Novel therapeutic approaches for chronic kidney disease due to glomerular disorders

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Abstract

Improved understanding of glomerular disease mechanisms over the past decade has led to the emergence of new and targeted therapeutic strategies for chronic kidney disease (CKD). Most promising among these are the administration of recombinant mutated human Angiopoietin-like 4, sialic acid related sugars that induce sialylation in vivo, compounds related to Bis-T-23, and immune-depletion of the soluble urokinase receptor from the circulation. Taking these therapeutic strategies into clinical trials will be the first step away from repurposed and relatively toxic drugs currently used for treating kidney disease.
None of the drugs currently used to treat glomerular disease or chronic kidney disease (CKD) due to glomerular diseases were originally developed for these disorders. Over time, nephrologists have adapted drugs like corticosteroids, cyclophosphamide, cyclosporine, and many others to treat glomerular disease and slow the progression of CKD associated with proteinuria with limited success (2). Over the past two decades, two major lines of investigation have moved the study of glomerular disease to the forefront. First, the genetics revolution that started with the discovery of mutations in the NPHS1 gene in children with congenital nephrotic syndrome, and evolved rapidly with the discovery of several other, mostly podocyte expressed genes mutated in different forms of glomerular disease (3). The genetics approach has led to the identification of new pathways, some of which may become amenable to drug therapy once these pathways are fully worked out. The second approach has relied on classic differential mRNA or protein expression studies in animal models, or the study of disease mechanisms, followed by confirmation of human relevance in human samples like kidney biopsies, plasma and urine. This approach has resulted in the development of all of novel therapeutic strategies discussed here. The advantage of the second approach over the first is that by the time the studies are published, a substantial part of the molecular pathways have been defined, whereas most genetics studies when published are limited to identification of human gene mutations, and sometimes limited exploration of molecular pathways.
Over the past 5 years, four studies published in Nature Medicine (4, 5, 11, 13) have identified novel mechanism based therapies designed specifically for glomerular disease and CKD associated with proteinuria. These new mechanism-based strategies can be broadly divided into two categories: those that involve administration of novel therapeutic agents, and others that involve depletion of a pathogenic circulating protein. The unique feature of all of these therapeutic strategies is that they have been developed specifically to treat glomerular disease, and are not merely existing agents that are repurposed to treat kidney disease.

Administration of novel therapeutic agents

Recombinant mutated human Angiopoietin-like 4 (Angptl4): Angptl4 is the first member of the circulating glomerulophilic proteome (6) in which all of Koch’s postulates have been fulfilled. This class of therapeutic agents was developed by Chugh and colleagues to manipulate novel physiological feedback loops identified by this group to a therapeutic advantage (2, 5, 6, 8). As part of the progression from proteinuria to nephrotic syndrome, the rise in the plasma free fatty acid (FFA) to albumin ratio due to asymmetric urinary loss of low FFA containing albumin beyond a threshold level promotes entry of FFA into skeletal muscle, adipose tissue and heart, followed by secretion of the soluble sialylated glycoprotein Angptl4 from these organs into the circulation. Angptl4 secreted in this manner has two major effects: In the capillaries of organs from where it is
secreted, it inhibits the activity of lipoprotein lipase, an endothelium-bound enzyme that breaks down triglycerides to release FFA for uptake in these organs, causing reduced triglyceride derived FFA entry and resulting in hypertriglyceridemia. This forms a local feedback loop that controls the entry of FFA into, and secretion of Angptl4 from these organs. In glomeruli, it binds to endothelial αvβ5 integrin (at the very least) and modifies putative endothelial – podocyte feedback loops to reduce proteinuria. This is the systemic feedback loop initiated by the development of proteinuria. Recombinant Angptl4 is eminently suited for development as a biological therapeutic agent for proteinuric disorders, since it naturally forms very high order oligomers (glycosylated monomer 65-70 kDa) with an effective size larger than the largest plasma proteins, thereby reducing significantly the likelihood of urinary losses following parenteral administration. Chugh and colleagues developed several forms of mutated human Angptl4 that are modified at normal cleavage sites to increase the half-life of the intact protein, and at sites important for its interaction with lipoprotein lipase to avoid hypertriglyceridemia. A single intravenous dose of recombinant mutated human Angptl4 significantly reduces proteinuria without causing hypertriglyceridemia by participating in the systemic feedback loop and ignoring the local feedback loop over a three week period in rat models of diabetic nephropathy and focal and segmental glomerulosclerosis (FSGS). Studies to assess the effect of subcutaneous long term administration on chronic kidney disease due to diabetic nephropathy and FSGS are in progress.
Sialylation based therapeutics: Sialic acid is a carbohydrate synthesized in humans from glucose. The sialylation-based therapeutics approach was developed by Chugh and colleagues to modify a form of Angptl4 that lacks adequate attachments of sialic acid residues (hypo-sialylated Angptl4) secreted only by podocytes in minimal change disease (1, 4). This podocyte secreted hyposialylated form of Angptl4 is pro-proteinuric, and repletion of sialylation using N-acetyl D-mannosamine (ManNAc), an orally bioavailable precursor of sialic acid, improves sialylation and reduces proteinuria in rat models of MCD. Partial efficacy of ManNAc is also noted in diabetic nephropathy (2). Mild upregulation of podocyte Angptl4, which is not associated with production of the hypo-sialylated form, also occurs in membranous nephropathy, and therefore efficacy of sialic acid or its precursor is not anticipated in this condition. The production of hyposialylated Angptl4 selectively in podocytes appears to be related to a demand – supply imbalance in these cells during the development of glomerular disease (2). Whereas the concept of sialylation based therapeutics remains the dominant orally bioavailable therapeutic strategy for the future, the efficacy of sialic acid precursor compound ManNAc in humans is not known, since activity of the sialic acid synthesis pathways in the podocyte in humans and rodents may be very different. Based on the knowledge of molecular pathways, alternative sugar derivatives more likely to have efficacy in humans are being developed.

Bis-T-23 and related compounds: Bis-T-23 is a small molecule of relatively short half-life that promotes actin-dependent dynamin oligomerization, noted by Sever
and colleagues to have efficacy in improving podocyte ultrastructure and proteinuria in rodent models (11). Two mouse models of FSGS and chronic kidney disease (α-actinin 4 and CD2AP mutant mice) and one model of type 1 diabetes and diabetic nephropathy (streptozotocin model) had significant improvement in proteinuria following administration of Bis-T-23. Since Bis-T-23 does not have chemical characteristics of a potential drug, high throughput screens combining in vitro and in cell assays will be developed to identify novel lead compounds with potential to become novel human therapeutics.

**Depletion of pathogenic proteins**

Depletion of circulating soluble urokinase receptor (SuPAR) using affinity columns: Reiser and colleagues showed a pathogenic role of SuPAR in experimental FSGS and documented elevated levels in FSGS patients (13). Using a combination of in vitro and animal studies, they were able to correlate the development of albuminuria and FSGS-like lesions in animal models with selective activation of α₅β₃ integrin in podocytes. Injection of recombinant SuPAR, but not a non-integrin binding mutant, in animals induced albuminuria. Substantial effort is being devoted to the identification of SuPAR glycovariants and fragments with greatest efficacy in binding activated podocyte α₅β₃ integrin (12). Additional animal models demonstrating the pathogenicity of high circulating SuPAR levels from adipose tissue specific overexpression are being characterized (14). Another recent study by Reiser and colleagues shows plasma
SuPAR levels to be the earliest known independent predictor of incident chronic kidney disease and furthermore predict decline of GFR in prevalent chronic kidney disease (7). Other studies have noted elevated SuPAR levels in renovascular hypertension (10) and highlight a role of SuPAR in cardiovascular disease in patients with mild to moderate CKD (9). Based on this data, strategies to immune-deplete circulating SuPAR using monoclonal antibody based affinity columns are currently being developed.

**Conclusion**

Given the diversity and complexity of human glomerular disease, it is unlikely that a single novel therapeutic strategy will emerge to treat the broad spectrum of CKD due to glomerular disorders. Since many different pathways are being targeted, it is more likely that some or all of the above therapeutic strategies will emerge after clinical trials in the form of combination therapy, as has been standard practice in the cancer field for decades. The next generation of drugs must have greater efficacy and more specificity for kidney disease, so as to minimize off target effects. The road to successful therapeutics is long and winding, but the goals are achievable by staying on focus. A positive outcome is always priceless.
References


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Competing financial interests

Sumant S. Chugh is Founder, President and Chief Executive Officer of GD THERAPY LLC, and filed patents related to the use of Angptl4 mutants (PCT/US2011/039255) and sialic acid related compounds (PCT/US2011/039058) for the treatment of glomerular diseases. SSC may benefit financially from these patents in the future. None of the other authors declared competing financial interests.