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Perspective/Viewpoint

Tegoprubart and the CD40L Pathway: Promise and Remaining Questions in CNI-Free Kidney Transplantation

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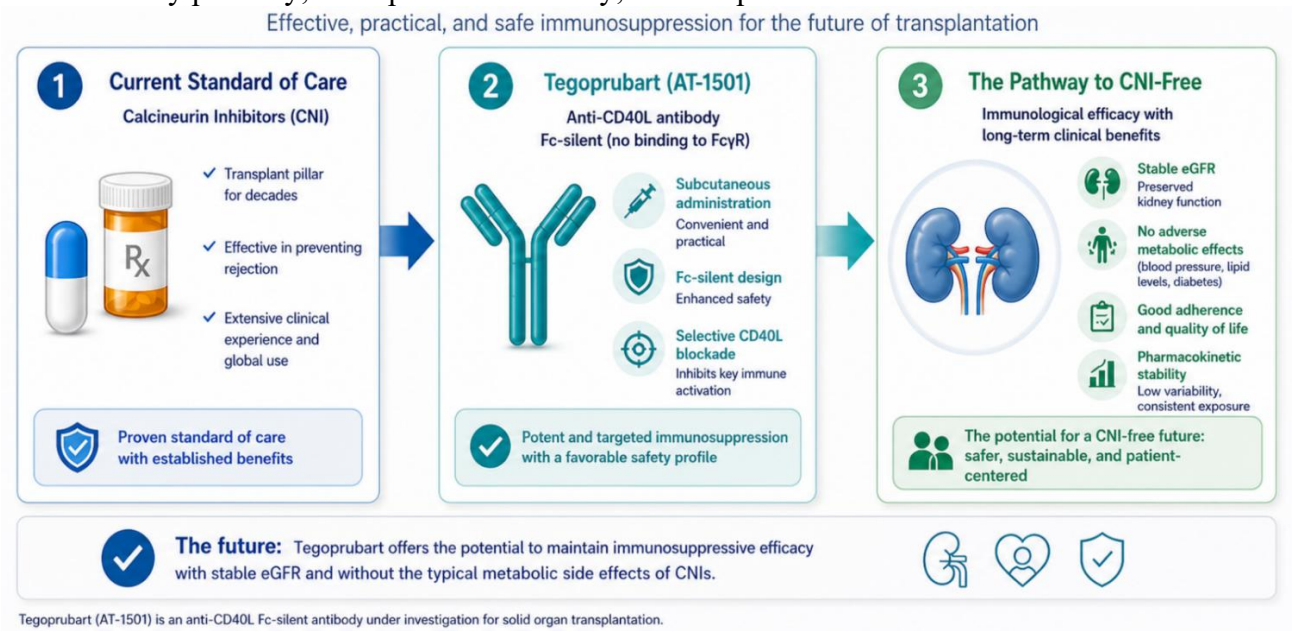
ABSTRACT

Calcineurin inhibitors (CNIs) remain the standard of care in kidney transplantation but are limited by chronic nephrotoxicity and high intra-patient pharmacokinetic variability (IPV), which drives late allograft loss. While costimulation blockade has emerged as a CNI-sparing alternative, the clinical adoption of belatacept is hindered by the logistics of intravenous administration, and recent receptor-targeting strategies, such as iscalimab (anti-CD40), have shown clinical limitations. This Perspective examines the re-emergence of CD40L as a viable therapeutic target through tegoprubart, an Fc-silent, subcutaneous anti-CD40L monoclonal antibody. We argue that targeting the ligand provides superior mechanistic pleiotropy compared with receptor blockade, more effectively suppressing T follicular helper cells and preventing endothelial prothrombotic activation. Furthermore, we highlight that tegoprubart's subcutaneous delivery represents a critical pharmacokinetic advance, shifting maintenance immunosuppression from a behaviorally dependent daily regimen to a biological steady state. While early Phase 2 data (BESTOW trial) show promising renal preservation without de novo donor-specific antibody (DSA) formation, we caution that deep costimulatory blockade carries an inherent, long-term risk of opportunistic infection. The ultimate success of tegoprubart will depend not on 12-month efficacy, but on its ability to maintain host defense over a decade of use.

Keywords: Kidney transplantation; CD40L blockade; Calcineurin inhibitor-sparing; Tegoprubart; Costimulatory pathway; Intra-patient variability; Donor-specific antibodies.



Graphical abstract. Shifting the renal transplantation paradigm: From CNI-based regimens to selective CD40L blockade. The schematic illustrates the transition from the current standard of care, centered on calcineurin inhibitors (CNIs) and their associated chronic nephrotoxicity, toward CNI-free strategies using tegoprubart. This anti-CD40L monoclonal antibody features a silent Fc domain to prevent thromboembolic events while maintaining robust costimulatory blockade. This approach aims to preserve long-term graft function by optimizing the eGFR profile and eliminating CNI-induced metabolic toxicities. Abbreviations: CNI, calcineurin inhibitor; CD40L, CD40 ligand; eGFR, estimated glomerular filtration rate; Fc, fragment crystallizable.

INTRODUCTION

The Shifting Paradigm of CNI-Sparing Immunosuppression

Calcineurin inhibitors (CNIs), particularly tacrolimus, remain the bedrock of maintenance immunosuppression, having revolutionized short-term graft survival. However, their chronic use exacts a severe toll: nephrotoxicity, neurotoxicity, and metabolic derangements, notably new-onset diabetes after transplantation (NODAT).[1,2] While belatacept provided proof of concept for CNI-sparing via CD28/CTLA-4 blockade, its intravenous administration, risk of early acute rejection, and concerns about post-transplant lymphoproliferative disorder (PTLD) have limited its widespread adoption.[3,4] Consequently, the field has looked downstream in the immune synapse to the CD40/CD40L axis.[5]

The era of CNI-free immunosuppression may have finally found its tipping point. Recent clinical setbacks with receptor-targeting strategies (e.g., iscalimab) have highlighted the biological limitations of blocking CD40.[6] In contrast, tegoprubart (AT-1501)—a ligand-targeting, Fc-silent monoclonal antibody—has emerged not merely as another alternative, but as a potential paradigm shift.[5,7] By rehabilitating the CD40L pathway through advanced protein engineering and offering subcutaneous administration, tegoprubart challenges the current clinical hierarchy.[5,7,8,9] However, translating preclinical promise into long-term clinical reality requires navigating the complex legacy of costimulatory blockade.[5,10]

Box 1. The Evolution of Costimulatory Blockade in Transplantation

Generation 1 (Anti-CD40L + Fc active; e.g., Ruplizumab): Potent immunosuppression halted by catastrophic thromboembolic events due to Fc-receptor-mediated platelet activation.[5,10]
Generation 2 (CTLA-4 Ig; e.g., Belatacept): First successful CNI-sparing agent, but burdened by intravenous logistics, higher early rejection rates, and PTLD risk.[3,4]
Generation 3 (Anti-CD40L + Fc-silent; Tegoprubart): Decouples pathway inhibition from platelet activation. Adds subcutaneous delivery, aiming to combine the potency of Gen 1 with the safety and logistics required for modern outpatient care. [5,7,8,9]

Mechanistic Rationale: Why the Ligand Outperforms the Receptor

The CD40/CD40L axis is a master regulator of adaptive immunity, orchestrating T-cell help, B-cell maturation, germinal center development, and donor-specific antibody (DSA) production.[5] Initial clinical attempts to target CD40L in the early 2000s were derailed by thromboembolic complications, an effect later attributed to binding of Fc-gamma receptor (FcγRIIa) on platelets.[5,10] Tegoprubart was engineered with an Fc-silent modification, effectively separating pathway inhibition from the safety profile that rendered first-generation molecules unviable.[5,7]

However, the renewed interest in CD40L is not just about safety engineering; it is about mechanistic superiority over receptor-directed approaches. The recent clinical shortcomings of iscalimab (anti-CD40) serve as a critical "cautionary tale" regarding the efficacy of receptor isolation.[6] Blocking CD40 on the antigen-presenting cell (APC) leaves alternative CD40L interactions—such as those with CD11b on macrophages—intact.[5] In contrast, CD40L blockade by tegoprubart provides a more proximal and pleiotropic interruption of the immune synapse. Preclinical models suggest that targeting the ligand more effectively suppresses T follicular helper (Tfh) cells and germinal center activity, thereby leading to a more profound reduction in de novo DSA formation (Figure 1).[7]

This mechanistic distinction is further validated outside standard allotransplantation. In the highly demanding realm of porcine-to-human xenotransplantation, CD40L blockade has become the immunological backbone for preventing hyperacute and acute humoral rejection, particularly by halting the prothrombotic activation of the graft endothelium—a primary barrier to recent xenotransplantation milestones.[5,11,12] If CD40L inhibition is potent enough to bridge vast phylogenetic disparities and protect the endothelium, its application in standard kidney transplantation represents a logically robust, albeit clinically nascent, strategy.

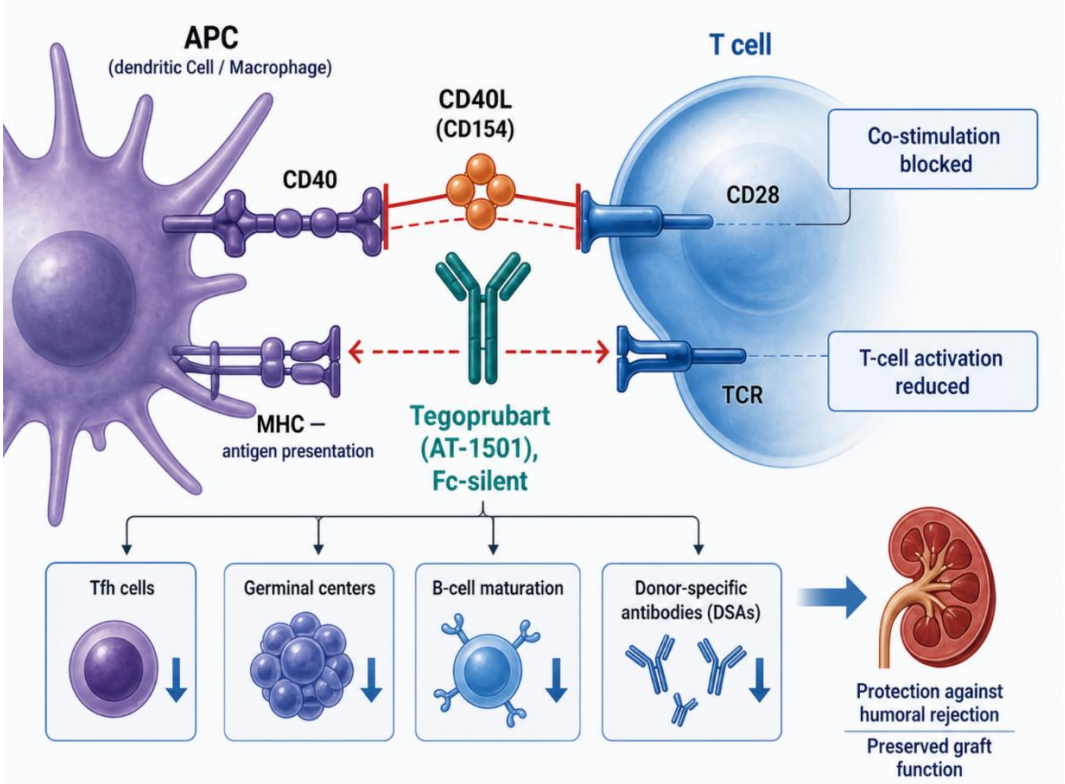


Figure 1. Mechanistic overview of tegoprubart-mediated CD40L blockade in kidney transplantation. Tegoprubart (AT-1501), an Fc-silent anti-CD40L monoclonal antibody, blocks CD40/CD40L-dependent co-stimulation, reducing T-cell activation, Tfh cell activity, germinal center responses, B-cell maturation, and donor-specific antibody formation. These effects may help protect against humoral rejection and preserve graft function.

The Subcutaneous Revolution: Eradicating Pharmacokinetic Valleys

Beyond mechanistic superiority, tegoprubart addresses a profound practical flaw in current maintenance therapy: pharmacokinetic (PK) variability. The reliance on daily oral tacrolimus creates notorious "troughs" in drug exposure and high intra-patient variability (IPV), which remains a leading cause of late allograft loss.[2] These subtherapeutic valleys are a primary driver of chronic antibody-mediated rejection (AMR) and de novo DSA formation, often exacerbated by patient non-adherence. Early pharmacokinetic data from Phase 1 trials and the ongoing BESTOW study (NCT05983770) demonstrate that tegoprubart's subcutaneous formulation achieves sustained therapeutic concentrations.[8,9] This shift to an SC-based maintenance regimen is not merely a convenience; it is a pharmacokinetic imperative to achieve therapeutic 'quiescence' in the immune synapse, bypassing the IPV inherent to oral CNIs. Conversely, belatacept, while avoiding PK valleys, demands monthly intravenous infusions, creating logistical bottlenecks and increasing costs for transplant centers.[3,4] Tegoprubart bridges this remaining gap. By providing a biologic agent with a prolonged half-life in a rapid outpatient injection format, tegoprubart could stabilize immunosuppression in a way that daily pills and monthly infusions cannot. In a Perspective focused on the future of the field, this shift from behavioral dependence to biologically steady state may prove to be as clinically significant as the drug's mechanism of action itself.

Clinical Evidence: The BESTOW Program

Human data, while still early, are beginning to validate this preclinical promise. Interim 12-month data from the Phase 2 BESTOW trial demonstrate that tegoprubart-based regimens maintain stable estimated glomerular filtration rates (eGFR) without the early signals of tremor, NODAT, or de novo DSA formation that typically plague CNI-heavy regimens.[9,13,14] While these results are derived from limited cohorts and require validation in larger Phase 3 trials, they represent the first successful translation of Fc-silent CD40L blockade into human kidney transplantation.

The Achilles' Heel: Immunologic Vigilance and the Infection Clock

However, maintaining scientific integrity requires acknowledging the inherent risks of deep costimulatory blockade. The transition from a 12-month safety signal to long-term clinical reality is fraught with peril. The CD40/CD40L pathway is critical for T-cell-dependent B-cell responses against viruses and malignancies.[5]

The field must heed the lessons from the 10-year follow-up of belatacept-based regimens, which demonstrated that while renal function is preserved, vigilance for cytomegalovirus (CMV), BK polyomavirus, and PTLD remains a lifelong necessity.[15],[16],[17] Does the more profound pleiotropic inhibition of CD40L (compared to CTLA-4 Ig or anti-CD40) confer a higher risk of opportunistic infection? The early BESTOW cohorts have not shown overwhelming infectious signals, but as any transplant immunologist knows, immunosuppression safety is a marathon, not a sprint. If tegoprubart eliminates nephrotoxicity only to increase the incidence of severe viral reactivation in years 3 or 4, its clinical utility will be severely marginalized. Therefore, rigorous, long-term pharmacovigilance must be the cornerstone of the ongoing BESTOW extension trials (NCT06126380).[18]

CONCLUSIONS

As transplantation medicine pivots away from its historical reliance on calcineurin inhibitors, the re-emergence of CD40L as a viable therapeutic target stands as a triumph of protein engineering overcoming clinical history. Tegoprubart is not merely a toxicity-sparing agent; it represents a mechanistic pivot. By learning from the thromboembolic failures of first-generation anti-CD40L antibodies, the logistical limitations of belatacept, and the recent efficacy shortcomings of anti-CD40 receptor blockade, tegoprubart enters the clinical arena uniquely positioned. Its Fc-silent design and subcutaneous delivery offer an unprecedented opportunity to achieve therapeutic 'quiescence' at the immune synapse. However, the definitive validation of this molecule will not rest solely on preserving short-term renal functional milestones already achieved by previous biologics—but on its potential to redefine long-term graft survival without compromising host immune surveillance. The promise is unprecedented, but whether we are witnessing the end of the era of chronic nephrotoxicity depends on rigorous, decade-long observation.

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