To date, the treatment of immune-mediated kidney diseases has only marginally benefited from highly specific biological drugs that have demonstrated remarkable effects in many other diseases. What accounts for this disparity? In April 2016, the International Society of Nephrology held a Nexus meeting on Translational Immunology in Nephrology in Berlin, Germany, to identify and discuss hurdles that block the translational flow of target identification, and preclinical and clinical target validation in the domain of immune-mediated kidney disease. A broad panel of experts including basic scientists, translational immunologists,
during the last decade, a plethora of novel anti-inflammatory and immunomodulatory drugs have been developed and demonstrated to have profound efficacy with diminished toxicity in inflammatory and autoimmune diseases of several medical specialties, including rheumatology, dermatology, and immunology. Nephrology has not yet significantly benefited from these innovations. Belatacept, a selective T-cell costimulation blocker, indicated for prophylaxis of kidney transplant rejection; rituximab (RTX), a CD20-directed cytolytic antibody, indicated for the treatment of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis; and eculizumab, a complement inhibitor, indicated for the treatment of atypical hemolytic uremic syndrome to inhibit complement-mediated thrombotic microangiopathy, remain, so far, the only significant US Food and Drug Administration-approved innovative treatments in nephrology. Many other promising drugs to reset immune tolerance and suppress inflammation failed to demonstrate efficacy in multicenter randomized controlled trials (RCTs). In particular, lupus nephritis has turned out to be a challenging area for drug innovations. Significant and cumulative concerns about conceptual hurdles in current translational kidney disease research2 (Table 1) prompted the International Society of Nephrology to organize a global Nexus meeting on the topic of “Translational Immunology in Nephrology,” which was held in Berlin, Germany, from 14 to 17 April 2016. During this meeting, experts and participants from basic science, clinical science, pharmaceutical industry, and regulatory bodies defined problems and discussed potential solutions (Figure 1).

This report summarizes the results of the meeting and provides the framework for coordinating further efforts to overcome existing hurdles and to improve the translational flow of target identification, validation, and eventually innovative drug approval for immune-mediated kidney diseases.

Three speakers from the meeting are featured in PowerPoint presentations with audio linked to this paper. Dr. Adeera Levin discusses translational immunology; Dr. Giuseppe Remuzzi explains how to set up a translational kidney research program; and Dr. Paul Brunetta covers the topic of biological drugs from bench to bedside.

### Challenges

**Global View**

The global challenges in nephrology are surprisingly similar in different parts of the world. The prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is increasing in developed and developing countries, because of increasing lifespan and skyrocketing rates of obesity, diabetes, and hypertension.3,4 Developing countries also face additional infectious and toxic triggers of kidney disease.5 In developing countries with limited or no access to renal replacement therapy (RRT), ESRD can only be avoided by preventing CKD progression.6 In countries with...
unlimited access to RRT, the majority of renal care providers are engaged in RRT, which together with the renal replacement industry has shifted academic research activities away from CKD prevention. Although programs in CKD/ESRD prevention are likely to be highly cost-effective for national health care systems all over the world, minimal coordinated efforts are made by public bodies, academia, industry, and society. The reasons for this lack of awareness at all levels are the asymptomatic nature of CKD, a generalized complacency because we have RRT and can often avoid death from renal failure, and the financial incentives of providing RRT. Although RRT catapulted nephrology to among the most attractive medical specialties some decades ago, the situation has dramatically changed in the recent years. The development of innovative drugs that promise cures for disease is currently revolutionizing many other medical specialties such as oncology, dermatology, and rheumatology, thereby attracting the attention of pharmaceutical companies, physicians in training, and medical students. Indeed, nephrology is no longer considered an attractive career option among medical residents.7,8

**Awareness**

The enormous unmet medical need for the prevention of ESRD requires defining suitable interventions. These can include awareness campaigns such as the World Kidney Day or smart phone apps to alert patients to take medications, make doctor appointments, and access lab results. Awareness is needed concerning the importance of maintaining an adequate nephron number throughout life, primary preventive measures such as avoidance of nephrotoxic drugs, control of hypertension, and control of diabetes, and secondary prophylaxis in those with nephron loss due to a previous acute kidney injury (AKI) episode or age-related nephropathy, which is relevant to large segments of the elderly population.

**Oversimplification**

Although such preventive measures may ultimately save more people from reaching ESRD, industry and academic researchers remain largely focused on druggable interventions for patients who already have kidney disease that is often well advanced. However, kidney disease categories are currently largely oversimplified. Although the community seeks cures for “AKI” and “CKD,” the concept of “nephron loss over a lifetime” might be more useful to appreciate the accumulating risk of ESRD in aging populations. In fact, the high prevalence of AKI as well as AKI on CKD largely mirrors underlying low nephron number (=CKD).9 This implies that any kind of kidney disease in the elderly involves a variable component of underlying irreversible nephron loss, which cannot be fixed by drugs targeting the supervening kidney disease.10 Only drugs with benefits on global mechanisms of kidney injury show significant renoprotective effects such as renin-angiotensin-system blockers that reduce glomerular filtration load and protect from secondary podocyte loss, glomerulosclerosis, and further nephron loss. However, drugs acting mainly on hemodynamic nephron injury fall short in immune-mediated kidney diseases with a significant autoimmune or inflammatory component. Conversely, the lack of significant renoprotective effects of immunosuppression could indicate that autoimmunity or renal inflammation is not the only driver of disease progression in diseases such as chronic lupus nephritis or IgA nephropathy.11

**Disease Entities and Subentities**

The definition of immune-mediated kidney diseases remains dependent on histopathological features (e.g., focal segmental glomerulosclerosis, lupus nephritis, pauci-immune, membranous, or membranoproliferative glomerulonephritis [GN]) or traditional biomarkers (lupus nephritis, ANCA vasculitis, diabetic nephropathy). However, drug development requires an understanding of common pathogenetic mechanisms rather than histopathological disease categories. Clinical trials recruiting patients based on histopathological lesions or biomarkers unrelated to disease mechanisms usually fail because only a small percentage of participants respond to the mechanism of action of the tested drug. Hence, further subclassification of disease entities seems warranted. Some progress has been made for phospholipase A2 receptor+ and phospholipase A2 receptor– membranous GN, typical and atypical hemolytic-uremic syndrome, and C3 glomerulopathy.12–14 With further subclassification of disease, one conclusion is obvious. Immune-mediated kidney diseases as individual conditions are largely rare diseases,
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Target Identities

identification of target identities in deeper analysis of current challenges and potential interactions between them. In the following summary, we provide a deeper analysis of current challenges and potential solutions in target identification and preclinical and clinical target validation (see Figure 2).

Translational Interactions

A further problem is that basic and preclinical researchers in the kidney domain are largely disconnected from the needs of the clinical domain. Cell biology, gene editing in mice, epidemiology, and RRT-related research are all strong fields with little interaction and knowledge flow from one domain to the other. To increase the translational flow, it is necessary that the domains of basic and clinical science talk to each other and both make efforts to close the gap between them. In the following summary, we provide a deeper analysis of current challenges and potential solutions in target identification and preclinical and clinical target validation (see Figure 2).

Target Identification

Bedside to Bench

The traditional bench-to-bedside concept is often inefficient and not cost-effective. Basic science has become a complex world on its own that is largely disconnected from the unmet needs of medical practice. It is now evident that the traditional approach of random basic science experiments identifying new therapeutic targets generates very few hits that later prove relevant in human disease in clinical trials.

Too many targets are proposed by in vitro studies, in vivo models, and immunostaining of human tissue sections that may be involved in a disease but not critical targets for human disease. For the sake of replicability, cell lines and simple disease models of inbred mouse strains have become standard tools of investigation but do not recapitulate the genetic diversity of human populations. The high failure rates of bench-to-bedside research together with the increasing availability of high-throughput analytical platforms such as genome sequencing, transcriptomics, proteomics, and metabolomics can reverse this traditional approach.

That is, translational research can now be initiated using better characterized human phenotypes, regardless of diversity. The development of low-density lipoprotein-lowering proprotein convertase subtilisin/kexin type 9 inhibitors is a good example of this approach. The target proprotein convertase subtilisin/kexin type 9 was found to be deficient by genome sequencing of individuals with unusually low serum low-density lipoprotein levels.

Similarly, the identification of APOL1 variants accounting for CKD progression in people of African descent only occurred when the comparison of gene profiles of different ethnic groups with CKD became feasible.

From bedside to bench: Targeting APOL1 overexpression to modulate CKD progression in those of African descent has become one of the hottest topics in kidney research.

Therefore, prospective phenotyping of patients with CKD is necessary and underway, for example, in patients with nephrotic syndrome or hereditary nephropathies (www.eurenomics.eu). However, a coordinated (global) approach is needed to identify subgroups of patients with similar pathological mechanisms of disease. This approach can no longer be driven by kidney pathology alone but requires integration of different analytical platforms to unravel pathological mechanisms.

In unselected cohorts, these platforms often only mirror already known pathways of tissue remodeling such as inflammation and fibrosis. It may therefore be more promising to initiate this process from more selected patient subgroups with unusual genotypes and/or phenotypes that show unique features or disease outcomes within the established disease entities.

This approach relies on study networks with standardized data collections and biomaterial sampling and repositories. Hence, efficient target identification may no longer be a single laboratory effort but rather a multinational effort with a good balance between standard-operating procedures and flexibility. Another example discussed in the meeting was identifying lack of or escape from CD8 T-cell exhaustion as a cause of relapsing autoimmune disease by performing network analysis of a patient cohort’s T-cell transcriptome.

Once identified this may serve as an early predictor of flares or as a therapeutic target to sustain T-cell exhaustion for the maintenance of remission.

Figure 2. Strategies to improve translational flow in immune-mediated kidney diseases. RCT, randomized controlled trial; RRT, renal replacement therapy.
Drug Repurposing

Another strategy worth exploring for immune-mediated kidney diseases is drug repurposing. Drugs that have already been shown in other diseases to affect the mechanistic pathways involved in immune-mediated kidney diseases can be tested. This approach saves on development time and expense, and safety profiles, at least in general, are usually well known. For example, drugs that target or deplete B and plasma cells in multiple myeloma may be useful in autoimmune diseases with a strong B and plasma cell contribution.30 Lupus nephritis is particularly attractive in this context because short-lived plasmablasts mirror systemic lupus erythematosus disease activity and persistent autoimmunity in systemic lupus erythematosus is imprinted into long-lived plasma cells that reside in bone marrow niches similar to myeloma cells.31 The failure of such agents in lupus nephritis may not reflect mechanistic efficacy, but more likely an imbalance between the drugs’ mechanism of action and our expectations of outcomes. Depleting B cells may be more effective at attenuating persistent autoimmunity as opposed to rapidly resolving an acute flare of lupus nephritis. Other immune-mediated kidney diseases that respond well to B-cell or plasma-cell-depleting agents include membranous GN and humoral allograft rejection.32,33

Another example of drug repurposing is the category of tumor necrosis factor inhibitors that suppress necroinflammation and are effective in rheumatoid arthritis and Crohn’s disease. Although a small open label trial demonstrated the efficacy of infliximab in ANCA vasculitis, a larger RCT of etanercept in granulomatosis with polyangiitis did not support this concept.34 This outcome led to a general disregard of tumor necrosis factor inhibitors as an option, but this may not be appropriate as the 2 agents work differently, and failure of etanercept when added to standard therapy in granulomatosis with polyangiitis does not exclude a potential benefit of infliximab in renal vasculitis.35 Finally, leflunomide, a dihydroorotate dehydrogenase inhibitor, is a potent suppressor of autoimmune arthritis and has been repurposed for the treatment of lupus nephritis in China, although its efficacy in other ethnicities remains to be demonstrated.36–38 Bedside-to-bench repurposing is exemplified by irinotecan, a topoisomerase inhibitor developed for the treatment of colorectal carcinoma that was found to effectively treat various mouse models of lupus-like immune complex GN, even at very low doses.39

Bench-to-bedside research and drug repurposing is captured by the broad enthusiasm for stem cell therapies. Mesenchymal stromal cells may have stem cell-like effects, but perhaps more importantly have paracrine immunomodulatory effects that appear to be relevant for promoting host immune response modulation against donor alloantigens and facilitating a protolerogenic environment in renal allografts.40,41 A number of multinational research consortia are exploring the potential of mesenchymal stromal cells in other diseases including diabetic nephropathy.32

Adoptive transfer of ex vivo expanded or induced regulatory T cells is also a promising therapy, now entering clinical trials. Drug repurposing of US Food and Drug Administration-approved drug products is often beneficial because of the previous knowledge and experience with these drugs, which make new development programs for the treatment of other conditions more targeted to the appropriate patient subgroups.

Target Optimization

Novel ideas may arise from the repurposing approach. For example, B-cell ablation with RTX was shown to have a limited capacity to deplete tissue-based CD20+ cells because effector cells needed for antibody-mediated cytotoxicity may not be in these tissue compartments. This finding initiated further efforts to refine the B-cell-targeting strategies beyond peripheral cell depletion. Besides depleting B cells, inhibition of B-cell activation and induction of inhibitory programs in B cells that interfere with humoral immunity are being examined in the context of kidney disease. Several pathways of B-cell activation (e.g., Bcl-2-associated death promoter [BAD], A proliferation-inducing ligand [Apirl], Bruton’s tyrosine kinase [BTK], PI3-kinase, Lyn, nuclear factor KB, and mammalian target of rapamycin [mTOR]) and B-cell inhibition (e.g., FcgRIIb, CD22, programmed cell death protein 1 [PD-1], Src homology 2 domain–containing phosphatase 1 [SHP-1], SHIP-1, and phosphatase and tensin homolog [PTEN]) have been identified and therapeutically addressed. Recently, cross-linkage of CD79 was recognized to induce a strong inhibitory program in B cells, thus interfering with a large set of different B-cell activators. This approach proved to be much more potent than RTX analogs in controlling autoimmune tissue injury in rodents and to interfere with the development of autoantibody production.43 Along the same lines, the approved systemic lupus erythematosus drug belimumab (anti–B-cell activating factor) is currently being tested in a multicenter RCT to evaluate repositioning it for lupus nephritis.44

Depletion of proinflammatory macrophages has also provided renoprotection in numerous animal models45 but has not yet been put forward to clinical trials. However, the spleen tyrosine kinase inhibitor fostamatinib strongly inhibits macrophage activation and is currently being trialed in IgA nephropathy (NCT02112838), whereas cell therapy with regulatory macrophages is being explored in living donor kidney transplant recipients (The ONE Study). Another
example of target optimization relates to the complement system, where the role of local extravascular synthesis of complement components contributing to renal transplant injury has led to site-specific targeting with clinically ready reagents.16,46,47

**Target Validation in Preclinical Disease Models Optimizing Predictability**

The concept of testing novel drugs in rodent disease models is under increased scrutiny not only from the public regarding animal welfare but also from the scientific community and industry, because too often results obtained in preclinical disease models have not been seen in subsequent RCTs. Although this discrepancy is likely to have many different explanations, it seems obvious that the current strategy needs to be refined as discussed in detail elsewhere.2,29 Animal models used to replicate kidney disease are often selected by the criteria of simplicity and histopathological lesions, which may have little, if anything, to do with the requirements of preclinical drug testing. Closing the gap between preclinical and clinical drug validation requires similar testing strategies. For example, to be of predictive value preclinical studies must apply the same primary and secondary endpoints as RCTs would use, such as glomerular filtration rate and urinary protein-to-creatinine ratio, an aspect often ignored in the fields of immune complex GN, diabetic nephropathy, or renal fibrosis.2 A combination of different experimental approaches such as consistent data sets from knockout mice, transgenic mice, and neutralizing compounds for a single biological target as well as the use of multiple disease models increases predictability. For example, the alternative complement pathway was found to be activated in patients with active ANCA vasculitis leading to increased C5a. Murine data showed that genetic C5 deletion, pharmacologic C5 inhibition by an antibody, and myeloid-specific C5a receptor deletion protected from necrotizing GN in several different murine disease models.59–51 Consequently, an oral blocker of the human C5a receptor was developed, tested in a mouse model, and is currently being evaluated in multicenter RCTs in patients with ANCA vasculitis.52,53 Another clinical trial tests a human regulator tested in a mouse model, and is currently being evaluated orally blocker of the human C5a receptor was developed, inhibition by an antibody, and myeloid-specific ANCA vasculitis leading to increased C5a. Murine data showed that the current strategy needs to be redefined as discussed elsewhere.2,48 Animal models used to replicate kidney disease are often selected by the criteria of simplicity and histopathological lesions, which may have little, if anything, to do with the requirements of preclinical drug testing. Closing the gap between preclinical and clinical drug validation requires similar testing strategies. For example, to be of predictive value preclinical studies must apply the same primary and secondary endpoints as RCTs would use, such as glomerular filtration rate and urinary protein-to-creatinine ratio, an aspect often ignored in the fields of immune complex GN, diabetic nephropathy, or renal fibrosis.2 A combination of different experimental approaches such as consistent data sets from knockout mice, transgenic mice, and neutralizing compounds for a single biological target as well as the use of multiple disease models increases predictability. For example, the alternative complement pathway was found to be activated in patients with active ANCA vasculitis leading to increased C5a. Murine data showed that genetic C5 deletion, pharmacologic C5 inhibition by an antibody, and myeloid-specific C5a receptor deletion protected from necrotizing GN in several different murine disease models.59–51 Consequently, an oral blocker of the human C5a receptor was developed, tested in a mouse model, and is currently being evaluated in multicenter RCTs in patients with ANCA vasculitis.52,53 Another clinical trial tests a human regulator that specifically targets the complement component C3 and its role in ischemic injury of donor kidney.54 Another possibility to increase the predictability of animal models for human disease is to conduct preclinical studies in a multicenter RCT-like fashion with defined inclusion and exclusion criteria, blinded randomization, and central blinded analysis similar to human trials.55,56

**Mechanism Not Lesion**

A major challenge is to create disease models that mimic central pathological mechanisms of human diseases. The bench-to-bedside approach chooses novel targets from basic science, tests several disease models, and often reports only positive results, and then proclaims that the disease model mimics the human disease.16,17 Prominent examples are models characterized by lesions that resemble those in “AKI,” “diabetic nephropathy,” “focal segmental glomerulosclerosis,” “renal fibrosis,” without considering that the model may not at all represent a relevant subset of patients or a clinical scenario suitable for therapeutic intervention. The bedside-to-bench approach starts from a target already proven to be relevant in patients and requires animal models that are suitable to explain the pathological mechanisms.58,59 Comparative transcriptome analysis may help to match human and rodent disease.60 This approach may also include transgenic models that have little to do with human disease but help to identify the molecular or cellular biology behind the clinical finding. However, target validation also requires disease models closely similar to human disease (Table 2). This is possible in monogenic renal disorders such as Alport syndrome, where mice with identical mutations to those found in humans mirror all aspects of human disease and are suitable to reliably predict the outcome of therapeutic interventions.61–64 In polygenic disorders, this is more difficult to achieve. An interesting example is the discovery of novel autoantigens in primary membranous GN. Several groups simultaneously described the thrombospodin type 1 domain-containing 7A antigen in a small subset of patients with this disease who were not positive for antibodies to phospholipase A2.

**Table 2.** Some rodent models of (immune-mediated) kidney disease with the theoretical (and sometimes proven) capacity to predict effects in human disease

<table>
<thead>
<tr>
<th>Disease model</th>
<th>Monogenic models of Alport nephropathy, primary FSGS, C3 nephropathy</th>
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<tr>
<td></td>
<td>Anti-GBM disease based on immunization with αs3(IV)NC1 antigen</td>
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<td></td>
<td>Polygenetic models of lupus nephritis, IgA, and type 2 diabetic nephropathy</td>
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<td></td>
<td>Transplanting wild-type bone marrow into Mpo–/– mice immunized with MPO.</td>
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<td></td>
<td>Experimental autoimmune vasculitis, based on immunization with MPO</td>
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<td>THSD7A-related membranous GN, Heymann nephritis</td>
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<tr>
<td>Tubulointerstitial disease</td>
<td>Monogenic models of polycystic kidney disease, primary hyperoxaluria, and other monogenic tubulointerstitial disorders (UMOD, etc.)</td>
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<td></td>
<td>Infective pyelonephritis</td>
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<td></td>
<td>Some kidney allograft rejection models</td>
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<td></td>
<td>Polymicrobial sepsis-induced AKI models</td>
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<td></td>
<td>Toxin-induced models of AKI/CDK that exist in humans (rhabdomyolysis, CyA, aristolochic acid, oxalate, cisplatin, etc.)</td>
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<tr>
<td></td>
<td>Contrast media-induced AKI</td>
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<tr>
<td>Mice with humanized immune system</td>
<td>Secondary tubular injury in glomerular models</td>
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<tr>
<td></td>
<td>AKI, acute kidney injury; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN, glomerulonephritis; IgAN, IgA nephropathy; MPO, myeloperoxidase; NC1, noncollagenous domain 1; THSD7A, thrombospondin type 1 domain-containing 7A; UMOD, uromodulin.</td>
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AKI, acute kidney injury; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GN, glomerulonephritis; IgAN, IgA nephropathy; MPO, myeloperoxidase; NC1, noncollagenous domain 1; THSD7A, thrombospondin type 1 domain-containing 7A; UMOD, uromodulin.
receptor. Injection of human anti-thrombospodin type 1 domain-containing 7A autoantibodies into mice can induce features of membranous GN. However, this passive approach ignores the elements of adaptive immune mechanisms of membranous GN that operate outside the kidney. The same applies to crescentic GN induced by glomerular basement membrane antisera, but autologous models of anti-GBM disease now exist and it remains to be explored if this is also feasible for thrombospodin type 1 domain-containing 7A-related GN. A more accurate model of anti-glomerular basement membrane disease can be induced in the rat, in which immunization with α3 (IV) noncollagenous domain 1 (the “Goodpasture antigen”) leads to severe crescentic nephritis similar to that in patients. This model has been of value in investigating novel therapeutic approaches, for example, the inhibition of spleen tyrosine kinase. Generating mice with a human immune system is another option to better mimic human immune targets in rodents. For example, such mice were used to assess the in vivo efficacy of small molecule antagonists against human CC chemokine receptor-2. This approach was proven to be predictive as a subsequent RCT documented in vivo efficacy of the lead compound in patients with type 2 diabetic nephropathy.

Target Validation in Clinical Trials
Performing RCTs in immune-mediated kidney diseases is challenging for many different reasons. One challenge is trial costs because relevant effect size, for example, on CKD progression can only be demonstrated in trials lasting years. This generates a hurdle difficult to bypass for academic investigators and even multinational consortia, if not funded by generous public bodies or private foundations. However, National Institutes of Health’s funding for kidney research is disproportionately low compared with other less common disease entities.

Orphan Diseases
Immune-mediated kidney diseases are mostly rare diseases; hence, single center studies, albeit frequently performed, are not sufficiently powered to reach reliable conclusions. Some diseases are suitable to test new interventions in trials with few patients. For example, cross-over designs or matched-cohort studies are able to considerably reduce the numbers of patients needed to gain evidence. The extreme of this approach is the “n = 1 trial” that sequentially assesses standard and experimental treatments in an individual patient. However, the latter approach is limited to diseases that demonstrate rapid and clear short-term responses to an effective treatment. For example, in thrombotic thrombocytopenic purpura, plasma exchange could be easily tested versus plasma infusion in a single patient using platelet count recovery as a short-term readout because the readout of response to treatment is rapid and robust. Testing less robust treatment effects is also possible in a step-up trial design, where a single or a small number of patients are treated with an innovative drug. Before more patients are exposed to the drug, the first patients are extensively phenotyped for drug exposure, biomarkers of mechanism of action, and treatment outcome to eventually adjust drug dosing and timing of the intervention. In this stepwise, or adaptive design, approach, optimizing these parameters is possible before moving to a larger or a controlled trial. In rare diseases, control groups in trials may not even be needed or may be simply unethical. Historical controls might be used instead. However, these approaches can hardly be used in GN and most other forms of immune-mediated kidney disease where such a short-term readout parameter is not available. To solve this problem, clinical trial networks need to be set up to bring together sufficient numbers of patients. Where such trial networks efficiently collaborate, for example, in the European Vasculitis Study Group (http://www.vasculitis.org/), the results of the numerous sequentially performed trials were able to set the current standards for patient management and the assessment of newer therapies, such as RTX. Recently, a network has been set up for lupus nephritis called the Lupus Nephritis Trial Network (http://lupusnephritis.org/). Such networks are also needed for other forms of GN to facilitate efficient multicenter RCTs.

Stratifying for Pathological Mechanism
Another challenge for RCTs is patient stratification for treatments with highly specific mechanisms of action. Current disease categories are often based on histopathological lesions and biomarkers, but individual patients have very diverse underlying pathological mechanisms. Identifying subgroups of patients with similar pathogenic mechanisms that are related to the presumptive mechanism of action of the innovative drug could be an important step forward in evaluating novel treatments that would otherwise fail to show significant treatment benefits in unselected patient cohorts. For example, such patient stratification can be achieved by genetic testing of patients with idiopathic nephrotic syndrome, as to exclude those with a genetic podocyte-opathy that would not benefit from immunosuppressive treatments. In lupus nephritis, a more sophisticated analysis of the blood leukocyte or even the kidney transcriptome may allow stratification of patient subpopulations that can be tested for unique pathological mechanisms and outcomes. Selecting specific treatments for certain patient subgroups would approach the innovative precision medicine concept currently
being established in the field of oncology. However, this still creates a challenge as subgroups in a rare disease might be so small as to prohibit an adequately powered trial or even arouse commercial interest.

Stratifying for Ethnicity?
Race and ethnicity affect the risk of CKD progression in many immune-mediated kidney diseases. Different outcomes in ethnic groups are now proven to be driven by genetic factors such as APOL1, which can affect the outcome of trials independent of drug efficacy. Ethnicity also influences drug dosing because drug metabolism clearly differs among ethnic groups, which affects drug efficacy and toxicity in trials with a fixed dosing regimen. Failing to take into account ethnicity-related heterogeneity of CKD progression and drug metabolism can drastically compromise the assumptions underlying statistical power and group size calculations in global multicenter RCTs or of regional RCTs in countries with multiethnic populations. Acknowledging this problem implies that the results of clinical trials may be limited to certain ethnic groups, until proven otherwise. For example, several trials have tested leflunomide, mycophenolate mofetil, or mycophenolate mofetil + tacrolimus only in cohorts of Chinese patients with lupus nephritis. The Caucasian Euro Lupus trials are another example, although the low-dose cyclophosphamide (CTX) dose-restricted Euro lupus regimen has recently been proven to be noninferior to high-dose CTX also in African Americans and Hispanics participating in the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study.

Add-on Design
Study design is much influenced by the disease being treated, standard of care for that disease, the anticipated effects of the investigational therapy, and ethics of giving clinical treatment versus placebo. For example, a number of studies of lupus nephritis conducted in the past used the add-on treatment design (standard of care plus placebo vs. standard of care plus investigational therapy) and sought statistical superiority. However, this design appeared most yielding when the magnitude of effect of the background treatment was smaller than that of the investigational treatment, best exemplified perhaps by the addition of a tumor necrosis factor-alpha inhibitor to methotrexate monotherapy in rheumatoid arthritis. A similar design in lupus nephritis may be less yielding for statistical demonstration of drug effect because the large doses of background steroids may mask the effect of adding on a new therapy, particularly if that therapy is of modest benefit. But as long as standard therapy consists of broadly immunosuppressant drugs, more selective immunosuppressant drugs with overlapping mechanisms of actions are unlikely to improve response rates. A study designed as a noninferiority comparison with the new drug replacing the steroid component of the standard of care might be more useful. Replacing steroids would address an important unmet medical need in lupus nephritis. Such a design, however, should be chosen carefully to ensure that patients receive the appropriate care that is effective in treating lupus nephritis flare regardless of the selected study design and treatment agents. In addition, non-inferiority designs require robust evidence characterizing the selected noninferiority margin. A prospective trial using RTX in addition to mycophenolate allowed early withdrawal of steroids. Such alternative trial designs need to be further explored in the field of immune-mediated kidney diseases.

Study Endpoints
The right study endpoints for RCTs remain a matter of debate. Nephron number would be a sensitive surrogate marker for CKD progression but is unfortunately not yet available. Currently, serum creatinine, estimated glomerular filtration rate, and proteinuria are used as trial endpoints for most forms of kidney disease although endpoints such as steroid dose, time to flare, or patient-oriented outcomes such as quality of life would also be meaningful. In addition, serum creatinine and proteinuria are not directly linked to the mechanism of action of immunomodulatory drugs and require years to reveal drug efficacy in chronic forms of GN. Kidney biopsy is the current gold standard to determine resolution versus ongoing intrarenal inflammation and should be ideally considered as mandatory for trial endpoints; if a negative impact on patient recruitment is an overwhelming concern, a repeat kidney biopsy should at least be an optional study endpoint for most trials. Post hoc analyses of previous trial data sets are a useful tool to refine future trial strategies in terms of minimizing variability and increasing trial power. Therefore, it is important that trial data become accessible to researchers and data sharing becomes a common standard. Collaborative efforts by the National Kidney Foundation and the US Food and Drug Administration in 2012 and a subsequent collaborative initiative together with the Lupus Nephritis Trial Network defined surrogate parameters for CKD progression in general and in lupus nephritis. In addition, Lupus Nephritis Trial Network members sharing their data from the Eurolupus, Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis (MAINTAIN) and Aspreva Lupus Management Study (ALMS) trials were able to reassess the predictive value of proteinuria response to induction and maintenance therapy as a
surrogate for CKD progression.\textsuperscript{95} Similar attempts were made on “failed” diabetes trials such as ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), SUN, treat-to-target (TREAT), Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE), Veterans Affairs Nephropathy in Diabetes (VA-Nephron), Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes (BEACON), A Study of Cardiovascular Events in Diabetes (ASCEND), where post hoc analysis retrieved important information to work out better composite endpoints that will help to minimize risk and maximize effect in future trials. Finally, induction of remission is not the only useful study endpoint. In relapsing diseases such as renal vasculitis, nephrotic syndrome, or lupus nephritis, monitoring early predictors of flares and comparing time to flare between treatment arms with different maintenance therapies should be considered as useful and relevant endpoints.

Cost-effectiveness

Controlling disease is the goal but at what cost? Many new drugs are costly and have only a modest effect size. By contrast, to see a strong effect size in kidney disease usually requires long and very costly trials. A careful analysis of the number-needed-to-treat, short-term, and long-term adverse events, impact on quality of life as well as direct and indirect costs will have a strong impact on whether a drug passes into routine clinical practice. For example, steroid treatment only has a modest impact on whether a drug passes into routine practice. For example, oral CTX involves drug costs of 72 Euros, whereas treatment with RTX, which was noninferior but not superior to CTX for the induction therapy of ANCA vasculitis, involves 17,500 Euros in drug costs and around 9000 Euros in hospitalization costs in France. These costs do not take into account routine lab monitoring for CTX, and cost modeling remains complex. RTX in granulomatosis with polyangiitis and microscopic polyangiitis was formally evaluated by the National Institute for Health and Care Excellence in the UK and guidance was issued for RTX use in 2014 with specific recommendations (https://www.nice.org.uk/guidance/TA308). Thus, once approved, novel drugs need to be carefully evaluated for cost-effective use. Clever drug development requires wise predictions on the result of this process as early as possible. Finally, we should not forget that the most cost-effective treatment in immune-mediated kidney diseases may sometimes simply be a rigorous conservative treatment of CKD as previously shown in 12 years’ follow-up of a single case with lupus nephritis or more recently for patients with IgA nephropathy.\textsuperscript{11,96}

<table>
<thead>
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<th>Table 3. Berlin roadmap</th>
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<tr>
<td>- Increase awareness for nephron loss along lifetime with risk for end-stage renal disease (ESRD) at advanced age and add-on nephron losses with any kidney disease, implying mid-age ESRD.</td>
</tr>
<tr>
<td>- Support initiatives that shift financial incentives from renal replacement therapy to prevention of ESRD to promote cost-effective use of kidney disease health care budgets.</td>
</tr>
<tr>
<td>- Raise interest in young doctors for nephrology by transforming the subject from renal replacement and maintenance oriented into a curative discipline.</td>
</tr>
<tr>
<td>- Support initiatives that try to overcome the disconnection of basic kidney research and clinical research. Support clinical scientists track and endorse bedside-to-bench research.</td>
</tr>
<tr>
<td>- Revise current preclinical animal testing. Endorse humanized animal models of kidney disease. Define models by the involved pathomechanisms not by histopathological lesions. To increase predictability of preclinical animal studies, these studies must be conducted using same protocols and endpoint analysis as performed in humans.</td>
</tr>
<tr>
<td>- Personalized and precision medicine in kidney disease requires stratifying patients within current disease entities for involved pathomechanisms. This requires suitable biomarkers and potentially genetic testing to match the right patients with available treatment options.</td>
</tr>
<tr>
<td>- Use this approach in future randomized controlled trials to avoid diluting drug effects by maintaining too many obvious nonresponders within the trial. This is also not done in clinical practice. Use post hoc analysis data from previous trials to define the right patient subgroups.</td>
</tr>
<tr>
<td>- Trials in immune-mediated kidney diseases may not necessarily be set up as superiority trials. Replacing steroids may be a better strategy, especially for drugs with overlapping mechanism of action to steroid treatment.</td>
</tr>
<tr>
<td>- Some renal diseases qualify for trial designs other than randomized controlled trial (RCT). Several alternative options exist including cross-over designs and even n = 1 trials.</td>
</tr>
<tr>
<td>- As immune-mediated kidney diseases are mostly rare diseases, forming multinational trial networks will be essential to conduct meaningful RCTs.</td>
</tr>
<tr>
<td>- Endorse national or international registries and open access databases on the epidemiology, phenotype, and renal care of kidney disease patients.</td>
</tr>
<tr>
<td>- Endorse studies on race/ethnicity differences of disease phenotypes, pharmacogenetics, and treatment outcomes.</td>
</tr>
<tr>
<td>- The genetic basis of adult kidney disease needs to be explored.</td>
</tr>
<tr>
<td>- A quantitative biomarker of nephron number is needed to define nephron loss from the number present at birth, during disease or as a structural comparative endpoint for clinical trials.</td>
</tr>
</tbody>
</table>

Conclusion

Many challenges compromise the translational flow of new therapies from bench to bedside in immune-mediated kidney diseases. Identifying the problems is the first step toward improvement. Further discussions and coordinated actions (Table 3) endorsed by national or international societies, industry, funding organizations, and regulatory bodies are needed to solve the pending issues. A more stringent focus on human rather than mouse disease with well-characterized human disease phenotypes ranging from relatively rare monogenic strong phenotypes to polygenic common phenotypes will stratify the patients with causative pathogenic mechanisms rather than only the histopathological pattern. This requires more efforts in human biomarker research and the bedside-to-bench research approach. Once clarified the clever design of shorter trials with robust endpoints for CKD progression is needed to bypass the traditional add-on design of immunomodulatory drugs that have
redundant mechanisms of action. The unmet medical need of kidney patients and the availability of well-characterized patient cohorts, modern bioinformatics, and big data analysis together with latest drug development tools also require an update of preclinical and clinical target validation to eventually come up with more innovative cures for our patients with immune-mediated kidney disease.

DISCLOSURE

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APPENDIX


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