Personalized Comments on Challenges and Opportunities in Kidney Disease Therapeutics: The Glom-NExT Symposium

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Summary: In the face of ever-increasing incidence and prevalence of kidney disease worldwide, the unmet need for new treatments is unprecedented. Precision medicine is defined as the use of modern technologies to identify mechanisms of diseases in individual patients, and thus deploy treatment using tailored, targeted approaches, in the hopes of avoiding unnecessary toxicities and complications. Is there a place for kidney disease therapeutics in this space? If so, what is required to make significant progress toward precision nephrology? To answer these critical questions, we present a series of personalized comments corresponding to the responses offered to these very questions during the Inaugural Glom-NExT Symposium held at Harvard Medical School on October 23, 2014, a national meeting focused exclusively on kidney disease therapeutics.

Keywords: Adaptive trials, consortium, patient-reported outcomes, kidney disease, proteinuria, nephrotic syndrome, podocyte, TRPC5, Rac1, cytoskeleton, clinical trials, precision medicine, B7-1, CD80, podocyte, synaptopodin, nephrotic syndrome, FSGS, integrin, rare disease, targeted therapy, recessive mutations, ADCK4, COQ6, ARHGDIA, APOL1, TRPC6, actinin-4, INF2, autosomal dominant

An Introduction to the Glom-NExT Inaugural Symposium: Toward Precision Medicine in Nephrology

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Keywords: Therapeutics, kidney disease, nephrotic syndrome, glomerular disease, podocyte, TRPC5, synaptopodin, angiotensin, Rac1

Dear Colleagues,

It is a great pleasure to have you all here today. As you can imagine, this meeting has been in preparation for quite a while, and I hope it is the first of many to come. Our mission statement for Glom-NExT is to discover personalized and targeted treatments to cure kidney disease. This is indeed a lofty goal, but one that we do need to tackle as a field. As I go through my talk today, I will mention the various speakers in the agenda for today and how their talks may tie into specific themes or ideas of what this center is about. Starting with the keynote speaker for today, many of you may have been surprised to see that we did not invite a nephrologist. Dr. George Demetri is an oncologist who has had a tremendous career trajectory in bringing novel experimental

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therapeutics to patients, so we are going to hear from him about his *tales of personalized cancer care*, and how we may be able to learn from him and his colleagues who have been successful in precision medicine approaches so that we may apply these concepts in our field. Another important acknowledgement as we start our meeting today is that this center and its physician-scientists really do stand on the shoulders of giants. Dr. Brenner has been a worldwide leader and pioneer in the field of glomerular disease through both elegant glomerular physiology studies in animals, which are now classic articles in our field,[1–3] and through landmark clinical studies such as the RENAAL trial.[4] This trial was the first proof of concept that a single agent can curb proteinuria as well as the rate of end-stage kidney disease progression.[4] Our challenge today is to build on his landmark work by showing that another agent, one that is independent of the renin-angiotensin-aldosterone pathway and can mitigate proteinuria and kidney disease progression.

I also want to recognize that while great focus today will be placed on the glomerulus, we are interested in novel therapeutics for all kidney disease, and we thus do need to consider all other parts of the nephron, including the tubular compartment, which Drs. Joe Bonventre and Ben Humphreys will discuss.

The patient population at stake in our discussions today is large and the unmet need is tremendous. According to the Centers for Disease Control, one in nine Americans lives with kidney disease, and one in three is at risk for kidney disease from obesity, diabetes, and hypertension (www.cdc.gov). Diabetes and obesity are in fact the main causes of an ever-increasing incidence of kidney disease worldwide.[5] On a global scale, we as nephrologists will be caring for tens of millions of patients requiring chronic kidney disease care or dialysis in years to come, and, most regrettably, we have very little, if anything at all, in our pipeline to address this massive problem.

Let me also make the comment at this point, as Dr. Brenner has written in the past,[6] that, in my opinion, in terms of dialysis, we in nephrology are the victims of our own success. Many of my patients tell me the same story: if their doctor tells them they have renal failure, they go to Wikipedia (www.wikipedia.org), and the first hit they find for "kidney failure" is a picture of a dialysis machine, explaining that dialysis is used to physiologically aid or replace the kidney in the setting of failure. While this sounds wonderful, it is falsely reassuring. The 5-year mortality related to dialysis is worse than most cancers, at nearly 50% of patients without diabetes, and a staggering 70% to 80% of patients with diabetes (www.cdc.gov). In no uncertain terms, halting chronic kidney disease progression to dialysis is the key objective for our field.

What do we know about diabetic kidney disease and its progression? Classic studies in rodents as well as ample clinical trial data support the simple yet powerful notion that when proteinuria increases, glomerular filtration rate decreases.[1,2,4,7,8] Therefore, understanding proteinuria is indeed a path to greater understanding of kidney disease progression. Proteinuria is a clinically useful biomarker of kidney disease in diabetic patients, as well as a strong and independent predictor of increased risk for all-cause mortality and cardiovascular mortality in patients with and without diabetes.[9,10] At this meeting, there are indeed many scientists who have contributed tremendous knowledge in this field.

In broad and basic terms, we now understand that proteinuria results from a damaged kidney filter. The filtration unit of the kidney, the glomerulus, is a highly specialized and complex corpuscle of capillaries capable of selective hydrostatic ultrafiltration of blood plasma, allowing the passage of wastes and retaining vital proteins.[11–13] The kidney filtration barrier comprises three layers: the glomerular endothelium, the glomerular basement membrane, and the podocyte. Podocytes are unique cells with complex cellular organization, including characteristic interdigitating foot processes with the interposed slit diaphragm that cover the outer aspect of the glomerular basement membrane.[11,13,14] Podocyte dysfunction and cytoskeletal disorganization leads to foot process effacement, disruption of the slit diaphragm, and proteinuria, and is thus a starting point for progressive kidney disease.[13,15] Thus, proteins regulating the plasticity of the podocyte actin cytoskeleton are critical for sustained glomerular filter function.[13,15] Autosomal-dominant mutations in nephrin,[16] podocin,[17] or phospholipase C epsilon[18] give rise to congenital proteinuric disease.[16,17] In addition, adult-onset focal segmental glomerulosclerosis (FSGS), as elegantly shown by Pollak et al (in this issue), and as we will hear today, has been associated with mutations in α-actinin 4,[19] CD2AP,[20] INF2,[21] TRPC6,[22] and synaptopodin,[23] which are thought to mediate disease through podocyte dysfunction. Similarly, many autosomal-recessive mutations, in tour-de-force work by Hildebrandt et al (in this issue), as we also will hear today, have converged on the podocyte actin cytoskeleton.[18,24–31] Taken together, human genetics mutations in these molecules have highlighted the central role of the podocyte actin cytoskeleton in kidney health and disease.

Failure of the podocyte actin cytoskeleton is recognized in both animal models and human biopsy specimens as foot process effacement.[32–34] But how does the disease progress to ultimately affect kidney function and glomerular filtration rate? Focal segmental glomerular sclerosis, as we hear from Peter Mundel (in this issue), may provide some insights to disease progression, characterized by the ultimate loss of perhaps the most precious, terminally differentiated population of cells in the kidney, the podocytes.[35]

An interesting paradigm by which to further underscore the importance of podocytes in kidney disease