key pathway involved. Recent data confirmed that 72% of nonsensitized pediatric kidney recipients showed evidence of de novo DSA within the graft when DSA was present in the serum, but the presence of graft DSAs was not, per se, predictive of graft loss [91].

Therefore, accommodation should not be interpreted as resistance to injury but is better described as a process that repairs injury and regenerates tissue functions. Barbosa *et al.* [92] summarized this new model of accommodation as a period of vulnerability countered by transiently induced cytoprotection that is followed by ongoing loss of vulnerability, reflecting persistent cellular, and biochemical changes. Viewed in this way, it is understandable that excess accommodation can also have downsides that include a lack of viral control and control of malignant tumor cells as described for hepatitis C and multiple cancer entities [93–95].

From the above-described understanding, modern strategies focus on controlling but not inhibiting the interaction between circulating antibodies and the graft. However, treatment strategies involving the complement cascade (eculizumab) or targeted plasma cell inhibition (bortezomib) have only been partially successful to date [96]. Overall, our understanding of accommodation is limited and largely driven by data generated before the current era of highly sensitive assays to measure allospecific antibodies, protocol graft biopsies, and more precise histologic criteria for ABMR.

## The role of B cells beyond antibody

For a more complete understanding of B cells and their role in transplantation, aspects of B-cell biology other than antibody production must be considered. Setting

antibody aside, B cells function in other ways, some of which promote rejection, and some of which have the potential to promote tolerance.

### B cells as antigen-presenting cells

Although chronic rejection is commonly considered an antibody-mediated process, Zeng *et al*. [97] have provided evidence that B cells are capable of promoting chronic rejection independently of antibody production. In a mouse model of heart allotransplantation using costimulation blockade-based immunosuppression (CTLA4Ig and anti-CD40L), they showed that animals genetically modified to lack circulating antibody (AID/μS KO mice) still went on to develop chronic allograft vasculopathy (CAV), a pathognomonic feature of chronic rejection found in heart, kidney, liver, and pancreas transplantation. On the other hand, animals genetically modified to lack both B cells and circulating antibody (μMT mice) were protected from CAV. CAV could be elicited in μMT mice by infusing B cells from AID/μS KO mice, even though these B cells were incapable of antibody production. One possible mechanism to account for this phenomenon could be the role of B cells as antigen-presenting cells. In another study of mouse cardiac allotransplantation, Noorchasm and colleagues reported that indirect alloantigen presentation by recipient B cells plays a critical role in the activation of alloreactive CD4+ T cells [98]. In mice, B cells have also been reported to play an important role in helping alloreactive CD4+ and CD8+ T cells differentiate into memory T cells [99]. In general, B cells may contribute to allograft rejection independently of antibody production by shaping the T-cell response through a combination of antigen presentation, cytokine production, and costimulation [100–103]. Additionally, one important role of B cells may include supporting the basic architecture of lymphoid tissue to allow optimal interaction between T cells, dendritic cells, and other components of the immune response [100–102].

### B-cell response to tissue injury

The traditionally understood pathological role of B cells in transplantation is about B-cell differentiation into antibody-secreting cells. However, as described above, B-cell function as antigen-presenting cells was also recognized [9,97]. Additionally, it is well known that B cells acutely respond to ischemia/reperfusion injury [104–106]. Recently, Cippa *et al*. [107] suggested that kidney injury in ischemia/reperfusion injury and transplantation are both mediated by a B-cell response to dysfunctional tissue repair. Interestingly, patients who developed chronic rejection already showed elevated B-cell activities and other common gene signatures for acute kidney injury including genes related to fibrosis (e.g., COL1A1, DPT, and MMP7) and inflammation (e.g., CD52, CXCL10, and CCL21). Based on a nontransplant (ischemic injury) mouse model, they found that the B-cell response to tissue injury is able to contribute to chronic kidney injury or chronic rejection in the absence of an alloimmune response. Based on transcriptional analyses, it was hypothesized that memory B cells infiltrate, expand, and gradually switch to a plasma cell population after ischemic injury and later became CD138 negative polyclonal B cells. Such cells may play a crucial role in developing ectopic germinal centers in the kidney, causing chronic kidney injury. Overall, B cells could have an important role in late immune-mediated kidney injury and repair responses including chronic rejection.

### Role of B cells in promoting tolerance

B cells are often thought to boost inflammatory responses. However, like their counterpart T cell, B cells can also suppress the immune response. Originally, B cells with immune regulatory function were identified by their function, such as their capacity to produce inhibitory cytokines (IL-10). Additionally, their ability to induce or recruit regulatory T cells (Tregs) has recently been implicated [108,109].

In transplantation, B cells were previously thought to have only a pathogenic role; however, growing evidence demonstrates that B cells may play a pivotal role in the induction and maintenance of transplant tolerance [110]. Regulatory B cells (Bregs) have proven their importance in controlling immunity in a number of mouse models of allergy and autoimmunity [103,111,112]. Although a number of subsets have been described as Bregs, the two B-cell subsets that are best characterized are $CD5^{+}CD19^{+}CD1d^{hi}$ B10 and $CD19^{+}CD21^{hi}CD23^{hi}$ $CD24^{hi}$ transitional-2 (T2) Breg cells. While no true consensus definition of Bregs has been agreed upon, characterizations generally center around the secretion of IL-10 [113]. Likewise, no signature set of phenotypic markers for Bregs is analogous to the markers CD25 and FoxP3 that characterize Tregs. Candidate phenotypic profiles for Bregs include $CD5^{+}CD1d^{hi}$ B cells and T-cell Ig and mucin domain protein 1 ($TIM\text{-}1^{+}$) B cells [114–116]. Mechanistically, Bregs function through IL-10 and through secretion of other cytokines (TGF-β, IL-35) to suppress CD4+ T-cell proliferation, suppress CD8+ effector T-cell function, induce T-cell apoptosis through

binding the FAS and PD-1 receptors, induce Tregs, suppress antigen-presenting and cytokine secretion by dendritic cells and M1 macrophages, and suppress natural killer (NK) cells and neutrophils [113]. Evidence for Bregs' salutary effect is sometimes inferred from experiments involving pan-B-cell depletion, which has been shown to accelerate rejection in models of heart and skin allotransplantation [117–119] and in human clinical heart and kidney transplant trials [120,121]. In accordance with this, agents that target specific Breg cell populations, such as daratumumab (anti-CD38mAb), showed skewing toward memory T-cell dominance in multiple myeloma [122] and accelerated T-cell-mediated rejection in a NHP model [123] possibly by reducing immune regulatory cells including Bregs, which are known to express CD38 [124,125]. More direct evidence for the role of Bregs in contributing to tolerance comes mainly from B-cell profiling in operationally tolerant transplant patients.

Recently, Lino *et al.* [126] characterized a subset of "natural regulatory plasma cells" identified by expression of the marker LAG-3. These cells appear to be a pre-existing "natural" subset and rapidly produce IL-10 in response to toll-like receptor stimulation. They also express the inhibitory receptors PD-L1, PD-L2, and CD200. Finally, B cells have been identified as the critical antigen-presenting cells involved in anergizing CD4+ memory T cells. In work by Dalai *et al.* [127], B2 follicular B cells—not DCs—were responsible for inducing anergy in the CD4+ memory T-cell compartment in a mouse model.

## B-cell signature of transplant tolerance

A major goal of the transplant community has been to identify a "signature" of tolerance in transplant patients. This might allow patients demonstrating this "tolerance signature" to wean off immunosuppression and maintain normal graft function. While much of the focus in studying operational tolerance has emphasized the role of T cells, recent evidence has pointed to a B-cell signature of tolerance in transplant recipients. To study this phenomenon, a population of operationally tolerant kidney transplant patients who were no longer taking immunosuppression but maintained normal graft function were identified and compared to control patients that remained on immunosuppression with stable graft function. In 2010, two groups identified a transcriptional signature in peripheral blood showing that upregulation of B-cell-related genes and their molecular pathways were associated with tolerance [29,128]. Furthermore, Newell *et al.* [29] demonstrated that this B-cell signature had upregulated in cells found in urine and found increased numbers of naive and transitional B cells in peripheral blood by flow cytometry. Additional work by these groups and others has identified that operationally tolerant patients have distinct B-cell phenotypes in peripheral blood that exhibit a more regulatory phenotype than patients with stable graft function on immunosuppression [129–132].

Collectively, these studies have suggested a role for B cells, in particular Bregs, in promoting or maintaining tolerance in kidney transplant recipients. Several studies in animal models have also shown a key role for B cells in transplantation tolerance since B-cell depletion can prevent tolerance induction by various methods, perhaps due to the loss of immune regulation by B cells [115,118,133,134]. More recent evidence in the operationally tolerant human kidney transplant recipients has identified the same B-cell signature of tolerance by transcriptional analysis of peripheral blood in both spontaneously tolerant individuals as well as those who underwent specific tolerance induction protocols [135]. In addition, a significant proportion of patients with stable long-term graft function while on immunosuppression demonstrated this B-cell tolerance signature [135–137]. A recent meta-analysis of the gene signatures of operationally tolerant kidney transplant patients validated the concept that the majority of biomarkers associated with tolerance were in fact B-cell-related [138].

## B-cell targeting, pros and cons

B-cell-targeted therapies have shown success in treating and reducing the incidence of ABMR, treating sensitized patients, and inducing tolerance. However, these advantages are balanced with shortcomings of solely targeting B cells owing to their regulatory role and interaction with other immune cells.

Investigations into preventing and treating ABMR have gained traction in the transplant community for this leading cause of graft failure. Rituximab (anti-CD20 monoclonal antibody) has been used prominently in renal transplantation for the treatment of ABMR, often in conjunction with IVIG, plasmapheresis (PP), or other agents, to prevent and reduce the incidence of ABMR [139,140]. Other solid organ transplant specialists have followed suit [141,142]. Traditionally, desensitization regimens relied on the removal of DSAs through PP, which is costly, invasive, and difficult to apply pretransplant in deceased donor transplantation [143]. B-cell targeting provides a noninvasive alternative approach. In a randomized controlled study of rituximab by van den Hoogen *et al.* [143], sensitized patients experienced less rejection episodes

compared to the placebo group. The role of B cells extends to the controversial topic of transplantation tolerance. Liu *et al.* [117] showed that B-cell depletion therapy might provoke a bias toward a regulatory phenotype and promote long-term islet allograft survival in nonhuman primates. A subsequent study showed that a possible explanation for this earlier finding might be that Bregs promote Treg cell development via TGF-b production [144]. There are ongoing investigations to explain these findings.

Limitations of B-cell-targeted therapies warrant a discussion to optimize their use in the clinical setting. Several studies have found that B-cell-focused therapies ignore the importance of T-cell-directed immune responses, resulting in allograft rejection and tolerance failure [118,119]. Clatworthy *et al.* [121] examined the benefit of B-cell depletion by using rituximab as a sole induction therapy in a randomized controlled trial, but the study was halted after a high incidence of acute cellular rejection was noted in the rituximab group. The authors hypothesized that depletion led to a loss of Breg activity and subsequent cytokine storm that activated T cells. However, the study's enrollment was small and the findings would need to be replicated with larger cohorts to confirm these findings. Furthermore, B-cell depletion with rituximab does not address PCs. Rituximab has been added to desensitization regimens to deplete B cells, reduce PC generation, and prevent antibody production in sensitized patients [145]. However, B cells no longer express CD20 once they differentiate into PCs and become "out of reach" of rituximab [146,147]. Clinically, depletional therapies with rituximab have many side effects, such as heightened risk of infection leading to sepsis [148,149] and cardiovascular disease (CVD) [150–152]. CVD is emerging as a highly morbid complication of rituximab-treated patients. Tyden and colleagues showed in their randomized controlled study that the rituximab group experienced higher mortality due to CVD with no difference in the incidence of AMR, T-cell-mediated rejection, or de novo DSA production. Kyaw *et al.* [151] showed that a possible explanation of such finding may be due to the depletion of atheroprotective B-lymphocyte populations with rituximab. Notably, the incidence of CVD in rituximab-treated patients is not limited to transplant patients; many cases have been reported in clinical trials in non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis, among others [152].

## Concluding remarks

Clearly, alloantibody is detrimental for long-term graft survival. The plethora of new agents targeting either the B cell, plasma cell, related cytokines, or complement has led to new transplantation research and clinical trials. B cells fall into several functionally distinct subpopulations, and broad B-cell depletion may bring undesired immunologic side effects including increased rejection. Understanding how to selectively control B cells that contribute to the humoral response against donor antigens will continue to be an important and challenging area of research and potentially lead to improved long-term transplant outcomes.

## Funding

This work was partially supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health as part of the Nonhuman Primate Transplantation Tolerance Cooperative Study Group under U19AI131471 (awarded to S.J.K.) and Opportunities Pool Round 13 (awarded to J.K.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## Acknowledgment

We would like to gratefully acknowledge Lauren Halligan (Department of Surgery, Duke University) for her contribution in creating the illustrations in the manuscript.

## Conflicts of interest

The authors have declared no conflicts of interest.

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