NIH Glomerular Disease Conference Leads to New Opportunities for Advancing Knowledge and Treatments

By Charles E. Alpers

Major research advances in the past 2 decades have provided a greatly enhanced understanding of mechanisms underlying glomerular disease. These include the identification of proteins specific to podocytes and the slit diaphragm, and the diseases that may develop as a consequence of mutation or dysfunction of these proteins. Research has also demonstrated the pathogenic contribution of abnormally galactosylated immunoglobulin A (IgA) to the development of IgA nephropathy; pin-pointed SpeB as the major inciting antigen of acute poststreptococcal glomerulonephritis; and identified the phospholipase A2 receptor (PLA2R) as the principal antigen in most cases of idiopathic membranous nephropathy.

Other studies have provided evidence that a specific circulating factor (soluble urokinase receptor [suPAR]) is implicated in the pathogenesis of focal and segmental glomerulosclerosis (FSGS), and that another factor (the hypothesized form of angiotensin-like protein 4 [ANGPTL4]) may be involved in the pathogenesis of minimal change disease (MCD). However, the extent to which these factors may be causative remains to be established. Despite these and other major accomplishments in understanding their pathogenesis, there has been a lack of corresponding advances in therapeutics for these diseases.

Given this background, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in conjunction with the ASN Glomerular Disease Advisory Group, organized the “Glomerular Disease Pathophysiology, Biomarkers, and Registries for Facilitating Translational Research” conference, which was held at the National Institutes of Health (NIH) campus in Bethesda, MD, on April 17 and 18, 2012. The conference goals were to identify approaches to build upon this body of knowledge; develop an infrastructure that would facilitate implementation of clinical trials of new therapeutics in glomerular disease; and foster a dialogue between academic researchers, private-sector entities (including biotechnology companies and major pharmaceutical companies), and the U.S. Food and Drug Administration (FDA) that would ultimately serve to reduce the obstacles in bringing new agents for treatment of glomerular diseases to clinical trials.

The conference began with presentations by leaders of clinical trial networks from outside the glomerular disease field, including Frank Accurso, MD, of the University of Colorado on behalf of the Cystic Fibrosis Foundation Therapeutics Development Network, which now supports phase III trials conducted at 77 sites, and Neil Solomon, MD, of Vifor Pharma, speaking on behalf of the Aspreva Lupus Management Study (ALMS).

Discussion subsequently focused on specific disease entities and the potential for therapeutic interventions in each category. The keynote overview speaker, former ASN President William Couser, MD, reviewed both areas of progress made in the past 4 decades—including the identification of key pathogenic molecules described above—and the residual critical gaps in our understanding. The latter include insufficient knowledge of the initiating events in most glomerular diseases and of the best targets for therapeutic intervention.

A major problem in the care of patients with glomerular diseases is that most therapeutics in current use were developed for application in other medical fields, such as transplantation and rheumatology, that require systemic therapy and do not target specific glomerular processes. An advantage of more tightly targeted therapeutics is that they offer the possibility of reduced toxicities and off-target effects.

Other presentations, followed by break-out discussion groups, focused specifically on the MCD/FSGS spectrum of diseases, IgA nephropathy, membranous nephropathy, vasculitis, and the recently emerging entity C3 glomerulopathy. Discussion centered on clinical trial assessment, and the need for a durable multi-institutional clinical trials infrastructure with the necessary bioinformatics and biorepository support to what has been accomplished with the cystic fibrosis network and the large oncology group study networks, such as the Southwest Oncology Group (SWOG). Such an infrastructure would enable the recruitment of a sufficient number of patients for meaningful trial results and would obviate the need to create a trial network anew for each potential clinical study of a glomerular disease therapeutic.

A topic discussed at length, but not resolved at this meeting, was achieving agreement among representatives of the FDA on acceptable surrogate markers for progressive glomerular disease. This has been a particularly challenging issue because end points, such as development of ESRD or death, are neither inevitable nor necessarily early events in the evolution of glomerular disease. The most obvious surrogate marker for glomerular disease—proteinuria—has too many vagaries to be currently acceptable to the FDA as a biomarker across different glomerular disease categories. The identification of specific pathogenic moieties, such as anti-PLA2R antibodies in membranous nephropathy and circulating suPAR in FSGS, may allow development of future assays that could be disease specific and fulfill a biomarker function for monitoring disease progress in future clinical trials.

There were several important outcomes from this conference. First was the issuance of a request for applications from the NIDDK (RFA-DK-12-014, application due date February 27, 2013) to fund consortium sites that will establish and longitudinally follow cohorts of patients with common glomerular diseases (MCD, FSGS, IgA nephropathy, and idiopathic membranous nephropathy) who can then be entered into clinical trials and studies that validate biomarkers of disease progression and other relevant clinical and translational studies. Second, as highlighted in the ASN President’s Address by Ronald Falk, MD, FASN, at Kidney Week 2012, this conference furthered a dialogue that contributed to the development of the Kidney Health Initiative (KHI), a partnership of ASN and the FDA.

The mission of KHI is to advance scientific understanding of the kidney health and patient safety implications of new and existing medical products and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which FDA and the greater nephrology community can interact to optimize evaluation of drugs, devices, biologics, and food products. For more information about KHI, please visit http://www.asn-online.org/khi/.

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