Whitepaper:

CONVERGING PATHWAYS: REPURPOSING THERAPIES USED IN NATIVE IMMUNE MEDIATED RENAL DISEASES (PREDOMINANTLY IGAN) TO TREAT ALLOGRAFT REJECTION

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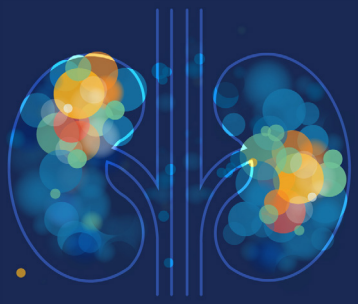

OUTLINE

Treatment of antibody-mediated rejection (ABMR) and native glomerular diseases present significant challenges for nephrologists and current treatment regimens are lacking standardization and evidence to support efficacy. Additionally, these therapies may present significant risks and increase burden of disease to affected patients.

ABSTRACT

Kidney transplantation remains the gold standard for end-stage kidney disease (ESKD), yet long-term graft survival is limited by antibody-mediated rejection (ABMR) and chronic allograft nephropathy. Current standard-of-care immunosuppression (calcineurin inhibitors, antimetabolites) effectively targets T-cell alloimmunity but is fundamentally insufficient against the humoral cascade and the progressive interstitial fibrosis that dictate long-term graft attrition. Concurrently, the therapeutic landscape for IgA Nephropathy (IgAN) has undergone a paradigm-shifting revolution, validating new drug classes that target the "upstream" source of autoimmunity (mucosal B-cell priming, plasma cell survival) and the "downstream" effectors of injury (complement activation). This review proposes that these pathophysiological mechanisms—complement dysregulation, B-cell maturation, and maladaptive fibrosis—are shared between native IgAN and allograft rejection. We examine the potential of repurposing IgAN-validated therapies, specifically Alternative Pathway complement inhibitors (e.g., Iptacopan), BAFF/APRIL antagonists (e.g., Atacicept, Sibeprenlimab), anti-CD38 therapies (e.g., Felzartamab), and dual endothelin/angiotensin receptor antagonists (e.g., Sparsentan), to interrupt the alloimmune cascade. By shifting focus from broad immunosuppression to targeted mechanistic blockade, these agents offer a novel paradigm for renal allograft rescue.

INTRODUCTION: THE MECHANISTIC CONVERGENCE OF NATIVE AND ALLOIMMUNE INJURY

The traditional clinical dichotomy between "native glomerular disease" and "alloimmune rejection" is becoming increasingly obsolete when viewed through the lens of molecular pathology. Historically, IgA Nephropathy (IgAN) was conceptualized strictly as an immune-complex glomerulonephritis driven by galactose-deficient IgA1 (Gd-IgA1), while antibody-mediated rejection (ABMR) was understood as an alloimmune phenomenon mediated by donor-specific antibodies (DSA) engaging the allograft endothelium. However, deep tissue phenotyping and transcriptomics reveal a shared "final common pathway" of structural injury. Both pathologies are initiated by a pathogenic antibody trigger. Both heavily rely on the complement cascade to amplify microvascular inflammation (manifesting as mesangial hypercellularity in IgAN and peritubular capillaritis/glomerulonephritis in ABMR). Ultimately, both progress to a terminal phase of intraglomerular hypertension, endothelial-to-mesenchymal transition (EndMT), and irreversible interstitial fibrosis/tubular atrophy (IF/TA).

While the standard solid-organ transplant pharmacopeia (e.g., Tacrolimus, Mycophenolate Mofetil) exhibits profound efficacy in mitigating acute T-cell mediated rejection, it fails to induce plasma cell apoptosis or arrest the complement cascade once DSA binds to the graft. This review details how the robust pipeline of newly approved and late-stage investigational drugs for IgAN precisely targets these glaring unmet needs, positioning them as prime candidates for repurposing in transplantation.

THE COMPLEMENT BRIDGE: DISARMING THE AMPLIFICATION LOOP

The IgAN Precedent:

- The pathogenesis of IgAN is intimately linked to the Alternative Pathway (AP) and lectin pathway of complement. The landmark APPLAUSE IgAN trial, which evaluated Iptacopan (a first in-class oral Factor B inhibitor) demonstrated that blocking the AP proteinuria and stabilizes eGFR. This confirmed that the AP is not merely a bystander, but a critical "amplification loop" that drives sustained glomerular inflammation, independent of the initial immune complex deposition.

The Transplant Application:

- In ABMR, the binding of DSAs to human leukocyte antigens (HLA) on the graft endothelium triggers the Classical Pathway via C1q. However, the magnitude of the ensuing tissue injury is heavily dependent on the recruitment of the AP amplification loop, culminating in the assembly of the Membrane Attack Complex (C5b-9) and the release of potent anaphylatoxins (C3, C5a) that recruit macrophages.

Therapeutic Repurposing:

- Moving Proximal to C5: Eculizumab (a terminal C5 inhibitor) has been utilized in atypical HUS and severe ABMR, but it only blocks the formation of MAC. It does not prevent generation of C3a or the dense deposition of C3d on the endothelium, which continues to drive microvascular inflammation and opsonization.
- Proximal Inhibitors – Iptacopan & Pegcetacoplan (C3/Factor B Inhibition): By utilizing upstream inhibitors derived from IgAN protocols, clinicians could theoretically halt the entire downstream cascade. Suppressing Factor B or C3 directly prevents both the terminal cytolytic damage and the upstream anaphylatoxin-driven cellular infiltration that characterizes chronic active ABMR.

THE PLASMA CELL NICHE: STARVING THE HUMORAL SOURCE

The IgAN Precedent:

- IgAN is fundamentally driven by the overproduction of aberrantly glycosylated IgA1 by the mucosal-derived B-cells and plasma cells. Consequently, interrupting the B-cell maturation axis has yielded profound results. Trials targeting the BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand) cytokines – such as the ORIGIN trial (Atacicept), ENVISION (Sibeprenlimab), and studies on Telitacicept – have shown massive reductions in pathogenic Gd-IgA1 titers by depriving B-cells of essential survival signals.

The Transplant Application:

- The Achilles' heel of treating ABMR is the Long-Lived Plasma Cell (LLPC). Residing in the protective niches of the bone marrow, LLPCs continuously secrete DSA. Crucially, mature plasma cells downregulate CD20, rendering standard therapies like Rituximab entirely ineffective. Proteasome inhibitors (Bortezomib) have high toxicity and transient efficacy.

Therapeutic Repurposing:

- Direct Plasma Cell Depletion (Felzartamab): This Anti-CD38 monoclonal antibody directly induces apoptosis in mature plasma cells. Following successful Phase 2 data in IgAN (the IGNAZ trial), Felzartamab is currently undergoing rigorous evaluation in the TRANSCEND trial for kidney transplant recipients with late active ABMR. This represents the vanguard of parallel drug repurposing.
- BAFF/APRIL Antagonism: In transplantation, BAFF levels often surge following standard immunosuppression or B-cell depletion, paradoxically promoting the survival of alloreactive B-cells. Repurposing agents like Atacicept or Sibeprenlimab could neutralize this surge, "starving" the plasma cell niche and facilitating deeper desensitization or halting the *de novo* generation of DSA.

HEMODYNAMIC & FIBROTIC SURVIVAL: PRESERVING NEPHRON MASS

The IgAN Precedent:

- The PROTECT trial firmly established Sparsentan – a dual endothelin (ETA) and angiotensin II type 1 (AT1) receptor antagonist (DEARA) – as a disease-modifying therapy for IgAN. Endothelin-1 is a potent driver of both vasoconstriction and renal fibrogenesis. Sparsentan effectively lowers intraglomerular pressure, protects podocyte architecture, and directly antagonizes pro-fibrotic signaling.

The Transplant Application:

- Irrespective of the initial immunologic insult, failing allografts converge on a phenotype of "Transplant Glomerulopathy" – characterized by glomerular basement membrane double contours, endothelial stress, and progressive IF/TA. Even if the immunologic fire of ABMR is extinguished, the architectural damage results in hyperfiltration of the remaining nephrons, leading to inevitable graft failure.

Therapeutic Repurposing:

- Sparsentan: Utilizing dual ETA/AT1 blockade in the allograft setting could disrupt the EndMT process and limit allograft fibrosis. While a current trial (NCT07219121) is investigating Sparsentan for recurrent IgAN and FSGS post-transplant, the mechanistic rationale strongly supports extending its use to non-recurrent chronic allograft dysfunction to maximize the dialysis-free survival of the organ.

THE MUCOSAL HYPOTHESIS: MODULATING THE SYSTEMIC TONE

The IgAN Precedent:

- The NefIgArd trial validated Nefecon, a targeted-release formulation of budesonide designed to deliver drug specifically to the Peyer's patches of the terminal ileum. By dampening the local mucosal immune response, Nefecon dramatically reduces the systemic production of Gd-IgA1, proving that local gut immunomodulation yields systemic renal benefits.

The Transplant Application:

- The concept of the "Gut-Kidney Axis" is rapidly gaining traction in solid organ transplantation. Transplant recipients suffer from profound gut dysbiosis due to chronic antibiotic and immunosuppressant exposure. This dysbiosis breaks down the intestinal barrier, leading to the translocation of endotoxins and a skewing of the immune system away from regulatory T-cells (Tregs) toward pro-inflammatory Th17 cells, thereby lowering the threshold for alloimmunity.

Theoretical Repurposing:

- Modulating mucosal immunity (via Nefecon-like targeted steroids or microbiome-modulating therapies) in transplant recipients could theoretically calm the systemic inflammatory tone. By suppressing immune priming at the gut level, clinicians may be able to reduce systemic alloreactivity, potentially allowing for the minimization of highly toxic systemic immunosuppression like calcineurin inhibitors.

OPERATIONAL CONSIDERATIONS FOR MECHANISM-DRIVEN TRANSPLANT TRIALS

The emerging generation of transplant trials evaluating complement inhibition, plasma cell therapies, and fibrosis-modifying agents introduces operational complexity beyond immunosuppression studies. These studies require seamless management of laboratory assessments, biomarker endpoints, adaptive risk monitoring, and real-time safety oversight. Effective execution depends on tightly integrated clinical, laboratory, imaging, data, and medical review capabilities rather than siloed models.

As a full-service CRO, Medpace utilizes an outsourcing model that preserves clear accountability, takes advantage of established process efficiencies, and significantly reduces the oversight needed by the Sponsor. Sponsors can employ a strategic oversight model, leveraging resources across the entire portfolio of outsourced trials. This model is particularly well suited for complex renal transplant studies where multiple mechanistic endpoints and safety signals must be evaluated concurrently across global sites.

Medpace is a global leader in nephrology and has notable experience in the management of studies in renal transplant recipients. This expertise is compounded through our Transplant Working Group, ensuring our teams are well versed in the scientific methodology, standard of care (SOC), evolving regulatory requirements, and operational considerations necessary to effectively manage transplant studies. Successful application of experience extends collaboratively to clients, coupled with ready-made connectivity with leading investigators, Key Opinion Leaders (KOLs), and sites globally.

Integrated Services: Streamlining Transplant Clinical Trials

Medpace's comprehensive CRO services are supported by our wholly owned Central Laboratories, Bioanalytical Lab, Imaging Core Lab, ECG Core Lab, and Phase I Unit, as well as a Clinical Trial Management System that ties all study data together in a single platform, ClinTrak®. This integrated infrastructure enables coordinated evaluation of immunologic, histopathologic, and functional endpoints that are central to trials targeting ABMR and chronic allograft injury.

ClinTrak® can combine multiple sources of unstructured data into easy-to-use dashboards for real-time operational oversight of critical study data. These dashboards aggregate laboratory biomarkers, biopsy timing and results, safety data, and patient-reported outcomes into role-specific views that support proactive decision-making by clinical, operational, and medical teams.

Risk Management in Renal Transplant Trials

Risk is inherent in every clinical trial and to ensure trial success, steps must be taken to proactively anticipate and mitigate the unique risks. Development of a risk management plan, including the identification of risk mitigations and contingencies, is initiated at the start of each trial. Ongoing risk assessment and modifications to the risk management plan are made in response to protocol amendments and other key events.

Examples of risk mitigation strategies in IgAN and Transplant trials include:

- Supporting enrollment by developing strategies to trigger specific patient referral pathways, including nephrology clinics to search their databases, educate patients' usual renal staff at hospitals where the transplant takes place, provide referral materials like patient flyers to dialysis centers and collaborate with advocacy groups and forums to advertise the trial
- Decreasing patient burden by arranging study visits close to SOC visit frequency and providing support with concierge services
- Ensuring quality patient reported data by coordinating patient training for diary completion with timely follow-up to ensure diary/questionnaire/patient-reported outcome completion
- Providing comprehensive training to sites for sampling and biopsy requirements to ensure high-quality samples are obtained

Medpace's Risk Based Monitoring (RBM) approach is a holistic, adaptive process, evaluated on an ongoing basis throughout the lifecycle of a trial across each functional area for all our clinical trials. This approach is operationalized through centralized analytics and visual dashboards that enable cross-functional teams to identify emerging safety, data quality, and endpoint integrity risks in real time.

This cross-functional approach ensures effective study conduct by directing focus and activities to the areas of greatest risk via protocol evaluations, centralized monitoring activities, including centralized data reviews, remote monitoring visits, and on site monitoring visits with potentially reduced source data verification, as applicable for larger multicenter studies.

Patient Recruitment and Retention in Renal Transplant Trials

Enrollment challenges are inherent to clinical trials and measures can be taken to support patient recruitment and retention. Physician referral networks can be established that include partnerships between transplant surgeons, nephrology physicians, advanced clinical practitioners, other specialists (e.g., infectious diseases), primary care providers, and KOLs. Patient referrals also can be facilitated by providing engaging study recruitment materials such as trial flyers and brochures for patients to read in the waiting room.

Use of social media and involvement of patient support groups can also be beneficial for patient recruitment. Patient retention is also critical to study success, and patient burden should be minimized by developing a comprehensive patient retention plan that includes travel and reimbursement services, which can be coordinated through the Medpace Patient Concierge Services, and the production of patient-centric educational materials that explain study expectations, outline which study procedure will occur at each study visit, and provide milestone gift items to patients at specific visits to recognize ongoing participation in the trial.

Endpoint Protection

Study endpoint protection is critical to trial success. Medpace's global experience in nephrology trials has led to innovative efforts to protect endpoints related to proteinuric assessments, including the development of best practice workshops, training tools and specific site training to assist in the optimization of urine collections used for endpoint analyses.

Medpace's central laboratories are highly adept regarding standardized methodology for eGFR calculations and utilizes both creatinine and cystatin C assays that are traceable to Isotope Dilution Mass Spectrometry (IDMS) and International Federation of Clinical Chemistry (IFCC) standards thus minimizing variability and ensuring accuracy of these calculations.

Our in-house nephrology team understands the unique patient population and will ensure appropriately defined critical laboratory alerts have accelerated review allowing rapid identification and management of potential safety issues, alongside maintaining efficient communication with sites and appropriate follow-up. In addition, Medpace's integrated functional areas and use of visual analytics allows both real-time and aggregate medical/safety review allowing for robust monitoring of this complex high-risk patient population. Integration across laboratory, medical, and clinical operations enables full contextualization of safety and efficacy signals rather than isolated data review.

Medpace teams acknowledge that abbreviated and full iBox composite scores may be used in endpoint analyses. The full iBox system includes histological analyses of interstitial fibrosis/tubular atrophy (IFTA), glomerulitis (g), peritubular capillaritis (PTC), interstitial inflammation (i), tubulitis (t) and transplant glomerulopathy (cg).

Medpace teams from both the CRO and Imaging Core Lab have experience working with the Banff criteria, including the Banff Endpoint Working Group, delivering specific recommendations for the successful incorporation of histological endpoints into studies. This includes ensuring that a panel of central pathologists review whole slide images alongside sufficient clinical information such as donor specific antibody status to prevent interoperator variability in individual lesion scoring.

For patient reported outcomes (PROs), comprehensive site training is key to reduce variability and ensure consistency across all sites. It is essential that sites are educated to ensure all patients complete PROs consistently. Providing patient-facing instruction leaflets aid in the completion of PROs. It is also helpful to allow subjects to correct entry errors at the time of ePRO entry.

CONCLUSION

IgA Nephropathy has effectively become the vanguard testing ground for the next generation of targeted nephrologic therapeutics. The successful clinical validation of proximal complement inhibitors, plasma cell depletors, and hemodynamic stabilizers in IgAN provides a highly de-risked and mechanistically sound roadmap for solid organ transplantation. By strategically repurposing these agents, and providing operationally sound infrastructure in the process, we can move beyond the blunt toxic instrument of broad T-cell suppression and specifically neutralize the antibody-mediated and fibrotic pathways that drive long-term allograft loss.

ABOUT THE AUTHORS

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Amit Govil, MD, FAST, FASN, is the Robert G. Luke Endowed Chair in Nephrology, Director of the Division of Nephrology, and Medical Director of the Kidney Transplant Program at the University of Cincinnati. His work focuses on kidney transplantation, transplant outreach, delayed graft function, transplant outcomes, and innovative strategies to improve access to transplantation. He has received multiple national awards for excellence in transplant care, education, and leadership.

Sara Rhoten, MSN, RN
Advanced Clinical Practitioner, Medpace

Sara Rhoten is a board-certified nurse practitioner with nearly 20 years of clinical expertise in kidney disease management and transplantation. Specializing in the care of kidney and pancreas transplant recipients, she brings extensive experience across the entire transplant continuum, from pre-transplant coordination, desensitization, and waitlist management to post-operative care and long-term immunosuppression management. Her background includes serving as a pre- and post-kidney-pancreas transplant coordinator, providing direct nursing care to solid organ transplant recipients (kidney, pancreas, and liver), and managing dialysis patients on the kidney transplant waitlist. She is experienced in the treatment of post-transplant complications and infections such as BKV and CMV.

Ajay Srivastava, MD, FASN
Vice President, Medical Department, Medpace

Dr. Ajay Srivastava is a board-certified interventional nephrologist currently serving as Vice President, Medical Department at Medpace. In this role, he leverages over 20 years of clinical and academic expertise to advance the development of safe, effective medical therapeutics on a global scale. Prior to joining the CRO space, Dr. Srivastava held a series of prestigious leadership positions, including Division Chief of Nephrology and Interim Chair of Medicine. His background also includes significant roles as Medical Director of Dialysis facilities and Director of Nephrology Fellowship Training. A graduate of the University of Rochester (BA, Psychology (Honors)) and the University of Texas Medical Branch (MD), he completed his postgraduate residency and Nephrology fellowship at the University of Rochester Medical Center.

Nel Van Lommel
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Nel Van Lommel is a seasoned clinical research professional with over 28 years of experience in clinical trial management across pharmaceutical and biotechnology industries. Specializing in the oversight of complex global clinical programs, she brings extensive expertise spanning Phase I-IV studies in diverse therapeutic areas including nephrology, rare diseases, immunology, musculoskeletal disorders, and rheumatology. With 18 years dedicated to clinical trial project management, Nel currently serves as Senior Director of Clinical Trial Management at Medpace in Leuven, Belgium, where she leads the company's Transplant Working Group.

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